Gynecologic Cancers
A Multidisciplinary Approach to Diagnosis and Management
Kunle Odunsi, MD, PhD • Tanja Pejovic, MD, PhD

The treatment of gynecologic cancer has become increasingly complex, requiring the comprehensive review and assessment of multiple issues including genetics, radiology, surgery, molecular diagnostics, chemotherapy, and more. As a result, the collaboration among these specialties facilitated by a multidisciplinary team approach is crucial in providing the best care to patients and ensuring successful treatment. Gynecologic Cancers, written by a team of authors representing a range of disciplines, is a valuable resource for physicians, fellows, nurses, physician assistants, physical therapists, and all health care providers involved in the treatment of gynecologic cancer. Gynecologic Cancers summarizes the state-of-the-art issues related to the treatment of gynecologic cancer and describes an approach for optimal multidisciplinary care for women who have been diagnosed with or who are at higher risk to develop gynecologic cancer.

All Current Multidisciplinary Oncology Titles Provide:
- Consolidation and integration of the varied aspects of multidisciplinary care for major topics in oncology
- Coverage of all related topic areas, including medical and surgical oncology, radiation oncology, pain, pathology, imaging, psychological support, and the primary disease
- A chapter focusing on special populations and the disease’s differing impact on them
- Discussion of quality-of-life issues
Gynecologic Cancers
A Multidisciplinary Approach to Diagnosis and Management
Current Multidisciplinary Oncology Series
Charles R. Thomas, Jr., MD
Series Editor

Breast Cancer
A Multidisciplinary Approach to Diagnosis and Management
Alphonse G. Taghian, Barbara L. Smith, and John K. Erban

Lung Cancer
A Multidisciplinary Approach to Diagnosis and Management
Kemp H. Kernstine and Karen L. Reckamp

Cancers of the Colon and Rectum
A Multidisciplinary Approach to Diagnosis and Management
Al B. Benson III, A. Bapsi Chakravarthy, Stanley R. Hamilton, and Elin R. Sigurdson

Gynecologic Cancers
A Multidisciplinary Approach to Diagnosis and Management
Kunle Odunsi and Tanja Pejovic

Prostate Cancer
A Multidisciplinary Approach to Diagnosis and Management
Adam P. Dicker, Wm. Kevin Kelly, and Edouard J. Trabulsi
Gynecologic Cancers
A Multidisciplinary Approach to Diagnosis and Management

Edited by

Kunle Odunsi, MD, PhD
The M. Steven Piver Professor and Chair
Department of Gynecologic Oncology
Director, Center for Immunotherapy
Roswell Park Cancer Institute
Buffalo, New York

Tanja Pejovic, MD, PhD
Associate Professor
Department of Obstetrics and Gynecology
The Knight Cancer Institute
Oregon Health & Science University
Portland, Oregon
Acquisitions Editor: Rich Winters
Compositor: NewGen Imaging
Printer: Bradford & Bigelow

Visit our website at www.demosmedpub.com

© 2014 Demos Medical Publishing, LLC. All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the publisher.

Library of Congress Cataloging-in-Publication Data
Gynecologic cancers (2013)
p. ; cm. — (Current multidisciplinary oncology)
Includes bibliographical references and index.
I. Odunsi, Kunle, editor of compilation. II. Pejovic, Tanja, editor of compilation. III. Title. IV. Series: Current multidisciplinary oncology.
RC280.G4
616.99'46—dc23 2013023405

Medicine is an ever-changing science. Research and clinical experience are continually expanding our knowledge, in particular our understanding of proper treatment and drug therapy. The authors, editors, and publisher have made every effort to ensure that all information in this book is in accordance with the state of knowledge at the time of production of the book. Nevertheless, the authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this book and make no warranty, expressed or implied, with respect to the contents of the publication. Every reader should examine carefully the package inserts accompanying each drug and should carefully check whether the dosage schedules mentioned therein or the contraindications stated by the manufacturer differ from the statements made in this book. Such examination is particularly important with drugs that are either rarely used or have been newly released on the market.

Special discounts on bulk quantities of Demos Medical Publishing books are available to corporations, professional associations, pharmaceutical companies, health care organizations, and other qualifying groups. For details, please contact:

Special Sales Department
Demos Medical Publishing
11 W. 42nd Street, 15th Floor
New York, NY 10036
Phone: 800-532-8663 or 212-683-0072
Fax: 212-941-7842
E-mail: special sales@demosmedpub.com

Made in the United States of America
13 14 15 16  5 4 3 2 1

© Demos Medical Publishing, LLC.
Contents

Series Foreword vii
Preface ix
Contributors xi

I. Cervical Cancer and Precancerous Lesions
1. The Biology of Human Papillomavirus and the Etiology of Female Genital Tract Cancers 3
   Eugene P. Toy
2. Cervical Cancer Prevention: HPV Vaccines 9
   Michelle Berlin
3. Cervical Cancer Prevention: Screening and Diagnostic Accuracy 13
   Terry Morgan, Emily Meserve, and Michelle Berlin
4. Management of Cervical Dysplasia and Precancerous Lesions 21
   Joyce Varughese, Elena Ratner, and Masoud Azodi
5. Management of Recurrent Cervical Cancer 25
   Lori E. Weinberg and Peter G. Rose
6. Multimodality Treatment of Rare Cervical Cancer 37
   Molly A. Brewer
7. Principles of Radiation Therapy for Cervical Cancer 43
   Daniel R. Simpson, Catheryn M. Yashar, Loren K. Mell, and Arno J. Mundt

II. Multidisciplinary Approach to Cancer of the Uterine Corpus
8. Surgical-Pathologic Features of Uterine Cancers 53
   Bojana Djordjevic and Russell R. Broaddus
9. Multidisciplinary Approach to Treatment of Endometrioid Uterine Carcinoma 61
   Jim Fanning and Joshua P. Kesterson
    Tijana Skrepnik and Shona Dougherty
11. Multidisciplinary Management of Serous Carcinoma of the Endometrium 73
    Dana M. Roque, Alessandro D. Santin, and Peter E. Schwartz
12. Multidisciplinary Approach to Diagnosis and Treatment of Uterine Sarcomas 83
    Matthew L. Anderson and Nonna Kolomeyevskaya

III. Epithelial Ovarian Cancer
13. Molecular Pathogenesis of Ovarian Cancer 95
    Premal H. Thaker and Anil K. Sood
    Susan J. Ramus
15. Surgical Management of Ovarian Cancer 115
    John O. Schorge and Dennis S. Chi
16. Multidisciplinary Approach to Treatment of Epithelial Ovarian Carcinoma 127
    Jay P. Shab and Devansu Tewari

© Demos Medical Publishing, LLC.
17. Recurrent Ovarian Cancer: Approach to Diagnosis and Treatment  139  
   Michelle M. Boisen and Robert P. Edwards

IV. Borderline Ovarian Tumors
18. A Multidisciplinary Approach to Diagnosis and Treatment of Borderline Ovarian Tumors  151  
   Ane Gerda Zahl Eriksson, Claes Göran Tropé, Janne Kaern, and Ben Davidson

V. Germ Cell Tumors of the Ovary
19. Germ Cell Tumors of the Ovary: Multidisciplinary Approach to Diagnosis and Treatment  161  
   Michael A. Bidus, Jay E. Allard, and Elizabeth A. Dubil
20. Nonepithelial Ovarian Cancer  171  
   William E. Winter, III

VI. Cancer of the Vulva
21. Precancerous Lesions of the Vulva  177  
   Colleen McCormick
22. Multidisciplinary Approach to Diagnosis and Treatment of Early Cancer  179  
   Katherine C. Fuh and Jonathan S. Berek
23. The Role of Sentinel Lymph Node Mapping  185  
   Elena Diaz and Oliver Dorigo

VII. Gestational Trophoblastic Disease
24. Choriocarcinoma  191  
   Roshan Agarwal, Neil J. Sebire, and Michael J. Seckl
25. Placental Site Trophoblastic Tumor  201  
   Emily Berry

VIII. Future Directions in the Treatment of Gynecologic Cancers
26. Laparoscopy and Robotic-Assisted Surgery in Gynecologic Oncology  209  
   Farr R. Nezbat, Eugenia Polosina, Susan S. Khalil, Tamara Finger, and Jason Sternchos
27. Innovations in Radiotherapy of Gynecologic Cancers  223  
   Tyler M. Seibert, Daniel R. Simpson, Catheryn M. Yasbar, Loren K. Mell, and Arno J. Mundt
28. PARP Inhibitors in Gynecologic Malignancies  231  
   Leslie Bradford, Allison Ambrosio, and Michael J. Birrer
29. Hormonal Treatment in Gynecologic Oncology  241  
   Ashley Ford Haggerty and Christina S. Chu
30. Genomic and Proteomic Biomarkers for Ovarian Cancer Screening, Prognosis, and Individualization of Chemotherapy  247  
   Sayeema Daudi, Heidi Godoy, and Kunle Odunsi
31. Incorporating Translational Research Into Gynecologic Cancers While Balancing the Focus of Personalized Medicine  271  
   Setsuko K. Chambers and Keith A. Joiner
32. Integrative Medicine in Gynecologic Oncology  277  
   Amy Stenson and Tanja Pejovic
33. Multidisciplinary Palliative Care  285  
   Paul Bascom

Index  293
Series Foreword

This volume in the series Current Multidisciplinary Oncology, devoted to gynecologic oncology, brings me great pleasure to introduce the practicing clinician to a valuable resource that will aid in the multidisciplinary approach of these common solid tumors.

Drs. Kunle Odunsi and Tanja Pejovic have put together a cadre of leading-edge investigators as contributors on the multidisciplinary approach to tumors of the female reproductive system.

Over the past decade, a myriad of advances in the diagnosis and treatment of gynecologic neoplasms have occurred. Some of the advances include, but are not limited to, diagnostic molecular tools that may aid in predicting a response to certain treatment approaches and/or in providing a guide of a prognostic outcomes for certain patients.

Thirty-three chapters have been compiled into well-defined sections by the volume co-editors.

Gynecologic neoplasms comprise some of the most common malignancies in the world and hence warrant intense efforts to find a cure. In recent years, investment of resources to help further understand the nature of this malignancy have increased.

Drs. Odunsi and Pejovic represent the current generation of academic, forward-thinking oncologists who have committed their careers to eradicating gynecologic cancer using multidisciplinary approaches. Their collective vision and ability to assemble an outstanding group of investigators in the field has provided a very high quality product that will be a useful resource to the busy clinician as well as those along various stages of the learning spectrum. I’m sure that you will enjoy this innovative and easy-to-read volume as you look for guidance in the multidisciplinary approach of your patients with gynecologic cancer.

Charles R. Thomas, Jr., MD
Series Editor
Department of Radiation Medicine
Oregon Health and Science University
Knight Cancer Institute
Portland, Oregon
The care of women with gynecologic cancer is best performed by multidisciplinary teams including gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, geneticists, social workers, and palliative care specialists. Such multidisciplinary care has become imperative as a consequence of rapid advances in the understanding of the clinical, cellular, and molecular basis of cancer. These advances are leading to the development of novel strategies for screening, risk assessment, diagnosis, personalized treatments, supportive care, and survivorship. Ultimately, multidisciplinary care is critical for improving the quality of care of gynecologic cancer patients.

It is against this background that we have assembled an extraordinary team of leading experts from across different disciplines to distill the most current information in a succinct format, with sufficient depth and breadth. While each chapter can stand alone, the final product is a unique textbook of gynecologic oncology with continuity of the multidisciplinary theme across chapters, covering the entire spectrum of gynecologic oncology topics. The book is designed to be a comprehensive text with up to date, relevant material for all providers of gynecologic cancer care including practicing physicians, nurse practitioners, physician assistants, residents, and fellows. It is our hope that we have accomplished our goal of providing a distinct reference text for the contemporary provider of gynecologic cancer care.

We are grateful to Dr. Charles Thomas for his scholarly vision and encouragement, and Mr. Rich Winters of Demos Medical Publishing for editorial guidance and timeliness. Finally we are indebted to our colleagues who contributed their time and knowledge toward this effort.
Contributors

Roshan Agarwal
Department of Oncology
Northampton General Hospital
Northampton, UK

Jay E. Allard, MD
Gynecologic Oncology
Naval Medical Center Portsmouth
Portsmouth, VA

Allison Ambrosio, BA
Gillette Center for Gynecologic Oncology
Massachusetts General Hospital Cancer Center
Boston, MA

Matthew L. Anderson, MD, PhD
Department of Obstetrics and Gynecology and
Dan L. Duncan Cancer Center
Baylor College of Medicine
Houston, TX

Masoud Azodi, MD
Division of Gynecologic Oncology
Department of Obstetrics/Gynecology and Reproductive Sciences
Yale University School of Medicine
New Haven, CT

Paul B. Bascom, MD
Palliative Medicine Physician
Portland, OR

Jonathan S. Berek, MD, MMS
Laurie Kraus Lacob Professor
Stanford Women's Center
Stanford Clinic Institute
Department of Obstetrics and Gynecology
Stanford University School of Medicine
Stanford, CA

Michelle Berlin, MD, MPH
Departments of Obstetrics and Gynecology,
Public Health and Preventive Medicine,
Medical Informatics and Clinical Epidemiology
OHSU Center for Women’s Health
Oregon Health & Science University
Portland, OR

Emily Berry, MD
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
Robert H. Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Chicago, IL

Michael A. Bidus, MD
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
Naval Medical Center Portsmouth
Portsmouth, VA

Michael J. Birrer, MD, PhD
Professor
Department of Medicine
Harvard Medical School
Department of Hematology/Oncology
Massachusetts General Hospital
Boston, MA

Michelle M. Boisen, MD
Division of Gynecologic Oncology
Department of Obstetrics, Gynecology, and Reproductive Sciences
Magee-Womens Hospital of UPMC
Pittsburgh, PA

Leslie Bradford, MD
Gillette Center for Gynecologic Oncology
Massachusetts General Hospital Cancer Center
Boston, MA

Molly A. Brewer, DVM, MD, MS
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
University of Connecticut School of Medicine
Farmington, CT

Russell R. Broaddus, MD, PhD
Department of Pathology
University of Texas
MD Anderson Cancer Center
Houston, TX
Setsuko K. Chambers, MD  
Division of Women’s Cancers  
University of Arizona Cancer Center  
Division of Gynecologic Oncology  
Department of Obstetrics and Gynecology  
University of Arizona  
Tucson, AZ

Dennis S. Chi, MD  
Memorial Sloan-Kettering Cancer Center  
New York, NY

Christina S. Chu, MD  
Obstetrics and Gynecology  
Division of Gynecologic Oncology  
Hospital of the University of Pennsylvania  
Jordan Center for Gynecologic Cancer  
Philadelphia, PA

Sayeema Daudi, MD  
Department of Gynecologic Oncology  
Roswell Park Cancer Institute  
Buffalo, NY

Ben Davidson, MD, PhD  
Institute of Clinical Medicine  
University of Oslo and Division of Pathology  
Oso University Hospital  
The Norwegian Radium Hospital  
Oso, Norway

Elena Diaz, MD  
Department of Obstetrics and Gynecology  
David Geffen School of Medicine  
University of California  
Los Angeles, CA

Bojana Djordjevic, MD  
Department of Pathology and Laboratory Medicine  
University of Ottawa  
The Ottawa Hospital  
Ottawa, Ontario, Canada

Oliver Dorigo, MD, PhD  
Manager  
Gynecologic Endoscopy  
Assistant Professor  
Gynecologic Oncology Institute for Molecular Medicine  
David Geffen School of Medicine  
University of California  
Los Angeles, CA

Shona Dougherty, MB, ChB, PhD  
Department of Radiation Oncology  
University of Arizona  
University Medical Center  
Tucson, AZ

Elizabeth A. Dubil, MD  
Walter Reed National Military Medical Center  
Bethesda, MD

Robert P. Edwards, MD  
Division of Gynecologic Oncology  
Department of Obstetrics, Gynecology and Reproductive Sciences  
Magee-Womens Hospital of UPMC  
Pittsburgh, PA

Ane Gerda Zahl Eriksson, MD  
Department of Gynaecological Oncology  
Oslo University Hospital  
The Norwegian Radium Hospital  
Oso, Norway

Jim Fanning, DO  
Division of Gynecologic Oncology  
Department of Obstetrics and Gynecology  
Pennsylvania State University  
Milton S. Hershey Medical Center  
Hershey, PA

Tamara Finger, MD  
Division of Minimally Invasive Surgery  
Department of Obstetrics and Gynecology  
St. Luke's Roosevelt Hospital  
New York, NY

Ashley Ford Haggerty, MD  
Division of Gynecologic Oncology  
Hospital of the University of Pennsylvania  
Jordan Center for Gynecologic Cancer  
Philadelphia, PA

Katherine C. Fuh, MD, PhD  
Division of Gynecologic Oncology  
Department of Obstetrics and Gynecology  
Stanford University School of Medicine  
Stanford Women's Cancer Center  
Stanford, CA

Heidi Godoy, DO  
Department of Gynecologic Oncology  
Roswell Park Cancer Institute  
Buffalo, NY

Keith A. Joiner, MD, MPH  
Health Promotion and Sciences Division  
Mel and Enid Zuckerman College of Public Health  
University of Arizona  
Tucson, AZ
Contributors

Janne Kaern, MD, PhD
Department of Gynaecological Oncology
Oslo University Hospital
The Norwegian Radium Hospital
Oslo, Norway

Joshua P. Kesterson, MD
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
Pennsylvania State University
Milton S. Hershey Medical Center
Hershey, PA

Susan S. Khalil, MD
Division of Minimally Invasive Surgery
Department of Obstetrics and Gynecology
St. Luke’s Roosevelt Hospital
New York, NY

Nonna Kolomeyevskaya, MD
Gynecologic Oncology Fellow
Roswell Park Cancer Center
Buffalo, NY

Colleen McCormick, MD, MPH
Compass Oncology
Portland, OR

Loren K. Mell MD
Division of Clinical and Translational Research
Department of Radiation Medicine and Applied Sciences
University of California San Diego
La Jolla, CA

Emily Meserve, MD, MPH
Brigham and Women’s Hospital
Boston, MA

Terry Morgan, MD, PhD
Departments of Pathology and Obstetrics and Gynecology
Oregon Health and Science University
Portland, OR

Arno J. Mundt, MD
Department of Radiation Medicine and Applied Sciences
University of California San Diego
La Jolla, CA

Farr R. Nezhat, MD
Division of Minimally Invasive Surgery
Department of Obstetrics and Gynecology
St. Luke’s Roosevelt Hospital
Columbia University Medical Center
New York, NY

Kunle Odunsi, MD, PhD
Department of Gynecologic Oncology
Center for Immunotherapy
Roswell Park Cancer Institute
Buffalo, NY

Tanja Pejovic, MD, PhD
Department of Obstetrics and Gynecology
The Knight Cancer Institute
Oregon Health & Science University
Portland, OR

Evgenia Polosina, MD
Division of Minimally Invasive Surgery
Department of Obstetrics and Gynecology
St. Luke’s Roosevelt Hospital
New York, NY

Susan J. Ramus, MD
Department of Preventive Medicine
Keck School of Medicine
USC/Norris Comprehensive Cancer Center
University of Southern California
Los Angeles, CA

Elena Ratner, MD
Department of Obstetrics, Gynecology, and Reproductive Sciences
Division of Gynecologic Oncology
Yale University School of Medicine
New Haven, CT

Dana M. Roque, MD
Department of Obstetrics, Gynecology, and Reproductive Sciences
Division of Gynecologic Oncology
Yale University School of Medicine
New Haven, CT

Peter G. Rose, MD
Section of Gynecologic Oncology
The Cleveland Clinic Foundation
Cleveland, OH

Alessandro D. Santin, MD
Department of Obstetrics, Gynecology, and Reproductive Sciences
Division of Gynecologic Oncology
Yale University School of Medicine
New Haven, CT

John O. Schorge, MD
Vincent Department of Obstetrics and Gynecology
Division of Gynecologic Oncology
Massachusetts General Hospital
Harvard Medical School
Boston, MA

Peter E. Schwartz, MD
Department of Obstetrics, Gynecology, and Reproductive Sciences
Division of Gynecologic Oncology
Yale University School of Medicine
New Haven, CT

© Demos Medical Publishing, LLC.
Neil J. Sebire  
Department of Medical Oncology  
Charing Cross Hospital Campus  
Imperial College NHS Healthcare Trust and  
Imperial College London  
London, UK

Michael J. Seckl  
Department of Medical Oncology  
Charing Cross Hospital Campus  
Imperial College NHS Healthcare Trust and  
Imperial College London  
London, UK

Tyler M. Seibert, MD, PhD  
Department of Radiation Medicine and Applied Sciences  
University of California San Diego  
La Jolla, CA

Jay P. Shah, MD  
Division of Gynecologic Oncology  
Department of Obstetrics and Gynecology  
Southern California Permanente Medical Group  
Assistant Clinical Professor  
University of California-Irvine  
Irvine, CA

Daniel R. Simpson MD  
Department of Radiation Medicine and Applied Sciences  
University of California San Diego  
La Jolla, CA

Tijana Skrepnik, MD  
Department of Radiation Oncology  
University of Arizona Medical Center  
Tucson, AZ

Anil K. Sood, MD  
Departments of Gynecologic Oncology and Cancer Biology  
Blanton-Davis Ovarian Cancer Research Program  
Center for RNA Interference and Non-Coding RNA  
MD Anderson Cancer Center  
Houston, TX

Amy Stenson, MD, MSc  
Oregon Health & Science University  
Department of Obstetrics and Gynecology  
Portland, OR

Jason Sternchos, MD  
Division of Minimally Invasive Surgery  
Department of Obstetrics and Gynecology  
North Shore University Hospital  
Manhasset, NY

Devansu Tewari, MD  
Division of Gynecologic Oncology  
Department of Obstetrics and Gynecology Orange County  
Southern California Permanente Medical Group  
University of California-Irvine  
Irvine, CA

Premal H. Thaker, MD  
Division of Gynecologic Oncology  
Department of Obstetrics and Gynecology  
Washington University School of Medicine  
St. Louis, MO

Eugene P. Toy, MD  
Division of Gynecologic Oncology  
Department of Obstetrics and Gynecology  
The University of Rochester  
Rochester, NY

Claes Göran Tropé, MD, PhD  
Department of Gynaecological Oncology  
Oslo University Hospital  
The Norwegian Radium Hospital and  
Institute of Clinical Medicine  
University of Oslo  
Oslo, Norway

Joyce Varughese, MD  
Department of Obstetrics, Gynecology,  
and Reproductive Sciences  
Division of Gynecologic Oncology  
Yale University School of Medicine  
New Haven, CT

Lori E. Weinberg, MD  
Section of Gynecologic Oncology  
The Cleveland Clinic Foundation  
Cleveland, OH

William E. Winter, III, MD  
Division of Gynecologic Oncology/Pelvic Surgery  
Compass Oncology: Rose Quarter/St. Vincent Cancer Centers  
Portland, OR

Cathryn M. Yashar, MD  
Division of Clinical Radiation Oncology  
Department of Radiation Medicine and Applied Sciences  
University of California San Diego  
La Jolla, CA

© Demos Medical Publishing, LLC.
Cervical Cancer and Precancerous Lesions

© Demos Medical Publishing, LLC.
The human papillomavirus (HPV) belongs to a family of papillomaviruses that have been discerned through the ages and studied in a variety of animal models. Genital warts portrayed by fig leaves have been the subject of classical art and sculpture dating back to ancient times. While equally as elegant and artful in terms of research, the bovine, canine, and cottontail rabbit (CTR) papillomavirus models are a few of the well-established animal systems employed over the years to study the virus (1–3). With difficulties in the propagation of papillomavirus presenting an obstacle to in vitro culture, reliance on these animal papillomavirus models has provided much information into mutagenesis of DNA sequence, overexpression of early and late gene products, and transcriptional regulation in order to better understand the viral replication cycle and design novel therapeutics for HPV-associated disease.

In spite of these models, little is known of the active phase of productive HPV replication following initial exposure and inoculation (4). The virus is highly epitheliotropic, entering through gaps or breeches in the cervix, vagina, and/or vulvar skin with great affinity, even to the extent of self-inoculation in directly opposed tissues such as the labia or with transmission via the “field effect,” which is not readily deterred by barriers such as condoms. Once penetrating the surface epithelium, the virus begins to express its early proteins under the regulation of the host promoter.

**VIRAL STRUCTURE AND GENOMIC ORGANIZATION**

The infectious viral particle of HPV is known as a virion and is composed of one molecule of double-stranded circular DNA, 8 kb in length, contained within an icosahedral structure formed from the natural assembly of its L1 and L2 proteins forming a protein coat or capsid (Figure 1.1).

**Sequence Homology**

Based on genotyping, the *Papillomaviridae* family contains over 100 types that can be recognized and grouped into 18 genera by sequence homology. While the mucosal infecting types, such as those associated with lower genital tract disease, belong to the *Alpha papillomavirus* genus, there is crossover of species from types causing benign warts to those causing low- and high-grade dysplasia (Table 1.1) with their associated disease manifestations seen in Figure 1.2.

**Regulatory Proteins**

**URR**—The “upstream regulatory region” where, under the influence of both cellular and viral factors, the main control of viral genome transcription is exerted, which leads to the encoded messages responsible for viral replication. Downstream from the URR, well-conserved gene sequences of the HPV genome produce the necessary viral proteins, which leads to active viral production in an orchestrated manner.

**Early Proteins**

**E2**—The main transcriptional regulatory protein that has four binding sites on the URR (6) and exerts control over the two predominant early proteins, E6 and E7, which are synthesized early in viral replication. Interruption of this viral control is found after the integration of the HPV viral genome into the host genome and results in unregulated overexpression of E6 and E7.

**E6**—Part of the dicistronic message produced early after initial viral infection leading to the production of both E6 and E7 in the basal layers of the epithelium shortly after infection. In oncogenic HPV types causing cancer, E6 binds the tumor suppressor protein p53, targeting it for the ubiquitination pathway and subsequent degradation.

**E7**—The distal part of the dicistronic message produced under the regulation of E2 protein. E7 from oncogenic HPV types will bind to pRb (retinoblastoma) protein and cause its inhibition, which also leads to subsequent loss of cell-cycle control from G1 to S phase.
E1—a “late” early protein subsumed by its counterpart E4 protein. It is involved in viral replication and controls gene transcription. It also is involved in the maintenance of the viral episome.

E4—the other “late” early protein that marks the onset of viral genome amplification and comprises the E1^E4 gene product that has been found to localize and bind to intermediate filaments of the cytoskeleton. In oncogenic HPV types, the E1^E4 protein will cause the collapse of the cytoskeleton, thus suggesting a role for viral propagation in cancer-causing types.

**Late Proteins**

L1—Major capsid protein that is involved in the formation of the pentamer structure, which comprises the virion, and is highly immunogenic in the native conformation of the virion, providing a neutralizing epitope.

L2—Minor capsid protein involved with the assembly of the virion and the formation of the infectious particle to be released. Not detected by the neutralizing antibody elicited by commercial vaccine, but still may provide protection by more sensitive second-generation assays (7).

### Table 1.1

Clinical manifestations of specific HPV types are shown. Most commonly associated types are presented first with more inclusive listing provided in parentheses.

<table>
<thead>
<tr>
<th>Biologic (Disease) Manifestation</th>
<th>Commonly Associated HPV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condyloma (benign lower genital tract warts)</td>
<td>6, 11</td>
</tr>
<tr>
<td>Low-grade dysplasia (productive infection)</td>
<td>42, 43, 44 (as well as 6, 11)</td>
</tr>
<tr>
<td>High-grade dysplasia (neoplastic infection)</td>
<td>31, 33, 35, 52, 58 (as well as types below)</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>16, 18, 45, 56</td>
</tr>
</tbody>
</table>

**VIRAL LIFE CYCLE**

### Early Infection

In the basal layer of the epithelium, the early E6 and E7 gene products are expressed under the regulation of the host promoter. HPV viral DNA synthesis occurs early after infection as part of an initial amplification of viral genomic DNA in order to reach a baseline number of approximately 50 to 100 DNA copies per infected cell (4). Little is known about the factors that control these events. Viral gene expression following this maintenance level of viral amplification is highly regulated and occurs only in cells that have lost their ability...
to divide. On histologic sections, cells that are found differentiating through the layers of the epithelium lose their ability to divide and become enucleated as seen in the superficial layer. Through these layers of cell maturation, there is production of early gene products necessary for virus production, with gene amplification occurring under the influence of E1, E2, and E4 with production on the order of 1000 copies of genome produced. Virion assembly occurs and cytopathic changes can be seen in the layer just below the surface epithelium. These classic cytopathic changes with pathognomonic wrinkled nuclei occur as a result of HPV infection. Release of infectious particles through the superficial epithelium may occur as a result of trauma or potentially as an effect of HPV E1^E4 protein in association with cytoskeletal elements leading to the collapse of the cell structure and subsequent release of viral particles (8).

**Viral Gene Transcription and Regulation**

The HPV genome exists in an extrachromosomal form known as an episome in low-grade lesions caused by HPV from both low- and high-risk types. The prevalence of high-risk HPV types in low-grade dysplasia of the cervix is quite evident from the ALTS (Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study) trial and had pre-empted the completion of the low-grade arm (9). This illustrates the importance of tight regulation of viral DNA transcription by E2 where its open reading frame (ORF) encodes the regulatory proteins controlling the transcription of E6 and E7 early proteins. E6 protein has many well-characterized roles that may function in a pleiotropic manner. It has the ability to cause heterologous viral infection as well as host-cell transcriptional transactivation (10). As it is part of a dicistrionic message with the E7 gene, E6 acts in concert with E7 during the early “basal” and productive phases of a viral infection. Both E1 and E2 proteins are required for this extrachromosomal DNA replication. However, due to the occurrence of alternate splicing, E1 is subsumed by E4, and the two act during the “late” early phase of the replication process, with E4 resembling the late proteins. The E5 gene product enhances the growth effects seen in the same layers beneath the surface where koilocytes are found manifest from the cytopathic effects of HPV. The HPV early proteins E2 and E1^E4 have been shown to elicit G2 arrest prior to cell division or mitosis (11). This function of E1^E4 is conserved in spite of this alternate splicing with several subtypes of HPV including 11, 16, and 18 also exhibiting E1^E4-induced G2 arrest. This delay prior to cell division may represent yet another level of control that these early proteins exert over viral replication.

The highly ordered process of natural virus infection and productive replication must be distinguished from aberrant neoplastic infection that leads to precancer and ultimately invasive cancer. This “abortive” type of infection represents a neoplastic process of viral replication that occurs with cancer-causing HPV types and leads to integration of the HPV genome into the host genome and loss of regulation by the host promoter (8). In addition, there is redundancy in the feedback loop of p53 that may also affect the G2 to M progression. On both levels from G1 to S and G2 to M, the deleterious effect of p53 degradation may enhance the pathogenesis process leading to HPV-induced dysplasia and neoplasia.

**Persistent Infection**

Persistence of high-risk HPV represents the one true risk factor associated in the development of invasive cancer. Although persistent infection occurs in 20% of women who have no overt evidence of disease on colposcopy, up to 30% will develop high-risk lesions within 2 years due to persistence of HPV infection (12). If clearance of the virus does not occur, as is the norm in over 90% of affected women, an alternating pattern of regression and progression may occur over the course of several years (13). Small lesions may be imperceptible on colposcopy, but with larger apparent lesions, there will be progression to invasive carcinoma about one-third of the time (14). Over time, with the E6 and E7 oncogenes becoming overexpressed after integration into the host genome combined with additional tissue differentiation due to hormonal effects, genetic instability due to epigenetic factors may lead to changes in the expression of host-cell genes and progression of these in situ lesions to become frankly invasive. An increase in telomerase activity by transactivation of hTERT by E6 protein and other chromosomal aberrations have both been cited as potential causes of this disease progression (15).

Natural or innate immunity to the HPV virus is responsible for 90% of clearance of initial viral infection in spite of the relative lack of detectable systemic humoral response and a blunted cellular immune response to the early proteins produced after infection (16). The innate immune response then kick-starts the adaptive immune response with Th1 (cell-mediated) and Th2 (humoral-mediated) responses. In the case of invasive cancer, an antibody response is generated against oncoproteins E6 and E7 and is clinically detectable (17). Otherwise, the L1 capsid protein is able to evoke a humoral response albeit slow in vivo (18), but has been found in vaccine trials to be highly protective for disease prevention based on serum transfer experiments in CTR, dog, and rhesus monkey models with currently available commercial vaccines produced from recombinant L1 protein providing vaccination levels 50–10,000× higher than natural infection. E6 downregulates toll-like receptors (TLR), while Langerhans cells are inactivated by E2. Such an immunosuppressed environment is commonplace in transformed cells (19). HIV patients are exemplary of the reduced clearance of
the HPV virus with reactivation of latent infection despite abstinence of new exposures from new sexual encounters (20). The E5 protein has been shown to be responsible for the virus’ ability to evade the immune system by interfering with antigen presentation. Ultimately, however, the resolution of active infection requires cellular immunity.

**Transformation and Integration of HPV DNA**

Once integration of the viral HPV genome takes place and/or E2 function is lost by mutation, there is a loss of E2-mediated control of E6 and E7 expression which then becomes unregulated (21). This corresponds with the transition of permissive HPV infection in its episomal form associated with low-grade dysplasia to an integrated form that results clinically in the neoplastic phenotype (Figure 1.2). E6 protein from these oncogenic-type HPV strains can bind to p53 causing its degradation and loss of checkpoint control in the cell cycle from G1 to S phase as the oncoprotein is overexpressed. This loss of cell-cycle regulation will allow damaged or transformed cells to progress through the cell cycle to cell division and produce daughter cells thereby perpetuating changes in DNA that have resulted from HPV infection.

HPV E7 protein acts in analogous fashion to bind to another tumor suppressor protein pRb, which is also involved in checkpoint control at G1 to S. When HPV E7 from oncogenic types binds pRb, it releases pRb inhibition of E2F, which is then free to act as a catalyst to cell-cycle progression from G1 to S.

Several years after these events are caused by “abortive” or nonproductive infection by HPV, there can be progression of dysplasia from moderate to severe disease, or even neoplasia. Just as permissive or productive infection can occur after chronic latent HPV infection over the course of many years, the time frame of neoplastic progression can take as long as a decade and is affected by multiple factors including age, immunocompromised status, histology, and tissue type (22). Intervention by ablative procedures, however, can usually abrogate this process of transformation but will not eliminate the viral cause of the pathogenesis.

**TISSUE-SPECIFIC PATHOGENESIS**

**Cervix**

Highly susceptible to the effects of HPV infection particularly in the adolescent cervix, the protuberance, known as the portio, provides a larger surface area for inoculation with HPV to occur. As puberty takes place, this expansive ectropion becomes exposed to the acid environment in the vagina and the process of squamous metaplasia takes place leading to creation of the transformation zone. This relatively thin, vulnerable region of epithelium represents the area at most risk for introduction of HPV and subsequent development of cervical dysplasia.

The endocervical canal is sequestered from the changes in vaginal pH. Glandular abnormalities occurring in this central portion of the canal most commonly are related to infection with types HPV-18 and HPV-16. The less common cancers with small cell and neuroendocrine-type histology are also found to contain HPV-18 but occur infrequently and have a very aggressive phenotype.

**Vagina**

While vaginal dysplasia is rare, it follows the same pattern of risk factors as with cervical dysplasia. Those with known history of treatment for cervical dysplasia or neoplasm are at significant risk for vaginal dysplasia with 30% of primary vaginal cancers having had a history of in situ or invasive cervical cancer within the prior 5 years, and the majority of these having undergone hysterectomy (23). Disease is most commonly found at the apex of the vagina, often following surgery. HPV infection with low-risk HPV-6 is associated with low-grade disease, while high-risk types, particularly HPV-16, place individuals at risk for high-grade squamous dysplasia and neoplasia as with its cervical counterpart, albeit at much lower frequency for progression of high-grade or severe dysplasia to invasive cancer (9%–10%).

**Vulva**

The bimodal distribution of disease illustrates the susceptibility of the vulvar skin to the effects of HPV infection after exposure, particularly in women of young reproductive age. Similar high-risk types such as HPV-16 responsible for cervical cancer are found in vulvar dysplasia and neoplasia. Smoking as a cofactor seems to be associated with this younger group at risk for high-grade dysplasia. While low-risk HPV types 6 and 11 are generally associated with vulvar condyloma, low-grade dysplasia can be found containing HPV-6 with the rare variant of verrucous carcinoma manifesting from malignant transformation of warty disease.

While high-grade cervical dysplasia portends approximately 30% of progression to invasive carcinoma from in situ disease and vaginal dysplasia even less, vulvar carcinoma in situ progresses to frank invasion in over 90% of cases if left untreated (24). Only 5% of treated high-grade dysplasia will progress to invasive disease. The high rate of progression may be related to difficulty in diagnosing invasive disease on preoperative biopsy prior to definitive resection in addition to noncompliance in the elderly population. Regardless, the relatively low incidence of this disease results in a lag in providing translational data as
is now becoming available from cervical cancer studies using molecular markers of progression.

### BIOLOGICAL MARKERS OF PROGRESSION

As surrogates for viral-induced carcinogenesis, markers of disease progression have been the subject of ongoing research in order to determine individuals most at risk for progression to invasive cancer. These markers reflect the sequelae of aberrant infection that does not necessarily result in productive viral infection but instead in the development of malignant transformation from preinvasive disease (Figure 1.2). These markers will become more crucial in triage of women in the era of HPV-vaccinated cohorts worldwide where the majority of HPV-16- and HPV-18-associated cancers will inevitably decline (25).

#### p16 INK4a

This protein normally functions as one of the cyclin-dependent kinase (cdk) inhibitors, which regulate cdk-4 and cdk-6 activity. When E7 oncoprotein interacts with pRB, p16 INK4a levels increase as negative feedback to the loss of pRB protein by the release of E2F. This increase in p16 can therefore represent a marker for loss of checkpoint control from G1 to S phase, which upregulates cell proliferation. The interaction of E7 and pRB is present in nearly all CIN2/CIN3 (88%–98%) and in invasive carcinoma and represents an important threshold for treatment intervention (26).

#### Ki-67

One of the markers of proliferation, it is found in all phases of the cell-cycle except for G0 or senescence. Thus, it reflects actively proliferating cells. It has been found to be overexpressed in a variety of cancers and is associated with malignant transformation. Dual staining with p16 has been used in triage of HPV+/normal PAP women (27).

#### Mini-Chromosome Maintenance (MCM)

The MCM proteins are a family of proteins that are involved in the initiation of the DNA replication complex. Among others in this family, MCM-5 expression in cervical dysplasia and neoplasia specimens has been shown to have the most potential clinical value with 100% sensitivity and 67% specificity. It is found expressed solely in the nucleus and reflects proliferating cells in the parabasal layer.

#### PCNA

Involved in the initiation of DNA synthesis, productive HPV virus replication requires host machinery, as the more superficial layers of the epithelium have lost their ability to divide. As another marker of proliferation, it has been used in conjunction with Ki-67.

### Methylisation Markers

The detection of methylisation sites of promoters where tumor suppressor function has been lost is also being used in clinical practice to predict disease progression. Hypermethylation occurs early during the transformation events leading to cervical cancer. Examples include the CADM1 and MAL-m1 promoter sites in high-risk HPV types. Epigenetic models with methylation of E2-binding sites have supported this pathway of progression (28).

#### Cyclin D

Functioning as regulatory subunits of the cdk-4 and cdk-6, cyclin D1 and D3 have been explored as surrogate markers of disease progression. As they exert negative control over the cdk's responsible for progression from G1 to S, decreases in cyclin D1 and D3 expression have been found associated with high-grade cervical dysplasia and invasive carcinoma (29).

#### Cyclins A and B

The regulatory subunits of cdk-2 and cdk-1, respectively, these cyclins, responsible for transition to M phase, have been studied particularly in invasive carcinoma of the cervix. Poor sensitivity using this test has limited its clinical utility although it has been found to have some correlation with the less common glandular adenocarcinomas.

### CLINICAL MODELS FOR HPV-RELATED DISEASE

With the inability to clear the virus causing persistent infection, the events that are responsible for progression through the spectrum of disease (Figure 1.2) into invasive cancer become harder to delineate. The wealth of clinical data in young adolescent patients supports the finding that even with high-grade changes noted on cytology, the majority of these lesions will regress. Infection and/or reinfection with high-risk oncogenic-type HPV portends the highest risk found for high-grade disease vs low-grade change where 90% regression rate is noted. Only a nominal few cases of invasive cervical cancer were noted from SEER data from 2002 in the under 20 age group in a time where screening of adolescents was more commonplace (30). Current admonition is for HPV co-testing in women 30 years of age and older.

The alternative scenario in older women presents another challenge to effective screening. With about a quarter of cervical cancer patients being in their...
postmenopausal years, lack of screening becomes the foremost reason for this increase in incident cases from this age group over 50. Again, the majority of women who had been exposed to HPV would have cleared their infection over the years. Guidelines for HPV testing in those women over age 65 have been established, and compliance with guidelines continues to be reinforced actively among primary care providers and gynecologic specialists (31).

■ REFERENCES