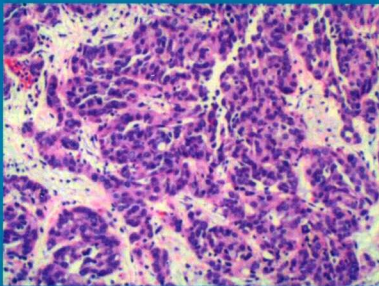


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Gynecologic Oncology Handbook

SECOND EDITION



AN EVIDENCE-
BASED CLINICAL GUIDE

Michelle F. Benoit
M. Yvette Williams-Brown
Creighton L. Edwards



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Gynecologic Oncology Handbook

An Evidence-Based Clinical Guide

Second Edition

Michelle F. Benoit, MD

*Gynecologic Oncology
Seattle, Washington*

M. Yvette Williams-Brown, MD, MMS

*Assistant Professor of Obstetrics and Gynecology
Gynecologic Oncology
Dell Medical School
The University of Texas at Austin
Austin, Texas*

Creighton L. Edwards, MD

*Professor of Obstetrics and Gynecology
Division of Gynecologic Oncology
Baylor College of Medicine
Houston, Texas*



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Gynecologic Oncology Handbook

*The second edition is dedicated to our mentor and friend,
Dr. Creighton Edwards, an outstanding clinician, educator, and role
model. He taught us to treat the whole patient, to stand up for what
is right, and gave us the resolve to always keep trying. He is our John
Wayne of medicine: he showed us that "courage is being scared to
death but saddling up anyway."*

—Michelle and Yvette

Preface

This handbook is structured to provide comprehensive care for the gynecologic cancer patient. It is directed toward clinicians at all levels of training and the chapters are tiered in this fashion. Basic diagnosis, workup, staging, and treatment are outlined first. Specific surgical and adjuvant therapies are then recommended reflecting the most current standards of care. Finally, the evidence-based medicine is summarized in support of recommended treatments. Thus, the medical student can have a dedicated overview, the resident can refer to directed patient care protocols, and the fellow and practicing physician can support their clinical decisions with easily accessible literature.

The updated second edition furthers the content to include: the latest cancer-screening information, new surgical technology and platforms, novel cytotoxic chemotherapy in addition to targeted and immunotherapy treatments, vaccination information, and the most current clinical trial outcomes. The 8th Edition AJCC staging guidelines have also been incorporated, providing accurate instructions for staging to keep the reader at the forefront of medicine. With this additional information, we provide a comprehensive and contemporary reference for clinical practice.

It continues to be our honor to assemble this handbook for our friends and colleagues. We again acknowledge the dedication it has taken from the physicians, support staff, and especially our patients, to design and participate in the trials that have advanced our knowledge of these difficult gynecologic cancers. In particular, we would like to acknowledge Hong Xiu Ji, MD, PhD, and Mr. James Romnes, PA, for providing the histology images. We hope the information provided herein can continue to guide high-quality care and reflect our commitment to the subspecialty.

Michelle F. Benoit, MD
M. Yvette Williams-Brown, MD, MMS
Creighton L. Edwards, MD

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CANCER SCREENING, PREVENTION, AND
PREINVASIVE GYNECOLOGIC DISEASE

1

Cervical Cancer Screening

The Lower Anogenital Squamous Terminology (LAST) project has developed terminology for lower anogenital tract preinvasive disease to create a unified histopathological nomenclature with a single set of diagnostic terms. It is recommended for all human papilloma virus (HPV) associated preinvasive squamous lesions regardless of anatomic site or sex/gender and has been adopted by the World Health Organization (WHO) (1).

In March 2012, the American Society of Colposcopy and Cervical Pathology (ASCCP) and College of American Pathologists definitively changed intraepithelial neoplasia from a three tier diagnosis to a two tier diagnosis. Therefore, preinvasive pathology from the cervix, anus, vulva, and vagina is classified as cervical-squamous intraepithelial lesion (SIL), anal-SIL, vulvar-SIL, and vaginal-SIL, respectively. Intraepithelial neoplasia is further categorized as Low-Grade LSIL (-IN 1) or High-Grade HSIL (-IN 2/-IN 3).

THE HUMAN PAPILLOMA VIRUS (HPV)

HPV has been found to cause over 90% of cervical cancers. It is a double stranded, circular DNA virus. The virus is organized into three regions: the upstream regulatory regions, the early region containing genes E1–E7, and the late region containing genes L1–L2.

- The early, or E, region proteins are related to viral gene regulation and cell transformation:
 - E1: ATP-dependent helicase for replication.
 - E2: transcriptional regulatory activities, regulates E6/7.
 - E3: ubiquitin ligases.
 - E4: structural proteins, expressed in late stages. These proteins disrupt the intermediate filaments and cornified cell envelopes. They facilitate the release of assembled virions. Produces koilocytosis.
 - E5: stimulates cell growth, complexes with EGFR. It is lost during cancer development.
 - E6: binds to and degrades p53, preventing cell death and promoting viral replication.
 - E7: binds to and inactivates tumor suppressor protein, Rb, cooperates with activated Ras; it activates cyclins E and A.
 - E6 and E7: the two primary oncoproteins of HPV.
- The late, or L, proteins are necessary for the virion capsid production:
 - L1: major capsid
 - L2: minor capsid

- HPV infection is limited to the basal epithelial cells in the lower reproductive tract. HPV binds to alpha 6 integrin on the host cell, stimulating mitosis when normally it would go dormant. The basal cells then divide with the potential for malignant transformation.
- HPV can be detected by either viral DNA, viral RNA, or by using cellular markers. Detection of HPV DNA is either by polymerase chain reaction (PCR) or hybridization. HPV RNA detection methods look for expression of E6/E7 by detecting mRNA. Finally, viral proteins or cellular proteins such as p16 or Ki-67 can be detected by immunohistochemistry (IHC) to determine HPV infection.
- Transmission is via direct contact. The majority of sexually active persons will acquire HPV at least once in their lives. HPV has also been detected in 3% of sexually naïve persons. The use of condoms reduces the rate of HPV infection by 50%. Fomite transmission has not been definitively documented.
- Most exposures produce a transient productive viral infection. One third of women develop low-grade cytological changes. Most changes clear spontaneously within 2 years. Less than 20% of women are still HPV+ at 2 years. Long-term or persistent infections occur in fewer than 10% of women at 2 years. Rates of HPV infection differ by age: if older than 29 years, there is a 31% infection rate; if younger than 29, there is a 65% rate of infection.
- The Addressing THE Need for Advanced HPV diagnostics (ATHENA) study documented the prevalence of cervical cytologic abnormalities. The prevalence of cytologic abnormalities in 42,209 women 21 years old or older undergoing screening was 7.1%. Liquid-based cytology (LBC) and HPV testing were performed. Atypical squamous cells of undetermined significance (ASC-US) and HPV positive patients were referred for colposcopy. The prevalence of high risk (HR) HPV, HPV 16, and HPV 18 was 12.6%, 2.8%, and 1.0%, respectively. HR HPV was detected in 31% of women aged 21 to 24 years, 7.5% of women aged 40 to 44 years, and 5% of women older than 70 years (2). Currently, virus typing in cervical HSIL (-IN 2/3) patients has revealed that HPV 16 is present in 45.3%, HPV 18 is present in 6.9%, and HPV 31 is present in 8.6%.

PAP SMEARS

Papanicolaou (Pap) smears (cytology), introduced in the 1950s, have promoted a significant decrease in the rates of cervical cancer. Between 1955 and 1992, the incidence and death rates of cervical cancer in the United States decreased by more than 60% (3).

- The false-negative rate of Pap smears is between 6% and 25%. The conventional Pap smear has a sensitivity of 51% and a specificity of 98% (4). The rate of cervical cancer following a negative normal Pap test is 7.5/100,000 women/year; for all women with HPV-negative testing there are 3.8 cervical cancers/100,000 women/year. For women who are both HPV negative and Pap cytology negative the rate is 3.2 cervical cancers/100,000 women/year. Liquid based cytology (LBC) screening has been widely adopted. LBC has the same sensitivity and specificity as conventional Pap smears. The Thin Prep and Mono Prep Pap tests both use a filter for cell separation. SurePath uses density centrifugation for cell