GYNECOLOGIC CANCER

M. D. ANDERSON CANCER CARE SERIES

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Gynecologic Cancer

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Springer

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Gynecologic Cancer

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Dedication

This book is dedicated to the memories of Dr. Felix Rutledge and Dr. Gilbert Fletcher, who together farsightedly developed the model for the multidisciplinary approach to gynecologic cancers, which has benefited countless patients worldwide.

Foreword

There is perhaps no better model of the importance of multidisciplinary interactions in the care of cancer patients than that found in the management of gynecologic malignancies. From the critical importance of primary surgical cytoreduction of advanced ovarian cancer preceding the administration of cytotoxic chemotherapy to the now-standard use of cisplatin as a radiosensitizer delivered with external-beam radiation therapy in the treatment of locally advanced cervix cancer, oncologists involved in the care of gynecologic cancer patients must understand the optimal utilization of multiple treatment modalities.

For more than 5 decades, the gynecologic cancer program at M. D. Anderson Cancer Center has been an innovative leader in helping to establish the standards of care in this group of malignancies and in developing novel surgical, pharmacological, and radiotherapeutic approaches to improve both the survival and quality of life of women diagnosed with a gynecologic cancer.

This well-written and comprehensive text describes the current management of female pelvic tumors, with chapters authored by nationally and internationally recognized senior leaders in their fields, as well as by more junior M. D. Anderson faculty who will soon be responsible for the new advances that will, without question, characterize the future of clinical research in gynecologic malignancies.

Maurie Markman, MD
Vice President for Clinical Research
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Preface

The treatment of gynecologic cancers has improved owing to strong multidisciplinary efforts over the years. These efforts have resulted in a sharp reduction in both the incidence and mortality of invasive cervical cancer and marked improvements in early detection of the disease. Now, emphasis is being placed on fertility preservation, and options are being explored in cervical cancer as well as in other cancers where this may be possible.

The treatment of vulvar cancer, which can be quite debilitating in its advanced stages, has followed an approach similar to that of breast cancer, where radical surgery has given way to a multimodal approach that emphasizes quality of life as well as survival.

The introduction of paclitaxel was a major development in the primary treatment of ovarian cancer. This monograph also describes the appropriate use of other cytotoxic drugs for the treatment of recurrence or for palliation. As this book goes to press, there is more cogent evidence that intraperitoneal platinum-based therapy is likely to become a part of the standard treatment in this disease. In addition to therapy advances, there have been improvements in diagnostic tools and their application in ovarian cancer.

We would like to acknowledge Walter Pagel, director of the Department of Scientific Publications at M. D. Anderson Cancer Center, for his role in continuing to make the M. D. Anderson Cancer Care Series a success. We would also like to thank the volume editors, Drs. David M. Gershenson, Patricia J. Eifel, John J. Kavanagh, and Elvio G. Silva, and the authors of this first monograph on gynecologic cancer for their significant efforts to assemble what we believe will be a most useful and important resource for any physician who diagnoses and treats gynecologic cancer.

Aman U. Buzdar, MD
Ralph S. Freedman, MD, PhD

Preface

This book represents the culmination of a process that has evolved over almost 6 decades since Felix Rutledge and Gilbert Fletcher first stepped onto the scene at M. D. Anderson Cancer Center. Their shared vision of a multidisciplinary approach to caring for gynecologic cancer patients has not only persisted to the present but has, indeed, flourished.

Gynecologic Cancer is the most recent—but not the only—work to detail the practice of gynecologic cancer care at M. D. Anderson. Proceedings of M. D. Anderson's Clinical Conferences on Cancer focused on gynecologic cancer were published in 1962, 1969, and 1987. These books principally outlined the M. D. Anderson multidisciplinary approach to the clinical management of gynecologic malignancies. In addition, Dr. Fletcher's *Textbook of Radiotherapy*, published in 1980, and a 1976 textbook authored by Dr. Rutledge, J. Taylor Wharton, and Richard Boronow—*Gynecologic Oncology*—further described treatment techniques and recommendations.

Over the past several years, the face of M. D. Anderson's Gynecologic Oncology Multidisciplinary Program has changed markedly. The faculty is much larger in number and considerably more diverse. Although evidence-based medicine is the guiding principle in clinical decision making, a myriad of clinical scenarios exist for which there is no single therapeutic strategy. In such instances, differing viewpoints are healthy, and the wealth of experience gained from a large-volume practice is a tremendous asset. Also, the value of the peer-review process used in our Multidisciplinary Planning Conference and Clinic cannot be overestimated.

Of course, the treatment recommendations and practice guidelines included in this text are anchored on past clinical trial research and are continually updated as results of new trials become available. Although the clinical trial portfolio of our multidisciplinary group is ever changing and little discussed here, research-driven patient care is of critical importance in advancing our mission.

Also, we would like to acknowledge and thank Dawn Chalaire, ChaRhonda Chilton, Stephanie Deming, Kim M. Dupree, Manny Gonzales, Vickie J. Williams, and Chris Yeager of the Department of Scientific Publications for editing and compiling this volume.

On behalf of all the contributors to this book, it is a pleasure to present this new work that reflects M. D. Anderson practice early in this new

millennium. And finally, we dedicate this book to all the women with gynecologic cancer who have undergone treatment at M. D. Anderson over the past 60-plus years.

David M. Gershenson, MD
Patricia J. Eifel, MD
John J. Kavanagh, MD
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1 Multidisciplinary Care of Patients with Gynecologic Cancers

David M. Gershenson, John J. Kavanagh, Patricia J. Eifel, and Elvio G. Silva

Chapter Outline

Chapter Overview

Almost from the establishment of M. D. Anderson Cancer Center, gynecologic cancer care has been characterized by a multidisciplinary approach. This chapter will briefly describe the current organization and infrastructure of patient care and clinical research within the Gynecologic Oncology Multidisciplinary Program.

Introduction

One of the first—if not the very first—multidisciplinary collaborations at M. D. Anderson Cancer Center began in 1948 when Dr. Felix Rutledge and Dr. Gilbert Fletcher, both legendary figures in their respective fields (gynecologic oncology and radiation oncology), started a "Disposition Clinic" in which patients with cervical and uterine cancers were seen and evaluated by them jointly and therapy decisions were formulated. This legacy of multidisciplinary care has permeated the fabric of gynecologic cancer care at M. D. Anderson ever since. For the first 40-plus years of its existence, this collaborative venture was in the form of a

biweekly clinic in which new patients with cervical and uterine cancers were seen. Typically, patient summaries would be presented by the gynecologic oncology fellow outside the examination room, after which the patient would be examined by both the gynecologic oncologist and the radiation oncologist. Beginning in the 1990s, the clinic was expanded to include all patients with gynecologic cancer who required a treatment decision. In addition, a multidisciplinary conference attended by gynecologic oncologists, radiation oncologists, medical oncologists, and pathologists was added in the hour preceding the clinic. Presentation of cases, accompanied by pathology slide review, was shifted to the conference, thereby leaving more time during the clinic to counsel patients and their families.

This introductory chapter will briefly describe the current organization and infrastructure of the multidisciplinary care of women with gynecologic malignancies at M. D. Anderson. Because research is such an integral part of the patient care delivered at M. D. Anderson (so-called research-driven patient care), the gynecologic oncology multidisciplinary research infrastructure and process are also described. In addition, practice guidelines for the 3 major gynecologic cancers—endometrial, ovarian, and cervical—are presented.

Organization of Multidisciplinary Clinical Trial Research

Clinical trial research is one of the highest priorities of the Gynecologic Oncology Multidisciplinary Program. Research-driven patient care requires an organization and infrastructure to support the myriad research activities and regulatory and oversight functions. The Gynecologic Oncology Multidisciplinary Program has several working groups that meet on a monthly basis to consider proposed protocols and to monitor ongoing studies. These working groups include the following: (1) Ovarian/Peritoneal/Fallopian Tube, (2) Uterine/Gestational Trophoblastic Disease, (3) Cervix/Vulva/Vagina, (4) Health Services Research, (5) Surgery, (6) Radiation Oncology, and (7) Gynecologic Oncology Group Operations. Thus, we have both organ-site and modality groups that review and approve protocols. Once a protocol is approved by the appropriate working group, it is forwarded to the Program Steering Committee for review and approval. It then is forwarded to the institutional Clinical Research Committee for scientific review and, finally, on to the Institutional Review Board.

The role of the working groups is to develop a portfolio of studies that fit into the framework of the multidisciplinary program's strategic plan. The primary criteria used by each working group for setting the research agenda are scientific merit and advancing the field. Other

important considerations include protocol prioritization (relative to competing studies) and the funding source. Research design and protocol prioritization are also reviewed critically by the Program Steering Committee.

Gynecologic Oncology Multidisciplinary Planning Conference

Since the mid-1990s, new patients have registered for appointments in the Gynecologic Oncology Center through either self-referral or physician referral. Approximately 1,400 new patients are seen in the center annually. These include patients with newly diagnosed disease who are coming to M. D. Anderson for definitive treatment and patients with either newly diagnosed cancers or recurrent disease who are seeking a second opinion. Following a history and physical examination, patients undergo further evaluation and testing, and pertinent clinical material obtained elsewhere, including pathology slides and imaging studies, is reviewed. Patients subsequently return to the Gynecologic Oncology Center for discussion of treatment options and final disposition.

On Tuesday and Thursday afternoons, a Multidisciplinary Planning Conference is convened. This conference is attended by physicians from the relevant specialties—gynecologic oncology, medical oncology, radiation oncology, and pathology—as well as by research nurses, advanced practice nurses, nursing staff, pharmacists, health service research investigators, and trainees. Each patient's case is presented, pathology slides are reviewed, and treatment options are discussed. Emphasis is placed on potential eligibility for clinical trials. These case discussions and resultant recommendations form the foundation for the discussions with patients and family members in the clinic. The outcome of the case discussions may be a unanimous consensus, a consensus, or no consensus at all. The latter outcome occurs most commonly in cases of patients with unusual or rare tumors or with conditions for which there is no standard therapy.

Gynecologic Oncology Multidisciplinary Planning Clinic

Following the Multidisciplinary Planning Conference, patients are seen by the attending physician, accompanied by a fellow, resident, or advanced practice nurse, in the Multidisciplinary Planning Clinic. Patients who are potential candidates for radiation therapy or chemoradiation are generally seen and examined jointly by the attending physician and radiation oncologist. All patients and their families are seen for a final disposition and discussion of treatment recommendations. Patients who may be

candidates for clinical trials also are provided by the appropriate research nurse with the information needed for them to give informed consent. Typical outcomes of the planning clinic include scheduling of primary or secondary surgery, enrollment on a clinical trial, initiation of a new systemic therapy, and initiation of chemoradiation. In addition, subsequent consultations may be sought with such services as pain management, nutrition, physical therapy, psychosocial services, and enterostomal therapy.

Gynecologic Cancer Practice Guidelines

Practice guidelines for the 3 major gynecologic malignancies—endometrial, ovarian, and cervical cancer—were first developed collaboratively several years ago by the Gynecologic Oncology Multidisciplinary Program. Subsequently, these guidelines have been reviewed and updated approximately annually by the respective organ-site working groups. These guidelines are outlined in the appendix and are meant to describe the M. D. Anderson approach to treatment of these 3 cancers within several different clinical settings. Of course, these guidelines do not cover every possible clinical scenario nor do they address the myriad types of less common or rare gynecologic cancers.

As with all M. D. Anderson treatment guidelines, the gynecologic cancer practice guidelines are based, whenever possible, on information from phase II and III clinical trials. Of course, in instances where no standard has emerged from clinical trial data, the guidelines are based on clinical experience only. As noted above, however, whenever possible, patients are encouraged to participate in clinical trials. A complete listing of current clinical trials of the Gynecologic Oncology Multidisciplinary Program can be found on M. D. Anderson's Web site: www.mdanderson.org.

Appendix: M. D. Anderson Cancer Center Treatment Guidelines for Endometrial Cancer, Epithelial Ovarian Cancer, and Cervical Cancer

These practice guidelines are based on majority expert opinion of the Gynecologic Oncology Center faculty at M. D. Anderson Cancer Center. The guidelines were developed using a multidisciplinary approach that included input from the following medical oncologists, radiation oncologists, and surgical oncologists:

Endometrial Cancer

Diane C. Bodurka, MD, Jubilee Brown, MD, Thomas W. Burke, MD, Patricia J. Eifel, MD, Anuja Jhingran, MD, Karen H. Lu, MD, Lois M. Ramondetta, MD, and Judith K. Wolf, MD

Epithelial Ovarian Cancer

Diane C. Bodurka, MD, Jubilee Brown, MD, David M. Gershenson, MD, John J. Kavanagh, MD, Karen H. Lu, MD, Anil K. Sood, MD, and Judith K. Wolf, MD

Cervical Cancer

Diane C. Bodurka, MD, Patricia J. Eifel, MD, Anuja Jhingran, MD, Charles F. Levenback, MD, Pedro T. Ramirez, MD, Lois M. Ramondetta, MD, and Judith K. Wolf, MD

Clinicians are expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care.

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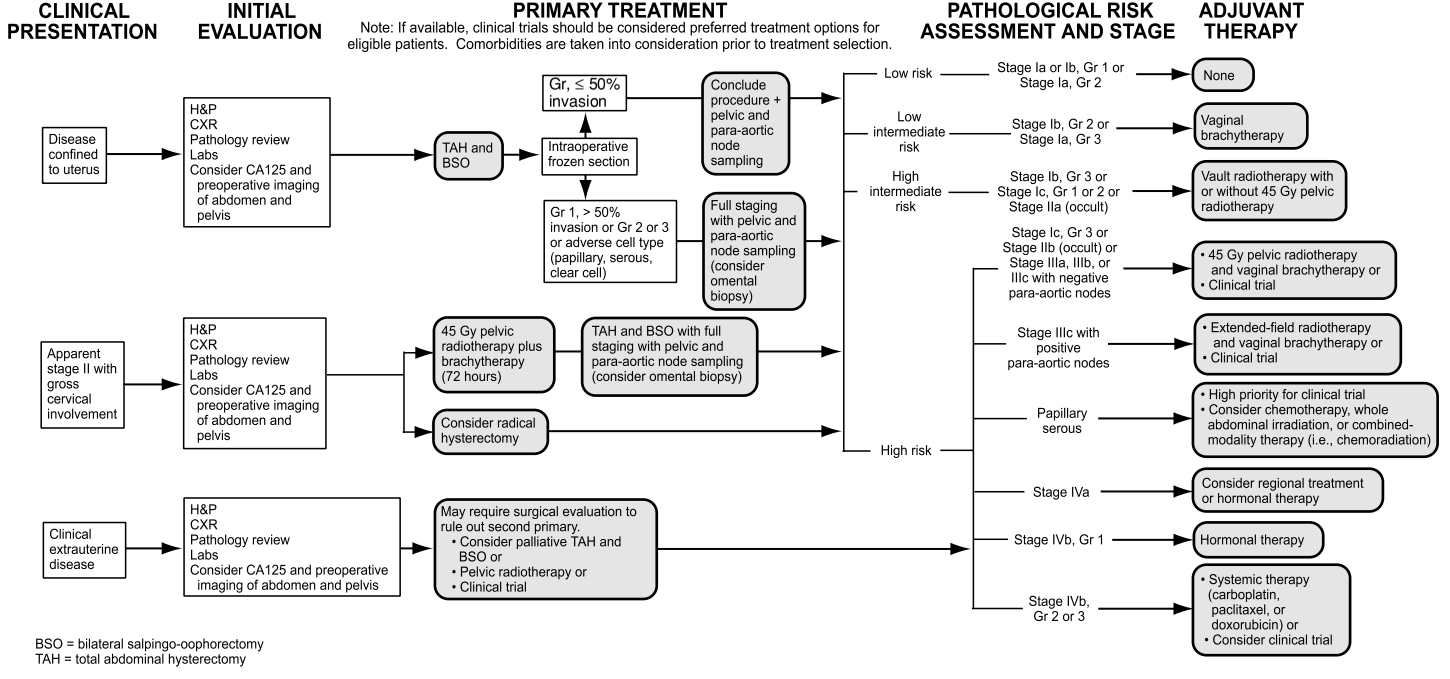
Endometrial Cancer

Treatment



BSO = bilateral salpingo-oophorectomy
TAH = total abdominal hysterectomy

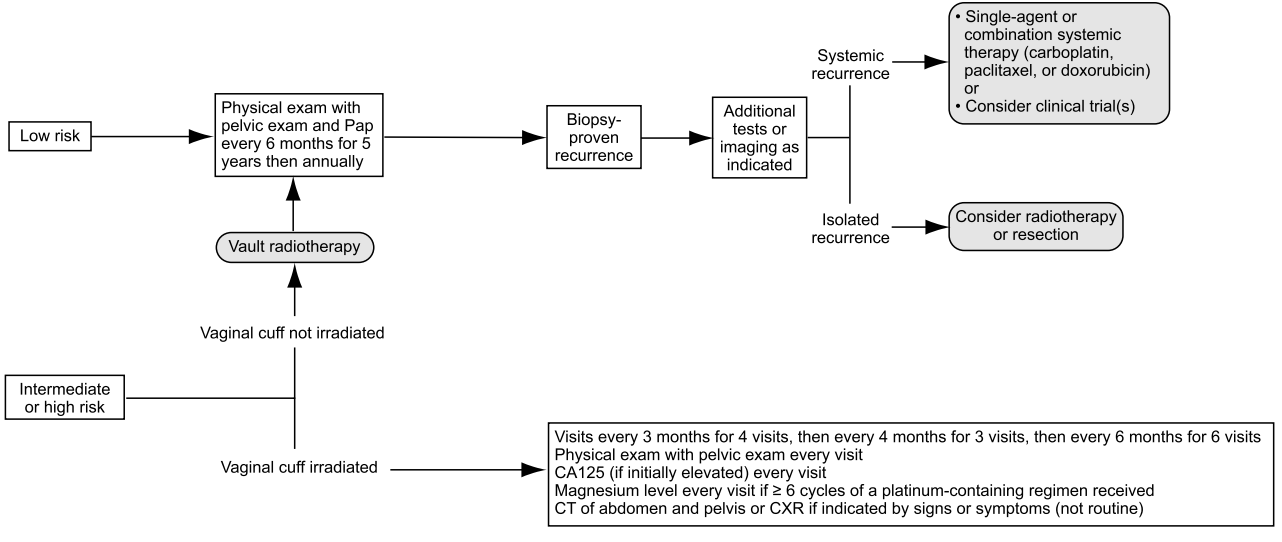
Please refer to American College of Obstetricians and Gynecologists (ACOG) guidelines for patient referral.

Endometrial Cancer

Treatment

SURVEILLANCE

Note: If available, clinical trials are considered preferred treatment options for eligible patients.
Comorbidities are taken into consideration prior to treatment selection.



Please refer to American College of Obstetricians and Gynecologists (ACOG) guidelines for patient referral.

David M. Gershenson et al

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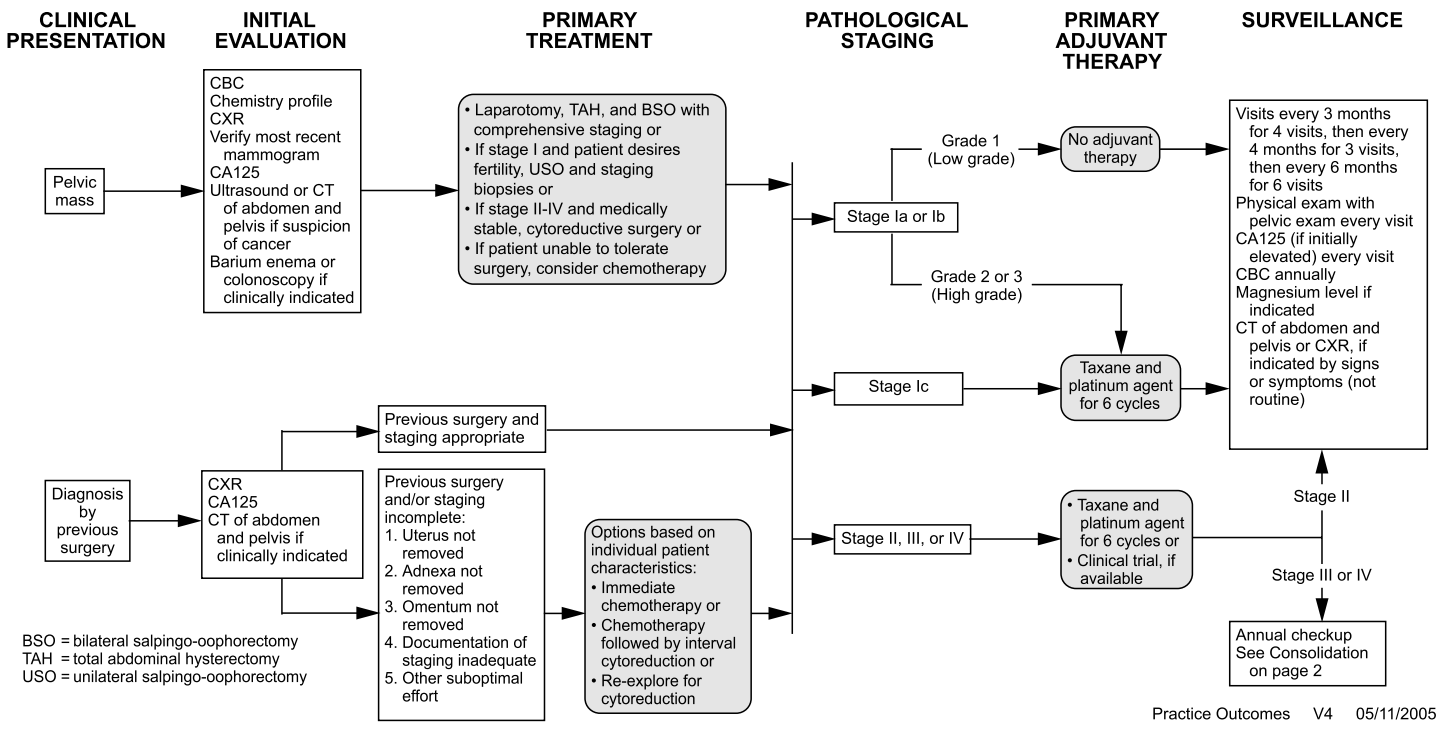
Epithelial Ovarian Cancer

Treatment

Note: Clinical trials are considered preferred treatment options for eligible patients.



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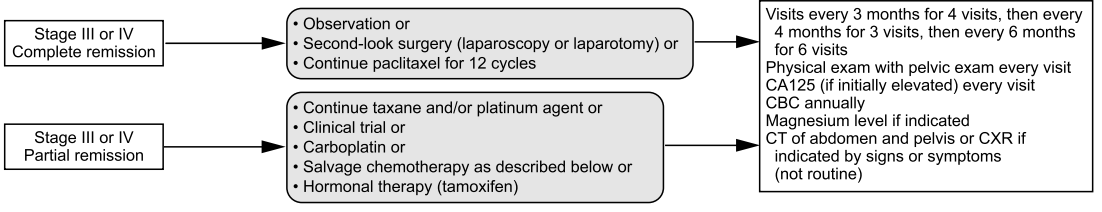
Epithelial Ovarian Cancer

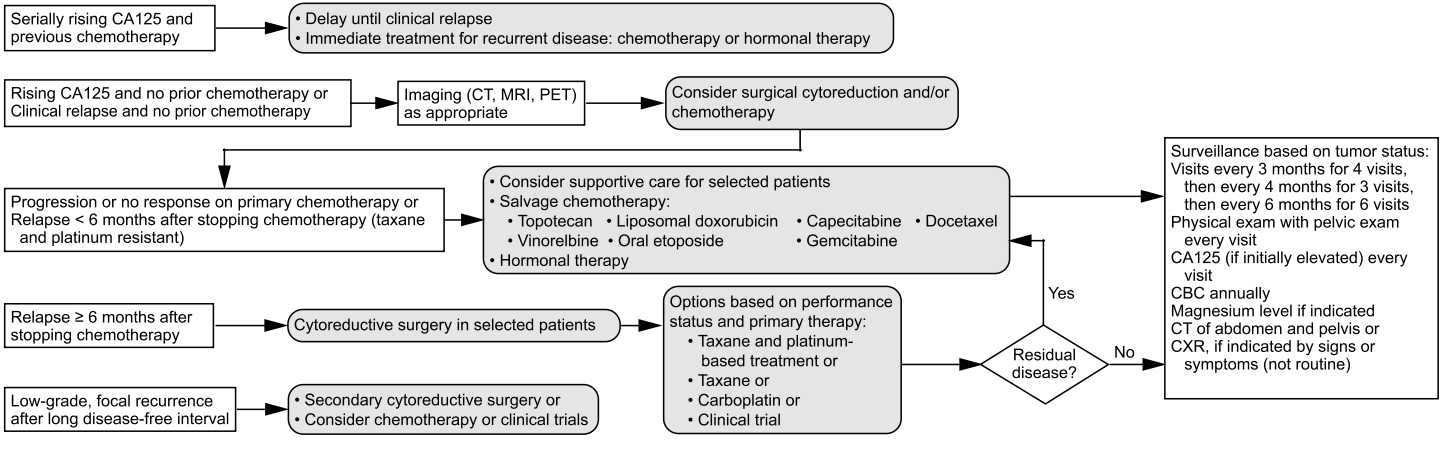
Treatment

Note: Clinical trials are considered preferred treatment options for eligible patients.

CONSOLIDATION TREATMENT



RELAPSE/PROGRESSION OR SALVAGE TREATMENT



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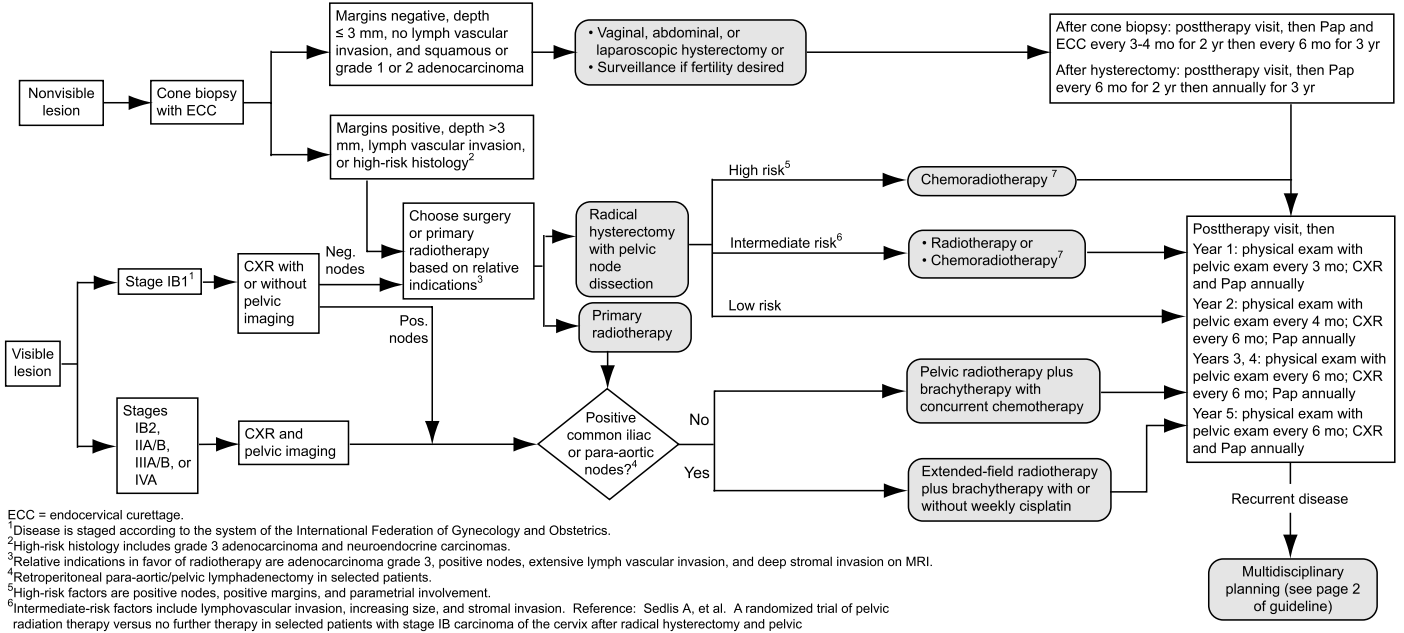
Cervical Cancer

Treatment

CLINICAL PRESENTATION | **INITIAL EVALUATION** | **PRIMARY TREATMENT** | **SURVEILLANCE**

Note: If available, clinical trials are considered preferred treatment options for eligible patients. Comorbidities are taken into consideration prior to treatment selection.



ECC = endocervical curettage.

[1]Disease is staged according to the system of the International Federation of Gynecology and Obstetrics.

[2]High-risk histology includes grade 3 adenocarcinoma and neuroendocrine carcinomas.

[3]Relative indications in favor of radiotherapy are adenocarcinoma grade 3, positive nodes, extensive lymph vascular invasion, and deep stromal invasion on MRI.

[4]Retroperitoneal para-aortic/pelvic lymphadenectomy in selected patients.

[5]High-risk factors are positive nodes, positive margins, and parametrial involvement.

[6]Intermediate-risk factors include lymphovascular invasion, increasing size, and stromal invasion. Reference: Sedlis A, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group study. *Gynecologic Oncology*. 1999;73(2):177-183.

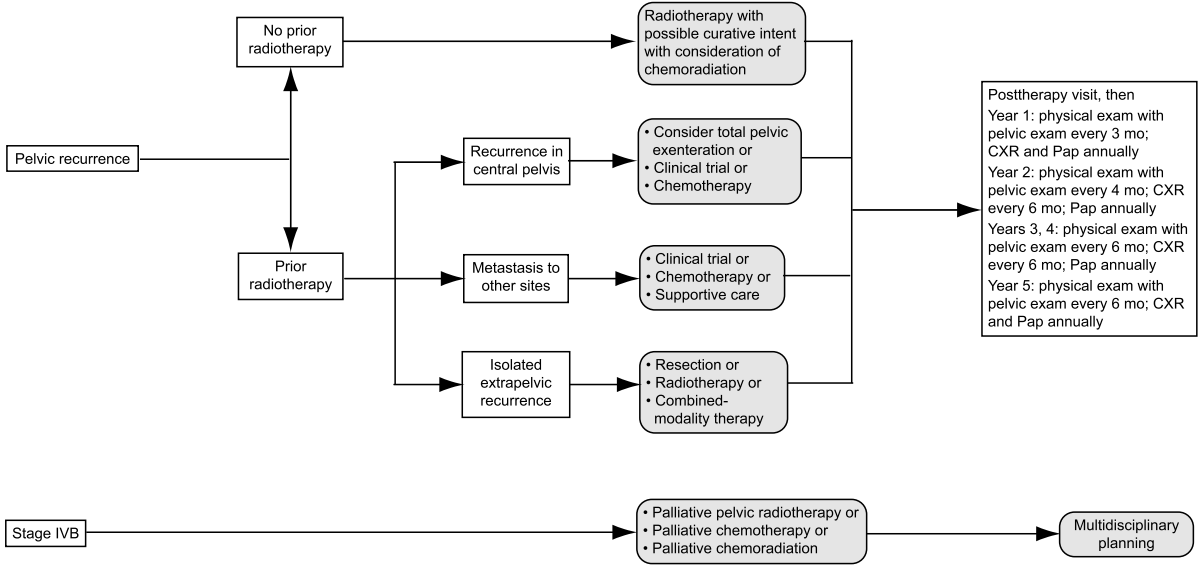
[7]Concurrent weekly cisplatin or cisplatin with fluorouracil.

Cervical Cancer

RECURRENT CANCER

Note: If available, clinical trials are considered preferred treatment options for eligible patients. Comorbidities are taken into consideration prior to treatment selection.

SURVEILLANCE



2 Prevention and Early Detection of Endometrial and Ovarian Cancers

Karen H. Lu

Chapter Outline

Chapter Overview

For both endometrial and ovarian cancer, diagnosis of disease at an earlier stage results in a higher cure rate. More than 70% of women with endometrial cancer are diagnosed with stage I disease because irregular vaginal bleeding is an early symptom. However, fewer than 25% of women with ovarian cancer are diagnosed with stage I disease. Strategies for the prevention and early detection of these cancers are different for women in the general population who are at average risk versus those known to be at increased risk of the disease, such as women with inherited cancer susceptibility syndromes. Women with Lynch syndrome have a 40% to 60% lifetime risk of endometrial cancer and a 10% to 12% lifetime risk of ovarian cancer. They are advised to participate in screening programs as well as to

consider surgical prevention. Women with hereditary breast-ovarian cancer syndrome have a 15% to 40% lifetime risk of ovarian cancer and are also advised to consider intensive screening and surgical prevention options. For women at high risk as well as those at average risk of endometrial and ovarian cancer, oral contraceptives are an excellent chemopreventive agent.

Introduction

In 2005, an estimated 79,480 women will be diagnosed with a gynecologic malignancy in the United States, and 31,010 women will die of a gynecologic cancer (Jemal et al, 2005). This chapter focuses on the prevention and early detection of endometrial and ovarian cancers. Papanicolaou testing and identification of premalignant cervical lesions are discussed in chapter 3.

Endometrial Cancer

Endometrial cancer is the most common gynecologic cancer. In 2005, an estimated 40,880 women will be diagnosed with uterine cancer, and 7,310 women are expected to die of the disease (Jemal et al, 2005). Women in the general population have an approximate 3% lifetime risk of developing endometrial cancer. Importantly, 70% of women with endometrial cancer are diagnosed with stage I disease. This is so primarily because postmenopausal or irregular vaginal bleeding is an early symptom of endometrial cancer. Currently, endometrial biopsy performed in the office setting is recommended for women who present with postmenopausal or irregular vaginal bleeding. Endometrial biopsy in the office setting, which consists of endometrial sampling using a Pipelle, has been shown to have sensitivity equivalent to that of dilatation and curettage (Dijkhuizen et al, 2000). If an endometrial biopsy in the office setting is not feasible or the amount of tissue obtained is inadequate, dilatation and curettage is recommended.

Prevention for Women at Average Risk

For women at average risk of endometrial cancer, 2 primary prevention strategies can be instituted. First, oral contraceptives have been shown to decrease the risk of endometrial cancer by 50%. Second, patients should be encouraged to maintain a normal weight, given that obesity is so strongly associated with an increased risk of endometrial cancer.

Prevention and Screening for Women with Lynch Syndrome

Certain individuals are at increased risk of endometrial cancer, and in these women, specific strategies for the early detection and primary prevention of endometrial cancer can be instituted. Hereditary nonpolyposis colorectal cancer syndrome, or Lynch syndrome, is an inherited autoso-

mal dominant cancer susceptibility syndrome (Aarnio et al, 1999). Women with Lynch syndrome are at significantly increased risk of endometrial, colon, and ovarian cancers. Recent studies have shown that women with Lynch syndrome have a 40% to 60% lifetime risk of endometrial cancer, a 40% to 60% lifetime risk of colon cancer, and a 10% to 12% lifetime risk of ovarian cancer. Given this increased risk, the proper identification of these women is crucial. Indications that a family may be affected by Lynch syndrome include (1) multiple individuals in the same lineage with colon or endometrial cancer or one of the less common Lynch syndrome cancers (ovarian, stomach, or ureteral cancer), (2) an individual in the family who has had more than 1 Lynch syndrome cancer, e.g., a woman with a history of colon and endometrial cancer, or (3) an individual in the family diagnosed with a Lynch syndrome cancer before the age of 50 years.

Clinical genetic testing for *MLH1*, *MSH2*, and *MSH6*, the genes responsible for Lynch syndrome in the majority of families, is now available. For both men and women who carry a mutation in 1 of these genes, yearly colonoscopy has been shown to decrease the mortality rate from colon cancer. In women who are known carriers of a mutation in 1 of these genes, appropriate counseling regarding endometrial and ovarian cancer prevention and early detection should be given, although the efficacy of specific prevention or screening strategies for endometrial or ovarian cancer in women with Lynch syndrome has not been proven.

Consensus statements recommend that women with Lynch syndrome undergo annual transvaginal ultrasonography and endometrial biopsy beginning at age 25 to 35 years (Burke et al, 1997). For prevention, young women of childbearing age can consider taking an oral contraceptive. Although the effectiveness of oral contraceptives in decreasing the rate of endometrial or ovarian cancer in women with Lynch syndrome has not been proven, oral contraceptives have been shown to decrease both endometrial and ovarian cancer risk in the general population. When childbearing is complete, a total abdominal hysterectomy and bilateral salpingo-oophorectomy should be recommended for women with Lynch syndrome. In addition, in women undergoing colon cancer surgery who have completed childbearing, prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy should also be considered. Most importantly, women with Lynch syndrome should be taught the symptoms of early endometrial cancer and counseled to understand the necessity of an endometrial biopsy should they develop postmenopausal or irregular vaginal bleeding.

Prevention and Screening for Women Taking Tamoxifen

Women who are taking tamoxifen are also at increased risk of endometrial cancer. Tamoxifen has been shown to significantly decrease the risk of breast cancer recurrence in women with a history of breast cancer. In addition, in the National Surgical Adjuvant Breast and Bowel Project P-1 trial, tamoxifen was shown to decrease primary breast cancer occur-

rence in women at increased risk (Fisher et al, 1998). While the benefits of taking tamoxifen to reduce the risk of primary breast cancer or breast cancer recurrence have been proven, women need to be counseled that tamoxifen increases the risk of endometrial cancer. Tamoxifen is a selective estrogen receptor modulator that has anti-estrogenic effects on the breast and pro-estrogenic effects on the uterus. The risk of endometrial cancer in women taking tamoxifen is approximately 2 to 3 times the risk in women not taking tamoxifen.

Currently, recommendations for women taking tamoxifen include a discussion of early symptoms associated with endometrial cancer, including postmenopausal, irregular, or heavy vaginal bleeding. Patients who present with these symptoms need to undergo an endometrial biopsy. A number of studies have looked at transvaginal ultrasonography for screening of asymptomatic women taking tamoxifen. Tamoxifen increases the thickness of the endometrial stripe; however, this increase is mostly associated with subendometrial cyst formation and has not been well correlated with endometrial cancer. Therefore, we do not recommend routine ultrasonographic screening for asymptomatic women taking tamoxifen.

Prevention and Screening for Obese Women

Obesity is strongly linked to an increased risk of endometrial cancer. Women who are 50 pounds over their ideal body weight are 10 times more likely to develop endometrial cancer than are women at their ideal body weight. In addition, obese women are more likely to have irregular periods and may not seek gynecologic care specifically for this symptom. Gynecologists who care for obese women should counsel them regarding their increased risk and the need to report any postmenopausal, irregular, or heavy bleeding. Also, an endometrial biopsy should be performed when symptoms of postmenopausal, irregular, or heavy bleeding are reported.

Ovarian Cancer

The incidence of ovarian cancer is low, with 1 case of epithelial ovarian cancer occurring for every 2,250 postmenopausal women in the United States annually. For each individual woman, the lifetime risk of ovarian cancer is approximately 1 in 70, or 1.4%. However, epithelial ovarian cancer is highly fatal. In 2005, an estimated 22,270 women will be diagnosed with ovarian cancer and approximately 16,210 women will die of the disease (Jemal et al, 2005). The high mortality rate from ovarian cancer is due to the fact that approximately 70% of women are diagnosed with stage III or stage IV disease, for which the chances of long-term cure are less than 20%. However, more than 90% of patients diagnosed with stage I ovarian cancer can be cured.