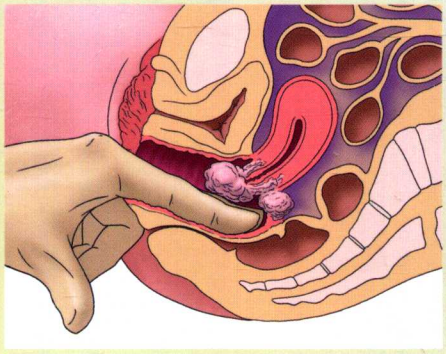
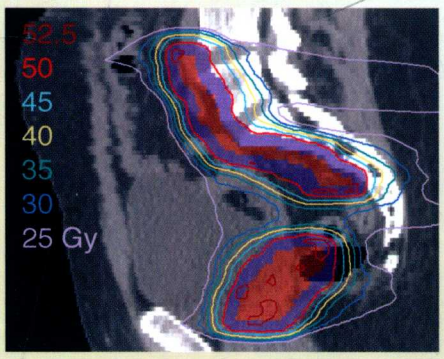
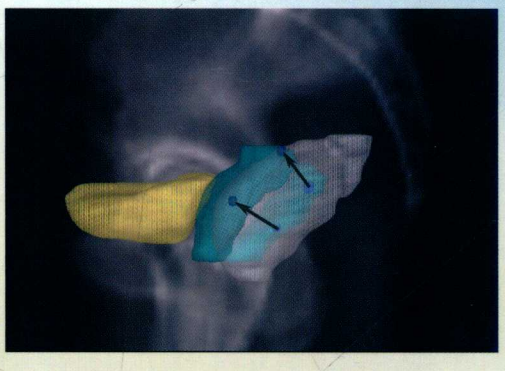
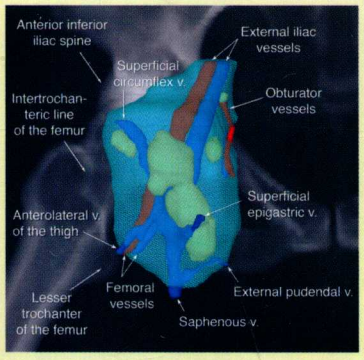
GYNECOLOGIC RADIATION ONCOLOGY

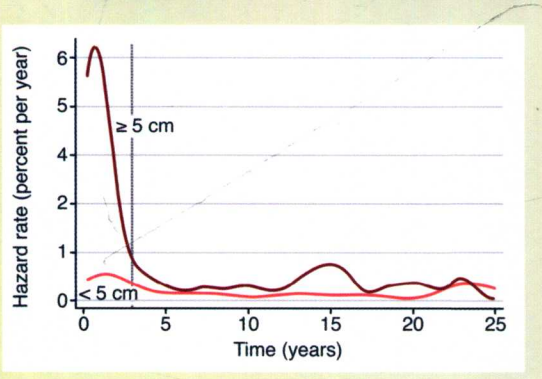
A Practical Guide

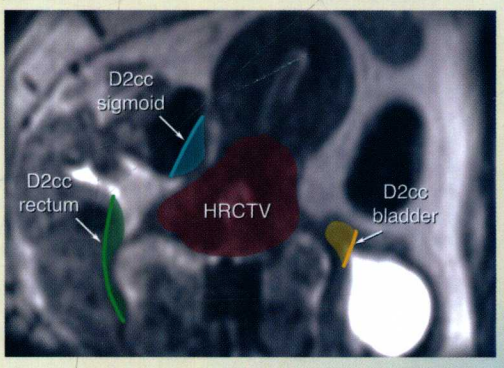












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PREFACE

The radiation treatment of gynecologic cancers can be challenging but also extremely rewarding. Specialized knowledge, skill, attention to detail, and close multidisciplinary collaboration are required to design and deliver highly successful treatments. However, those treatments are very often curative, and the satisfaction derived from knowing that a woman with locoregionally advanced gynecologic cancer has been successfully treated and gone on to lead a normal life is unmatched. We have been fortunate to be able to devote most of our careers to the study and treatment of these patients. During the years of our tenure at MD Anderson, approximately 10,000 patients have been treated on the gynecologic radiation oncology service; we have treated more than 1,500 gynecologic cancer patients with IMRT and have performed more than 5,000 intracavitary and interstitial brachytherapy procedures. The better part of our academic careers has been spent collating these experiences, analyzing and reporting outcomes, studying the findings of other investigators, and searching for ways to understand and improve the treatment of these diseases.

Our experiences and those of other dedicated gynecologic radiation oncologists have led to the publication of thousands of manuscripts, review articles, and textbook chapters. However, although peer-reviewed manuscripts and general textbooks can provide valuable insights about specific topics and useful surveys of relevant literature, they tend not to be ideal vehicles for describing the techniques, methods, and difficult deliberations that characterize the day-to-day practice of gynecologic radiation oncology. Also, the content of these scattered resources is not always readily accessible when it is needed in the course of daily practice.

With this book, our primary goal was to address practical aspects of gynecologic radiation oncology—how to evaluate the role of radiation therapy in various clinical settings; how to explain the rationale for treatment recommendations to referring physicians and patients; when and how to apply various external beam and brachytherapy techniques to address specific clinical problems; and how to monitor and manage patients during and after treatment. Although we have not attempted to exhaustively catalogue the gynecologic radiation oncology literature, we have cited references that we have found particularly helpful in our clinical decision making, emphasizing important clinical trials, meta-analyses of relevant data, and high-quality review articles. Throughout this book, and particularly in Chapter 2, we have tried to explain not only the insights gained from the clinical literature but also the opportunities for misinterpretation, suggesting how trial results can be more accurately applied to everyday clinical practice.

The concepts discussed in *Gynecologic Radiation Oncology* have been illustrated with more than 700 figures and tables. Using these aids and the accompanying text, we have sought to describe in detail each aspect of radiation oncology practice from the initial patient evaluation and treatment recommendation, through the process of radiation treatment planning and delivery, to the posttreatment monitoring of patients for recurrence and treatment-related side effects. Because the multidisciplinary and technical aspects of gynecologic radiation oncology tend to apply to gynecologic cancers of various types and sites of origin, the principles of tumor biology, multidisciplinary management, clinical evaluation, radiation therapy treatment planning and delivery, and symptom management are discussed in general terms in Chapters 1 to 9 of this book. Subsequent chapters focus more specifically on the features of individual disease sites and on the bases for site-specific management decisions. With this structure, we have minimized repetition of broadly relevant content; however, to help readers navigate the text, we have extensively cross-referenced the material contained in individual chapters. To further unify these concepts and to demonstrate how they can be applied in real clinical situations, we have included 54 case studies that are cited throughout the text; these are found at the end of the relevant disease site chapters, with each group of case studies preceded by a summary of the cases and a list of abbreviations.

The contents of this book have been informed not only by our direct clinical experiences, research, and knowledge of the literature but also by years of discussions with colleagues, visits to radiation oncology departments, and attempts to answer questions fielded from practicing radiation oncologists. These experiences have given us some sense of the variations in clinical practice and of the issues that clinicians find particularly

challenging in their care of gynecologic cancer patients. With this book, we have tried to suggest some practical approaches to common clinical problems. However, although our experience has given us some answers, it has also made us very aware of the many unknowns in our field. We recognize that some of the topics addressed in this book are controversial. However, clinical decisions must be made even in the face of controversy. We have done our best to explain the rationales behind our current approaches to the management of gynecologic cancers. However, others will disagree, and our own views will undoubtedly evolve as new information emerges. In the meantime, we hope that all of our readers find something in this book that will help them to care for their patients. We also welcome your feedback and encourage you to write us with your comments about the content and character of this book.

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Many members of our department made important contributions to this book. We give particular thanks to members of our medical dosimetry group, including, James Kanke, Kelly Perrin, Lehendrick Turner, Pamela Castillo, Paula Berner, Mandy Cunningham, and others who helped us to navigate our treatment planning systems and who created the comparative treatment plans for Chapter 6. We also want to thank Michael Kantor for always being available to troubleshoot problems as we attempted to use our treatment planning systems to create illustrations that were informative and free of clutter.

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PART I

PRINCIPLES OF GYNECOLOGIC ONCOLOGY

CHAPTER 1

Pathology, Molecular Biology, and Etiology of Gynecologic Cancers

INTRODUCTION

Radiation treatment recommendations for gynecologic cancers are guided primarily by the site of origin and the morphology of the primary tumor. Morphologically, similar gynecologic cancers from different sites of origin tend to share molecular features and demonstrate similar patterns of spread. However, even among morphologically similar cancers, the site of origin plays a critical role in the method and ease of initial cancer detection, the prognosis, and the patterns of regional spread (Chapter 5).

In recent years, research has greatly expanded our understanding of the molecular correlates of prognosis. Although the practical uses of this knowledge have focused primarily on refinements to diagnostic criteria, there is reason to hope that these findings will eventually contribute to the development of new, more effective treatments. In addition, better understanding of the roles of human papillomavirus (HPV) infection and heredity in the etiology of gynecologic cancers is leading to successful strategies for prevention of many cancers.

CORRELATES BETWEEN MORPHOLOGY AND BIOLOGIC BEHAVIOR

Most gynecologic cancers fall into three major groups: carcinomas, sarcomas, and germ cell tumors. Among gynecologic cancers, carcinomas are much more common than other types of cancers.

Carcinomas arise from the squamous or glandular epithelial linings of the vulva, vagina, cervix, uterus, fallopian tubes, or ovaries and account for the vast majority of gynecologic cancers that are treated with radiation. Squamous carcinomas predominate in structures that are normally lined by squamous epithelium (vulva, vagina, and cervix), while adenocarcinomas predominate in structures that are lined with glandular epithelium (uterus, fallopian tubes, and ovaries). However, adenocarcinomas can also arise from glandular elements of lower genital tract structures, and areas of squamous differentiation can be a prominent feature in endometrial and, occasionally, ovarian cancers.

Carcinosarcomas are defined by the presence of both a malignant epithelial and a mesenchymal component; these tumors can originate throughout the female genital tract but are most commonly found in the endometrium and ovary.

Sarcomas are derived from the mesenchymal components of female genital tract structures. The most common of which are leiomyosarcomas, which are derived from smooth muscle of the uterus and other structures, and endometrial stromal sarcomas, which are derived from endometrial stroma. Rarely, cancers are derived from hormone-secreting ovarian stroma; these include granulosa cell tumors, which are derived from the sex cord and are comparable to testicular Sertoli cell tumors, and thecomas, which are derived from gonadal stroma and are comparable to Leydig cell tumors of the testis. Tumors that contain a mixture of granulosa cell tumor and thecoma are called Sertoli–Leydig cell tumors.

Germ cell tumors in females arise from the ovary and include teratomas, dysgerminomas, yolk sac tumors (also called endodermal sinus tumors), embryonal carcinomas, and choriocarcinomas. Germ cell tumors are rarely treated with radiation, as they generally have a favorable prognosis with surgery alone (teratomas) or are highly chemotherapy sensitive (choriocarcinomas, dysgerminomas).

Müllerian Adenocarcinomas

Most gynecologic adenocarcinomas arise from cells that had their origin in the embryologic müllerian duct (Chapter 5). The shared developmental origin of these müllerian carcinomas explains the shared behavioral and biologic characteristics of müllerian adenocarcinomas arising in various sites. Grade is an important prognostic factor for all types of adenocarcinoma.

Subtypes of Müllerian Adenocarcinoma

There are four major subtypes of müllerian adenocarcinoma:

- *Endometrioid carcinomas* resemble normal endometrial glands in their differentiated state. The grade of endometrioid carcinomas is based on the percentage of the tumor area that has a solid growth pattern and tends to be correlated with the degree of nuclear atypia.
- *Mucinous carcinomas* resemble normal endocervical glandular epithelium. Many cervical adenocarcinomas have mucinous features.[1]
- *Serous carcinomas* resemble fallopian tube epithelium. They tend to have a papillary architectural pattern, but grade is based on cytologic features. Adnexal serous carcinomas can range from very low-grade lesions of uncertain malignant potential (so-called borderline tumors) to very pleomorphic, high-grade cancers. Serous carcinomas of any grade metastasize to peritoneal surfaces more frequently than other müllerian variants do. High- and low-grade serous carcinomas arise from the ovary, while uterine serous carcinomas are virtually always high-grade cancers.
- *Clear cell carcinomas* have glycogen-rich cytoplasm, which gives them the characteristic appearance of cleared cytoplasm. Although clear cell carcinomas are believed to be of müllerian origin, their precise origins are uncertain.[2]

Variants of müllerian adenocarcinoma arise throughout the gynecologic tract with varying frequency; however, they tend to occur more frequently in the tissues that share their differentiated features, for example, endometrioid carcinomas in the endometrium, serous carcinomas in the ovary or fallopian tube, and endocervical-type mucinous carcinomas in the cervix.

Type I and Type II Histologic Variants of Endometrial and Ovarian Cancer

Endometrial and ovarian cancers demonstrate greater morphologic variability than do cancers at other gynecologic sites, and all subtypes of müllerian adenocarcinoma play a major role. Endometrial and ovarian cancers have sometimes been grouped according to their likelihood of demonstrating aggressive behavior.

Endometrial cancers are frequently divided according to their morphologic features and aggressiveness into type I and type II cancers. Type I cancers, which include endometrioid and the relatively rare mucinous carcinomas, typically present at an early stage and have a relatively favorable prognosis. Type I cancers are thought to frequently develop as a consequence of excess estrogen exposure, which triggers proliferation in the estrogen-responsive endometrial cells. A higher lifetime risk of estrogen exposure is seen in women with early menarche, fewer pregnancies, exogenous estrogen exposure, or obesity, which increases estrogen exposure through aromatization of androgens from peripheral adipose tissues. Type I endometrial cancers classically arise in a proliferative endometrium with complex hyperplasia, supporting the suggestion that estrogen exposure fosters the development of these cancers. Other risk factors for type I endometrial cancer include hypertension, diabetes, anovulation, and polycystic ovarian syndrome. Type II cancers, which include serous carcinomas, clear cell carcinomas, and in some descriptions, carcinosarcomas, are more aggressive. Type II cancers typically arise in an atrophic endometrium in older patients than the ones in which the type I variants arise.

Ovarian cancers have similarly been divided into type I and type II tumors.[3] According to this classification, type I tumors include low-grade serous, low-grade endometrioid, clear cell, and mucinous carcinomas—subtypes that are more likely to present at an early stage and have a more indolent course. Type II tumors include high-grade serous and high-grade endometrioid subtypes, which are more likely to present at an advanced stage and have an aggressive course.

The various subtypes of müllerian adenocarcinoma are frequently admixed; in these cases, prognosis is usually dictated by the type II or highest grade lesion.

The gynecologic origins of müllerian adenocarcinomas can be traced by detecting the expression of PAX8. This transcriptional factor drives the development of müllerian tumors and is persistently expressed in many müllerian adenocarcinomas of gynecologic origin. Immunohistochemical staining for PAX8 can be used to determine the primary tumor site in the case of a metastatic tumor of unknown primary site.[4]

Squamous Carcinomas

Gynecologic squamous carcinomas arise predominantly from the squamous epithelium that lines the vulva, vagina, and cervix; most cancers involving lower genital tract sites are squamous. Although the cytologic grade of squamous carcinomas varies, grade is at most weakly correlated with prognosis. Squamous carcinomas of gynecologic origin, as well as squamous cancers arising at other mucosal sites, such as the head and neck, tend to behave more predictably than cancers of other histologic subtypes, first invading locally and then disseminating to regional lymph nodes before distant sites. HPV plays a critical role in the development of many gynecologic squamous carcinomas.

MOLECULAR BIOLOGY OF GYNECOLOGIC CANCERS

Methods of Molecular Characterization

Immunohistochemical techniques have played a critical role in advancing our understanding of the molecular features of gynecologic cancers. Immunohistochemical tests involve incubation of a labeled antibody on fixed, paraffin-embedded sections. The staining intensity is scored qualitatively, and generally only a single marker can be tested at a time. Because immunohistochemical studies are performed on fixed, paraffin-embedded tissue, these markers were most readily incorporated into practice. Many immunohistochemical markers with diagnostic, predictive, and prognostic potential in gynecologic cancer have been identified, but few have been developed into clinically useful tools.

More recently, techniques to comprehensively survey gene expression, copy number, and mutations (genomics) and protein expression (proteomics) have become more feasible. These techniques survey the entire landscape of a tumor rather than focusing on a single gene or protein. As a result, these studies can be used to simultaneously evaluate the functionality of hundreds of pathways. As the number of biologically targeted agents expands, the hope is that treatments can be tailored to the molecular profile of each patient's tumor. This approach holds great promise but remains investigational and is employed primarily in patients with advanced and recurrent disease. To date, molecular features have not proven to reliably identify which patients with gynecologic cancers will benefit from radiation therapy, but this is an active area of investigation that is likely to bring changes to clinical practice in the next decade.

Correlation of Molecular Markers with Morphology and Prognosis

Several molecular features of gynecologic cancers have been found to correlate with morphology. For example, in type I endometrial cancer, molecular analysis frequently detects mismatch repair deficiencies with areas of repeating DNA sequences, called microsatellite instability; mutations in genes such as *PTEN*, *KRAS*, *CDH1*, and *CTNNB1* are also common. In contrast, in type II endometrial cancer, mutations in *TP53*, *ERBB2*, and *TERT* are more common.

Type II, high-grade ovarian cancers have a higher rate of mutations in *TP53* and greater genomic instability than type I cancers. Type II ovarian cancers are also more likely to have disruption of *BRCA* gene function because of genetic or epigenetic changes.[3]

Molecular features have also been correlated with prognosis. The Cancer Genome Atlas recently reported a comprehensive analysis of molecular changes in endometrial cancers. The authors performed whole-genome sequencing, gene expression, methylation, and copy number analyses on 373 endometrial cancers.[5] Tumors were classified into four groups on the basis of features identified in the analysis. Of perhaps greatest interest was a small subgroup of tumors that had mutations in the catalytic subunit of DNA polymerase epsilon (POLE). These tumors were associated with an extremely favorable prognosis despite a high-grade, often serous, morphology; they were also characterized by tumor-infiltrating T cells and a high rate of mutations throughout the genome.[5,6] The Cancer Genome Atlas analysis also identified a poor-prognosis group of tumors with a high rate of increases in the number of copies of genes. These tumors had frequent mutations in *TP53* and included serous tumors, as well as 25% of grade 3 endometrioid cancers. In the future, these molecular subtypes may find clinical utility in the management of endometrial cancer.

Hormone Receptor Expression

Endometrial and ovarian cancers often express estrogen receptor (ER) and progesterone receptor (PR) on the cell surface, and evaluation of these receptors can be useful in determining the role of hormonal therapy. In general, signaling through the ER stimulates tumor cell proliferation, while signaling through the PR suppresses tumor cell proliferation. As a result, antiestrogen therapy has been investigated for patients with ER-positive tumors, and progestin analogs have been studied for patients with PR-positive tumors.

ER and PR are frequently expressed on well-differentiated and early-stage endometrial cancers.[7] For patients with recurrent or advanced ER- and/or PR-positive endometrial cancer, treatment with megestrol acetate with or without tamoxifen can be considered. However, response rates are low even with combined therapy.[8] Although use of antiestrogens, such as tamoxifen, has a strong biologic rationale, studies investigating the use of tamoxifen in endometrial and ovarian cancer have not been encouraging. Hormonal therapy appears to have limited benefit in high-grade ovarian cancers but have shown efficacy in the management of low-grade endometrial cancers that are more likely to be ER/PR positive and have more indolent clinical course.[9,10]

Women with squamous cancers who have experienced premature menopause are often given estrogen replacement therapy to treat vasomotor symptoms, but exogenous estrogen is often not recommended for women with endometrial or ovarian cancers because of concern that estrogen exposure could stimulate growth of residual tumor cells, thus increasing the risk of endometrial cancer recurrence in endometrial cancer survivors. However, the available literature in women with a history of endometrial cancer suggests that there is no evidence of higher rates of recurrence in women treated with estrogen replacement therapy.[10]

ROLE OF HPV IN GYNECOLOGIC CANCERS

HPV is detectable in nearly all cervical cancers, ~75% of vaginal cancers and 50% of vulvar cancers of both squamous and adenocarcinoma histology. Morphologically, HPV-positive carcinomas are not distinguishable from HPV-negative carcinomas, although HPV-positive vulvar cancers are frequently associated with characteristic basaloid or warty vulvar intraepithelial neoplasia (VIN).

HPV infection is the most common sexually transmitted infection; 20% of women aged 20 to 24 years test positive for high-risk subtypes associated with cervical, vaginal, and vulvar cancer.[4] For 90% of women, the infection is asymptomatic and is cleared completely. However, for a small percentage of exposed individuals, the infection persists. Expression of the viral proteins E6 and E7 can then disrupt function of the critical tumor suppressor genes *TP53* and *RB1*, leading to dysplasia. In the cervix, vagina, and vulva, this can lead to the development of an intraepithelial squamous lesion (cervical, vaginal, or vulvar intraepithelial neoplasia). Low-grade dysplastic lesions often regress spontaneously and can be carefully observed, whereas higher-grade lesions are ablated with or resected using various site-specific methods. In higher-grade lesions, HPV is often integrated into host DNA. The process of integration may disrupt the function of tumor suppressor genes or activate oncogenes, which facilitates the formation of malignant lesions. The process of development of a persistent viral infection, development of an intraepithelial lesion, and progression to invasive cancer may take years or even decades.[11]

Although invasive cervical cancers continue to express viral proteins, infectious viral particles are not released. Concerned partners and patients with HPV-associated cancers can be assured that there is no risk of HPV transmission from the cancer and that because the HPV infection was probably acquired years or even decades before the cancer was diagnosed, the presence of an HPV-related cancer does not suggest that either the patient or her partner was recently exposed to HPV.

Non–HPV-associated squamous cancers of the vagina and vulva have unique molecular and epidemiologic features. They typically occur in women in their seventh and eighth decades and are more likely to occur in smokers and in women with a history of lichen sclerosis of the vulva. *TP53* mutations are more common in women with non–HPV-associated vulvar and vaginal cancers than in women with HPV-positive vulvar and vaginal cancer in which p53 function is disrupted by the virally encoded E6 protein.[12]

HPV and Prognosis

In patients with oropharyngeal cancer, HPV status has been shown to be a favorable prognostic factor associated with higher rates of survival following radiation therapy.[13] Ongoing studies are designed to test whether radiation dose reduction is feasible in HPV-positive head and neck cancer. Cervical cancers are virtually all HPV positive. Data suggest that HPV-positive vulvar cancers tend to occur in younger women. However, initial studies of the impact of HPV status on vulvar cancer outcomes have reported mixed results regarding the prognostic implications of HPV status.[14,15]

Prevention of HPV-Associated Cancers

The risk factors for developing HPV-associated cancer are primarily related to exposure to HPV; these include early coitarche, higher number of sexual partners, other sexually transmitted diseases, and impaired immune function. HPV testing performed routinely in combination with a Pap test can more accurately identify women at higher risk for malignancy who need further investigation or more frequent surveillance. The current recommendation from the U.S. Preventive Services Task Force is to screen for HPV in combination with cytology for women between 30 and 65 years of age. HPV positivity is so common in women younger than 30 that routine screening is not recommended.

Vaccination against HPV has been proven to be highly effective at preventing HPV-associated lesions in women who have not previously been exposed to HPV. In large randomized trials, vaccination against HPV reduced by 98% the proportion of women subsequently diagnosed with cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV-16 or HPV-18 in women with no prior exposure to HPV.[16] The two approved HPV vaccines, Gardasil and Cervarix, deliver viral-like particles composed of a viral capsid protein, which is essential for viral entry. The vaccine is DNA free and thus carries no risk of infection. Because the vaccine generates an immune response to a capsid protein critical for viral entry into host cells, it prevents initial infection but does not impact recognition of tumor antigens. As a result, the vaccine has no role in the treatment of HPV-related cancers.

Because these vaccines are designed to prevent initial infection, they are recommended for girls between the ages of 11 and 12 to prevent HPV infection before coitarche. The vaccine produces lasting immunity, extending for at least 5 years and likely significantly longer.[17] Despite the efficacy of the vaccine, rates of vaccination remain relatively low. In the United States in 2013, 57.3% of adolescent girls and 34.6% of adolescent boys had received the HPV vaccine.[18]

HEREDITARY CANCER SYNDROMES

A list of heritable syndromes associated with gynecologic cancers is described in **Table 1.1**.

Lynch Syndrome

Lynch syndrome is an autosomal dominant disorder sometimes referred to as hereditary nonpolyposis colorectal cancer. Mutations in DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* lead to an increased risk of endometrial, colon, gastric, and ovarian cancer. Evidence for these mutations can be found by testing tumor tissue immunohistochemically to confirm the absence of proteins encoded by any of the four genes that are mutated in Lynch syndrome. If the tumor analysis shows loss of expression of these mismatch repair genes, patients can be referred to a genetic counselor for discussion of testing for germline mutations. At MD Anderson, tumor testing for evidence of Lynch syndrome is performed routinely in all patients with colon and endometrial cancers.[19]

TABLE 1.1 Hereditary Cancer Syndromes Associated with Gynecologic Cancers

Syndrome	Genes affected	Gene function	Percentage of cancers linked to syndrome	Family characteristics that should prompt screening	Interventions for individuals with syndrome
Lynch	*MLH1*, *MSH2*, *MSH6*, and *PMS2*	DNA mismatch repair	40%–50% of endometrial cancers 60%–80% of colon cancers	At least three relatives with any Lynch syndrome-associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis) One relative a first-degree relative of the other two At least two successive generations affected At least one individual diagnosed before age 50 y	Colonoscopy annually; endometrial biopsy annually after age 30–35 y; hysterectomy after childbearing
HBOC	*BRCA1* and *BRCA2*	Repair of DNA double-strand breaks	≈10% of ovarian cancers	Any of the following: Female breast cancer diagnosed before age 50 y TNBC diagnosed before age 60 y Male breast cancer Ashkenazi Jewish ancestry, particularly if the proband has been diagnosed with any HBOC-associated cancer	Screening with CA-125 and transvaginal ultrasonography annually; salpingo-oophorectomy after 40 y or when childbearing is complete
Li-Fraumeni	*TP53*	Cell cycle arrest in response to DNA damage	<1% of endometrial and ovarian cancers	Proband with sarcoma diagnosed before age 45 y First-degree relative with any cancer diagnosed before age 45 y First- or second-degree relative with any cancer diagnosed before age 45 y or a sarcoma diagnosed at any age	No ovarian-specific recommendations, but whole-body magnetic resonance imaging may be considered
Cowden	*PTEN*	Phosphatase that regulates cell growth	<1% of endometrial cancers	Combination of benign lesion syndromes and cancer history	Education regarding endometrial cancer and prompt response to uterine bleeding Consider annual endometrial biopsies and transvaginal ultrasonography beginning at age 30–35 y

HBOC, hereditary breast and ovarian cancer; TNBC, triple negative breast cancer.

BRCA-Associated Ovarian Cancer

Approximately 10% of patients with ovarian cancer have an inherited predisposition to developing ovarian cancer. The most common causes are the breast cancer susceptibility genes *BRCA1* and *BRCA2*.[20] The *BRCA* genes are involved in repair of double-strand DNA breaks, which are produced by agents such as platinum and radiation. Women with ovarian cancer with *BRCA* mutations have a more protracted course and a longer median survival than women with non–*BRCA*-associated ovarian cancer.[21] Women with *BRCA* mutations are more likely than women without such mutations to respond to platinum agents and also to poly(ADP-ribose) polymerase inhibitors. It is not known whether *BRCA* mutation status impacts the role of radiation therapy in treatment. Women with mutations in *BRCA* are also at an elevated risk of developing uterine serous cancers.[22]

Risk Reduction Strategies

Several criteria have been proposed to identify patients without endometrial cancer who should be screened for Lynch syndrome on the basis of family history, includ-

ing the Amsterdam and Bethesda criteria.[19] In a woman diagnosed with Lynch syndrome, the risk of endometrial and colon cancer can be reduced significantly with screening and prophylactic hysterectomy following childbearing. Recommendations include annual endometrial biopsy with total abdominal hysterectomy and bilateral salpingo-oophorectomy performed between the ages of 35 and 40 years or after childbearing is complete[23] and colonoscopy performed every 1 to 2 years between the ages of 25 and 40 years and annually thereafter.

Efforts to detect ovarian cancers early have focused on screening for serum biomarkers combined with ultrasound imaging. The best serum biomarker, CA-125, is elevated in 50% to 90% of women with ovarian cancer but is also elevated in many other conditions. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial tested the impact of annual screening with CA-125 and transvaginal ultrasonography in 78,216 women aged 55 to 74 years.[24] The number of ovarian cancers diagnosed was slightly higher (5.7 vs. 4.7 per 10,000 person-years) in the screened arm, but this did not translate to an improvement in ovarian cancer mortality, and surgeries performed to investigate positive findings led to complications. As a result, screening is not routinely recommended for women at average risk. Women with *BRCA* mutations are recommended to undergo CA-125 testing and transvaginal ultrasonography starting at age 35 years or 5 to 10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family. After childbearing is complete, oophorectomy is recommended for women with a *BRCA* mutation.

Pathologic analysis of fallopian tubes removed from women with *BRCA* mutations revealed the presence of premalignant lesions within the epithelium of the fallopian tubes.[3,25,26] This important observation led to the hypothesis that ovarian cancers may originate from the epithelium of the fallopian tube and subsequently implant and grow in the ovaries. The observation that there is a reduced risk of ovarian cancer in women who have undergone tubal ligation supports this hypothesis.[26] This has led to current investigations into whether salpingectomy can reduce the risk of ovarian cancer without the need for premenopausal oophorectomy, which is known to increase cardiovascular mortality.[27]

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