ACOG
PRACTICE
BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR
OBSTETRICIAN–GYNECOLOGISTS

NUMBER 65, AUGUST 2005

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology and the Society of Gynecologic Oncologists member contributors James Orr Jr, MD, Donald Chamberlain, MD, Larry Kilgore, MD, and Wendal Naumann, MD, and the editorial assistance of Joan Walker, MD, and Jonathan Berek, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Reaffirmed 2009

SGO™
Society of Gynecologic Oncologists

Management of Endometrial Cancer

Endometrial carcinoma is the most common gynecologic malignancy that will be encountered by almost every gynecologist. A thorough understanding of the epidemiology, pathophysiology, and management strategies allows the obstetrician–gynecologist to identify women at increased risk, to contribute toward risk reduction, and to facilitate early diagnosis of this cancer. The purpose of this document is to review the risks and benefits of current treatment options to optimize treatment for women with endometrial cancer.

Background

Epidemiology

Endometrial cancer is the most common female genital tract malignancy, with more than 40,000 cases estimated to be diagnosed in 2005 in the United States (1). Most women (90%) with endometrial cancer develop symptomatic bleeding or discharge, facilitating early diagnosis and resulting in an increased opportunity for cure. Currently, most endometrial cancers (72%) are diagnosed while in stage I; however, a significant number are in stage II (12%), stage III (13%), or stage IV (3%) (2). Despite this favorable stage distribution, endometrial cancer is responsible for 7,310 deaths each year, making it the eighth leading site of cancer-related death among American women (1).

It is estimated that 2.62% of women in the United States will develop uterine cancer during their lifetime, with a 0.5% lifetime mortality risk (whites 2.8%, 0.48%; blacks 1.7%, 0.73% respectively for risk of disease and death) (3). The 5-year survival rate for white women older than 65 years is 80.8% and for black women in the same age group is 53.3%. It is unclear whether the high mortality in black women is a result of delayed treatment, lack of access to care, or a higher likelihood of cancers with more serious prognostic characteristics. It is known that of women with endometrial cancer, only 52% of black women older than 50 years have disease confined to the uterus at the time of original

surgery, compared with 73% of white women older than 50 years. The overall incidence of endometrial cancer likely will increase in the future secondary to increasing obesity and the aging of the population.

Etiology

The etiology of most endometrial cancers has been well described (4). The most common cause is an excess of endogenous or exogenous estrogen unopposed by progestin leading to endometrial hyperplasia followed by cancer. This cause allows for prevention and early detection of the most common and most indolent form of endometrial cancer (type I or estrogen dependent). Type I endometrial cancer typically has lower grade nuclei, endometrioid histologic cell type, phosphatase and tensin homologue mutation, and a good prognosis.

The more lethal variety of endometrial cancer, type II, accounts for approximately 10% of cases. It has aggressive high-grade nuclei or serous and clear cell histology and P53 tumor suppression mutation. In contrast to type I, the background underlying endometrium generally is atrophic or associated with polyps. There is no clear epidemiologic profile for type II cancers (Table 1). Carcinosarcoma of the endometrium is the most aggressive form of endometrial cancer, and the classification of this lesion as a sarcoma or dedifferentiated carcinoma is controversial. Using endometrial sampling, carcinosarcoma may be interpreted preoperatively as adenocarcinoma, thereby making unexpected intraoperative findings more common.

Obtaining a family history may alert the gynecologist to women at increased risk for genetically linked cancers (eg, hereditary nonpolyposis colorectal cancer) in which young age at presentation of colon cancer is important. The most common manifestation of hereditary nonpolyposis colorectal cancer in women is endometrial cancer (40–60% lifetime risk), followed by colon cancer, then ovarian cancer. It is important to identify women at risk in order to provide them with appropriate screening, prophylactic surgery, and counseling (5). In addition, women with anovulatory disorders should be counseled about their long-term risk of endometrial cancer and modalities available for prevention.

Table 1. Risk Factors for Uterine Corpus Cancer

Factors Influencing Risk	Estimated Relative Risk
Older age	2–3
Residency in North America or Northern Europe	3–18
Higher level of education or income	1.5–2
White race	2
Nulliparity	3
History of infertility	2–3
Menstrual irregularities	1.5
Late age at natural menopause	2–3
Early age at menarche	1.5–2
Long-term use of high dosages of menopausal estrogens	10–20
Long-term use of high dosages of combination oral contraceptives	0.3–0.5
High cumulative doses of tamoxifen	3–7
Obesity	2–5
Stein-Leventhal disease or estrogen-producing tumor	>5
History of diabetes, hypertension, gallbladder disease, or thyroid disease	1.3–3
Cigarette smoking	0.5

*Relative risks depend on the study and referent group employed.

Reprinted from Gynecologic cancer: controversies in management, Gershenson DM, McGuire WP, Gore M, Quinn MA, Thomas G, editors. Copyright 2004, with permission from Elsevier.

Histologic Considerations

Endometrioid adenocarcinoma is the most common histologic cell type of endometrial cancer, making up more than three fourths of the cases. Benign or malignant squamous differentiation can coexist with the adenocarcinoma; however, the grade and prognosis are currently determined based only on the glandular component (6, 7). The ultimate prognosis depends on both the depth of myometrial invasion and the grade determined by glandular and nuclear cellular differentiation (8).

The precursor lesion of the endometrioid adenocarcinoma is endometrial hyperplasia, which produces a continuum of lesions that are difficult to differentiate by standard histologic characteristics. The classification of endometrial hyperplasias by the World Health Organization is shown in the box. An additional classification system is accepted by the International Society of Gynecologic Pathologists.

Atypical endometrial hyperplasia is commonly found coexisting with undiagnosed cancer in the uterus,

World Health Organization's Classification of Endometrial Hyperplasia

1. Simple hyperplasia
2. Complex hyperplasia (adenomatous)
3. Simple atypical hyperplasia
4. Complex atypical hyperplasia (adenomatous with atypia)

Data from Scully RE, Bonfiglio TA, Kurman RJ, Silverberg SG, Wilkinson ED, editors. Histological typing of female genital tract tumours. 2nd ed. New York (NY): Springer-Verlag; 1994.

or if found alone, it may progress to endometrial cancer in untreated women (9). A prospective trial was conducted to identify the prevalence of underlying cancer and to define more clearly the diagnostic criteria for atypical endometrial hyperplasia compared with cancer (10). In this study, 306 women had diagnosed atypical endometrial hyperplasia, established by community pathologists on preoperative biopsy, followed immediately, without medical treatment, by hysterectomy. More than 42% of women were found to have invasive cancer, and some even had high-grade lesions and deep myometrial invasion. The results demonstrate the futility of trying to make a "true" diagnosis before hysterectomy until protein or molecular biomarkers have been established (11, 12).

Papillary serous histology portends an increased risk of extrauterine disease and carries a poor prognosis. Although this cell type accounts for only about 10% of all cases, it represents most recurrent endometrial cancers (13). Clear cell histology is rare but also is associated with a poor prognosis (14). Carcinosarcoma, also known as malignant mixed müllerian tumor of the uterus, is another histologic cell type with a poor prognosis and may represent a subset of adenocarcinoma. This lesion is high grade and spreads intraperitoneally, through lymphatics and by hematogenous routes.

Prognosis

The 1988 International Federation of Gynecology and Obstetrics (FIGO) surgical staging system (Table 2) incorporates important pathologic risk factors associated with prognosis and recurrent disease, including histologic (FIGO) grade, nuclear grade, depth of myometrial invasion, cervical glandular or stromal invasion, vaginal and adnexal metastases, positive cytology, metastatic disease in pelvic or paraaortic lymph nodes, and the presence of intraabdominal or distant metastases (15–17). Other prognostic factors not included in this system are DNA ploidy and the presence of lymph–vascular space involvement (18–20). The latter has been associated with a worsened prognosis, even in the absence of documented lymph node metastasis (21).

The FIGO system emphasizes the overriding prognostic value of surgical staging information as well as its use in postoperative treatment planning. The prognosis of women with endometrial cancer is dictated primarily by the site of metastatic disease (Fig. 1). When disease has been systematically documented to be confined to the uterine fundus, the prognosis is based on grade, histologic cell type, and depth of invasion. The degree of lymph–vascular space invasion and the patient's race and age are important independent prognostic factors. Recently, the American Joint Committee on Cancer (AJCC) joined FIGO in recommending the use of surgical staging in order to adequately evaluate regional lymph nodes and to sample paraaortic and bilateral obturators and at least one other bilateral pelvic node group (22). These organizations recommend that findings be documented in the pathology or operative reports, or both. The AJCC further defined the difference between pathologic staging (p T, p N, p M) and clinical staging (c T, c N, c M).

Survival data generally are obtained from population-based registries such as those maintained by the American Cancer Society, the American College of Surgeons, and the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute. However, these data are limited by the diversity of interventions used, including surgical staging. In addition, clinical trial research organizations—Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC) study group in the Netherlands and Gynecologic Oncology Group in the United States—provide data that are not population based but are quality controlled for patients treated with a standardized surgery as well as prescribed postoperative therapy.

Clinical Considerations and Recommendations

▶ *What elements of preoperative evaluation are useful for women with endometrial cancer?*

Patients with endometrial cancer often have comorbidities, including obesity, hypertension, diabetes, and, frequently, cardiac and pulmonary dysfunction, making them high-risk or poor surgical candidates. Careful attention to functional status and medical history will assist in optimizing perioperative outcome. Perioperative risk assessment also serves as the basis for appropriate patient counseling of the risks and benefits of available treatment options.

Only a physical examination and a chest radiograph are required for preoperative staging of the usual (type I endometrioid grade 1) histology, clinical stage I patient. All other preoperative testing should be directed toward optimizing the surgical outcome. The use of computed tomography or magnetic resonance imaging is not necessary because the surgeon should be prepared to resect metastatic disease commonly found in patients with endometrial cancer.

A preoperative physical examination provides information that may affect the surgical approach and subsequent risks, and it assists with developing a therapeutic plan. For example, supraclavicular lymph node metastasis may make chemotherapy an appropriate first line of treatment. If the cervix appears to be enlarged (suggest-

Table 2. International Federation of Gynecology and Obstetrics and Tumor–Node–Metastases Surgical Staging Systems for Endometrial Cancer

TNM Categories	FIGO Stages*	Surgical–Pathologic Findings
Primary Tumor (T)		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	0	Carcinoma in situ
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium
T1b	IB	Tumor invades less than one half of the myometrium
T1c	IC	Tumor invades one half or more of the myometrium
T2	II	Tumor invades cervix but does not extend beyond uterus
T2a	IIA	Tumor limited to the glandular epithelium of the endocervix; there is no evidence of connective tissue stromal invasion
T2b	IIB	Invasion of the stromal connective tissue of the cervix
T3	III	Local and/or regional spread
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
T3b	IIIB	Vaginal involvement (direct extension or metastasis)
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)
Regional Lymph Nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis to pelvic and/or paraaortic nodes
Distant Metastasis (M)		
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to abdominal lymph nodes other than paraaortic, and/or inguinal lymph nodes; excludes metastasis to vagina, pelvic serosa, or adnexa)

FIGO indicates International Federation of Gynecology and Obstetrics; TNM, tumor–node–metastases.

*All cases of FIGO Stage I–IVA should be subclassified by histologic grade as follows: GX, grade cannot be assessed; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated or undifferentiated.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth edition (2002), published by Springer-Verlag New York, www.springeronline.com.

ing possible tumor involvement), the differential diagnosis of cervical adenocarcinoma should be considered. If cervical involvement is confirmed, treatment options may include radical hysterectomy or preoperative radiation therapy. The finding of vaginal, parametrial, or adnexal extension of disease also can complicate treatment planning, and special skills may be required for complete surgical resection.

Preoperative measurement of the CA 125 level may be appropriate because it is frequently elevated in women with advanced-stage disease. Elevated levels of CA 125 may assist in predicting treatment response or in post-treatment surveillance (23, 24).

▶ *What constitutes appropriate staging for women with endometrial cancer?*

Most women with endometrial cancer benefit from systematic surgical staging, including pelvic washings, bilateral pelvic and paraaortic lymphadenectomy, and complete resection of all disease. Appropriate surgical staging is prognostic and facilitates targeted therapy to maximize survival and to minimize the effects of undertreatment (eg, recurrent disease or increased mortality) and potential morbidity (eg, radiation injury) associated with overtreatment. Exceptions to the need for surgical staging include young or perimenopausal women with

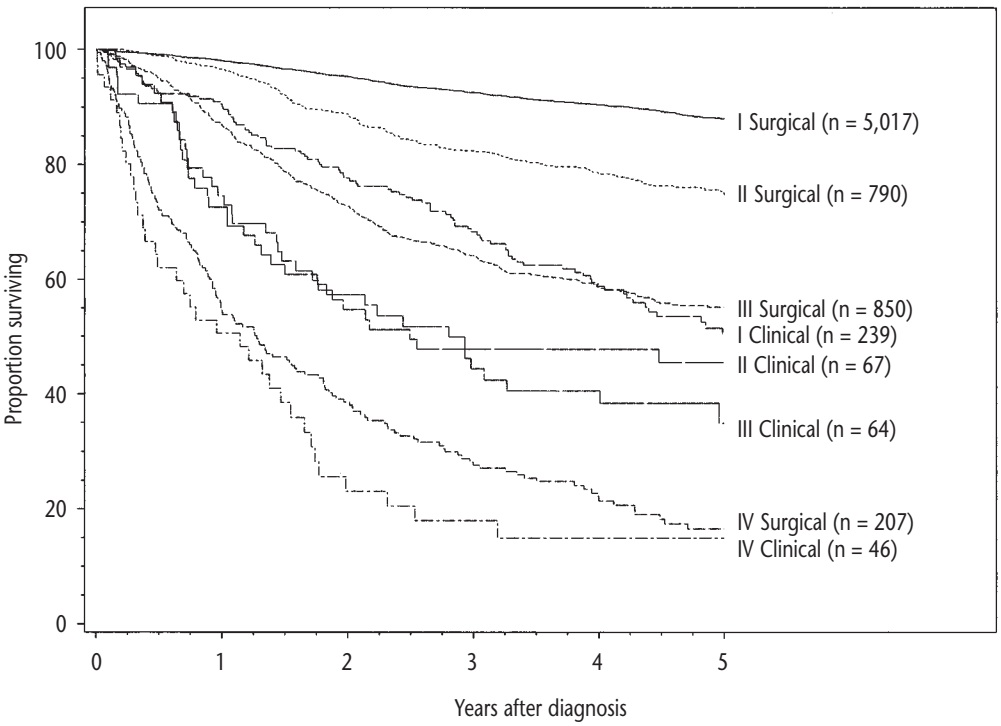

Figure 1. Carcinoma of the corpus uteri, patients treated 1996–1998. Survival by mode of staging, N = 7,280. (Reprinted from Int J Gynaecol Obstet, Vol. 83 (Suppl 1), Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, Heintz AP, et al. Carcinoma of the corpus uteri. p. 79–118. Copyright 2003, with permission from the International Federation of Gynecology and Obstetrics.)

grade 1 endometrioid adenocarcinoma associated with atypical endometrial hyperplasia and women at increased risk of mortality secondary to comorbidities.

Retroperitoneal lymph node assessment is a critical component of surgical staging and is associated with improved survival. Women testing negative for disease of the pelvic and paraaortic lymph nodes and for abnormal pelvic cytology have better survival rates than women with matched uterine histologic factors and positive results of testing of nodes or cytology (25). These negative results allow the adjuvant radiotherapy to be withheld and change the survival estimates from that of a clinical stage I patient to a surgical stage I. Palpation of the retroperitoneum is an inaccurate measure and cannot substitute for surgical dissection of nodal tissue for histopathology. Sampling of pelvic lymph nodes alone ignores the fact that 62% of women with any positive lymph nodes have paraaortic metastasis, and 17% have paraaortic disease alone (16, 26–29).

The incidence and severity of complications associated with extensive surgical staging of women with endometrial cancer frequently are related to the effects of existing medical comorbidities (ie, obesity, diabetes, coronary artery disease) (30, 31). The average hospital stay for abdominal staging is similar to that for benign hysterectomy (32).

In specific situations, hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and paraaortic lymphadenectomy can be completed successfully and safely with less perioperative morbidity by using a laparoscopic approach (33–35).

▶ *How are women with endometrial cancer treated postoperatively?*

The use of adjuvant radiation therapy in women with disease limited to the uterus based on systematic surgical staging is controversial. Many practitioners have abandoned teletherapy (whole pelvic radiation therapy) and replaced it with vaginal brachytherapy for selected patients (36). One study reported a 5-year survival rate of 92% for systematically staged IC patients treated with postoperative whole pelvic radiation, compared with 90% for those treated with surgery alone (37). The authors concluded that radiation should be tailored to sites of known metastatic disease or reserved for recurrence.

The large, randomized controlled PORTEC trial was conducted to determine the value of postoperative whole pelvic radiation therapy in women after hysterectomy and bilateral salpingo-oophorectomy without comprehensive surgical staging and lymphadenectomy. The

initial report included women with grade 1 deep myometrial invasion, grade 2 invasion of any depth, and grade 3 superficial invasion, and found a 5-year overall survival rate of 81% in the radiotherapy group and 85% for the controls (38). These results confirm the conclusions of another large randomized prospective study of 540 patients that there is no benefit to whole pelvic radiation therapy, except local control in the vagina and pelvis (39). Deaths generally result from disease recurrence outside the radiation field. Of patients treated with radiation, 2% have major complications, and 20% have minor complaints that affected quality of life.

The second PORTEC report focused on women with grade 3 histology with deep myometrial invasion, all women receiving whole pelvic radiotherapy (40). The 5-year survival rate for this group of women without comprehensive surgical staging was 58%. In contrast, when stage IIIC patients are appropriately staged, metastatic disease in the lymph nodes is removed, and treatment is delivered to the known sites of metastatic spread, the overall 5-year survival rate is 70–85%, demonstrating that radiation cannot overcome poor surgical treatment (29, 41, 42).

Women who do not receive postoperative radiation with surgical stage I endometrial cancer may have isolated recurrent disease in the vagina. Treatment of these recurrences demonstrated 60–75% survival (38). Another randomized trial also indicates that radiation does not improve survival or reduce distant metastases; it prevents only vaginal recurrences. These recurrences can be treated subsequently, avoiding the unnecessary exposure of radiation toxicity (39). Therefore, for patients with surgical stage I disease, postoperative radiation therapy can reduce the risk of local recurrence. In deciding whether to use radiation, the cost and toxicity should be balanced with the evidence that the therapy does not improve survival or reduce distant metastasis.

Evidence for the treatment of metastatic endometrial cancer has advanced significantly in the past decade. Recognition in multiple reports that most deaths are from distant failure secondary to hematogenous spread makes optimizing chemotherapy, possibly in combination with local brachytherapy, the foundation for future research.

A cost analysis of treatment options of intermediate-risk patients (surgical stage I, grade 2–3, deep myometrial invasion) who underwent complete staging made the following assumptions: 1) lymph node status is the most important prognostic factor, 2) removal of lymph nodes testing negative for disease improves survival, 3) lymphadenectomy has minimal morbidity, 4) lymphadenectomy improves the cost effectiveness, and 5) teletherapy can be eliminated for stage I–II disease (36). The analysis demonstrated a 12% cost reduction with routine lymphadenectomy by avoiding teletherapy and substituting brachytherapy (43). The same analysts also report a 31% cost reduction by avoiding routine brachytherapy and treating the high-risk women only when they develop recurrent disease.

What are the recommendations for women found to have endometrial cancer after a hysterectomy?

To counsel the patient appropriately on her risk of metastases, recurrence, and death, a multidisciplinary review of pathologic material is important (2, 15). In this clinical situation, therapeutic options include no further therapy and surveillance only, reoperation to complete the surgical staging, or radiotherapy to prevent local recurrence. The acceptable level of risk that determines the need for reoperation or radiation varies among individuals. The survival advantages of surgical staging must be weighed against the complications from a new major surgical procedure. This risk of additional surgery contrasts with the minimal difference in risk with planned, combined procedures of surgical staging with hysterectomy, bilateral pelvic and paraaortic lymphadenectomy, and peritoneal cytology tests. The advent of laparoscopic surgical restaging has resulted in less morbidity using this approach. One study on the use of laparoscopic restaging for endometrial cancer reported a hospital stay of 1.5 days and less than 100 mL estimated blood loss (44). Treatment decisions with endometrial cancer following hysterectomy are best made in consultation with a specialist with advanced training and demonstrated competence, such as a gynecologic oncologist.

What is the mode of therapy for patients with positive pelvic or paraaortic nodes?

Every patient found to have extrauterine disease (stage III, IV) is at significant risk for developing persistent or recurrent disease and should be considered a candidate for additional therapy (45). Factors influencing postoperative treatment decisions may include tumor histology, extent of disease, the presence of medical comorbidities, and the availability of research protocols. Regional or systemic therapeutic modalities may be considered.

Despite the potential therapeutic role of lymphadenectomy, most women with nodal metastases should receive adjuvant therapy. The addition of therapeutic pelvic radiation for the treatment of women with stage IIIC disease (and testing negative for disease of the paraaortic nodes) results in disease-free survival rates from 57% to 72% (42, 46).

Women with paraaortic nodal disease should have the tumor completely resected and should have postoperative imaging studies (eg, chest computed tomography or positron emission tomography scans) to detect or exclude the presence of occult extraabdominal disease (41, 47).

The addition of paraaortic radiation is associated with improved survival (median survival, 27–43 months) and is of significant benefit, particularly for those with microscopic nodal metastases (48–51).

Patterns of failure in women with stage IIIC disease suggest the possible benefit of concomitant or sequential systemic therapy. Retrospective studies of concomitant chemotherapy also support the benefit of systemic chemotherapy (29, 47, 50).

What is the mode of therapy for patients with intraperitoneal disease?

The primary mode of therapy for women with intraperitoneal disease includes an attempt at optimal tumor cytoreduction and the addition of systemic chemotherapy or radiation therapy or both (52). Optimal cytoreduction can be completed with limited morbidity and likely offers a survival benefit (53–56). The ability to resect isolated metastases when combined with additional therapy can result in long-term survival similar to the treatment of women with ovarian cancer (31).

Postoperatively, progestational agents or systemic cytotoxic therapy may be used alone or in combination with directed radiation. A randomized trial showed the superiority of the combination of doxorubicin, cisplatin, and paclitaxel systemic chemotherapy for advanced and recurrent endometrial cancer (57). The use of carboplatin and paclitaxel in combination, similar to use for ovarian cancer, is favored by some because of the combination's more favorable toxicity profile.

What is the mode of therapy for patients with cervical involvement?

In the absence of macroscopic cervical involvement, the preoperative diagnosis of stage II disease is difficult to establish. Endocervical curettage is notoriously imprecise for such use, with a reported accuracy of 50% (58). It is challenging to differentiate primary cervical adenocarcinoma from stage II endometrial cancer. Patients may benefit from HPV testing and immunohistochemistry or cone biopsy for further evaluation. The treatment plan for each diagnosis is markedly different. When the diagnosis is unclear, radical hysterectomy and lymphadenectomy can be performed, followed by tailored adjuvant therapy based on the pathologic findings.

Treatment of women with cervical involvement may include preoperative radiation combined with total hysterectomy, or radical hysterectomy with lymphadenectomy followed by the addition of adjuvant chemotherapy or radiation therapy directed toward known sites of disease (59, 60). The use of radical hysterectomy has been associated with improved local control and survival when compared with total hysterectomy at 5 years (94% versus 79%) and 10 years (94% versus 74%) (61, 62). It would appear that grade is more predictive of survival than depth of cervical invasion (63). Optimal treatment of women with stage II disease has resulted in survival rates approaching or exceeding 80% (64–66).

Is there a role for radiotherapy as an alternative to surgery?

The primary treatment of endometrial cancer typically involves hysterectomy. In the unusual instance (<3.5%) when a patient is deemed an exceptionally poor surgical candidate, primary therapeutic radiation may be considered for treating the uterine disease (67). Although primary therapeutic radiation is suboptimal, the use of brachytherapy to control disease offers reasonable results in this ultra-high-risk surgical population (68). The additional benefit of teletherapy remains unclear.

Radiation therapy alone does not allow for directed therapy and fails to eradicate the uterine cancer in 10–15% of cases. The cancer-specific 5-year survival rates in stage I inoperable patients (80%) are less than that of stage I operable patients (98%) (67) and are related to tumor grade (69). Others have reported lower survival rates of approximately 50% (69, 70). A significant number of these patients die of intercurrent disease (71). These results suggest that a careful preoperative evaluation and appropriate consultation be undertaken before denying any woman the benefits of hysterectomy.

Is there a role for progestin therapy in the treatment of atypical endometrial hyperplasia and endometrial cancer?

Atypical endometrial hyperplasia and endometrial cancer should be considered part of a continuum. The diagnosis remains uncertain as long as the uterus is in situ. For women who do not desire fertility, hysterectomy should be recommended for treatment of atypical endometrial hyperplasia because of the high risk of an underlying cancer. Women who desire to maintain fertility, whether they have a diagnosis of atypical endometrial hyperplasia or grade 1 endometrioid adenocarcinoma, may be treated with progestins in an attempt to reverse the lesion.

Progestational agents have been evaluated as a primary treatment modality of early grade 1 disease in women who wish to maintain their fertility or in those who are extremely poor operative candidates. Oral, parenteral, or intrauterine device delivery of progestin (72) has been successful, with response rates ranging from 58% to 100% (73–75). Although long-term outcomes are uncertain, the disease will likely recur in most patients. There is controversy about whether progestin should be prescribed continuously or cyclically, and these regimens are currently under investigation. Other hormonal

therapies have been reported to be effective but are less well studied (76).

Continued histologic monitoring is vital both to assure medication response and to exclude recurrence, which may approach 50% (73). Following therapy, patients should undergo serial complete intrauterine evaluation approximately every 3 months to document response. Progestin therapy may successfully reverse atypical endometrial hyperplasia as well as an early endometrial carcinoma; conception may then be attempted (76). A review of the literature found a 76% response rate for progestin therapy in 81 patients with a median age of 30.5 years (77). The median response time was 12 weeks, with a median treatment duration of 24 weeks. Of the 62 responders, 47 did not experience recurrence. Twenty patients became pregnant, and 12 required assisted reproductive technologies for conception.

▶ *What is the mode of treatment for patients with endometrial cancer and morbid obesity or other high-risk medical problems?*

Operative intervention should be considered for all women with uterine cancer; however, many of these women will have significant coexisting conditions that place them at higher risk of perioperative morbidity. Additionally, the staging procedure may predispose to some specific morbidities (eg, thromboembolism). Therefore, care for women with coexisting conditions should be individualized, with appropriate perioperative consultation sought. With disease-specific preoperative medical and intraoperative intervention undertaken, most of this population can undergo an appropriate surgical procedure.

Specialized long instrumentation is available for operative procedures in the obese patient; however, additional considerations such as incision placement (eg, upper abdomen), thromboembolic prophylaxis, and attention to recovery of postoperative pulmonary function are important in reducing morbidity. Panniculectomy has been advocated in women with a specific body habitus (large panniculus adiposus) (78).

Laparoscopy and vaginal hysterectomy may be of benefit for some patients. In a study of 125 elderly women (average age, 75 years), laparoscopic staging was successfully completed in 77.6% (79). The average hospital stay was 3 days, which compares favorably to the average 5.6-day hospital stay for total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and paraaortic lymphadenectomy. Thirteen patients underwent only vaginal hysterectomy because of medical conditions and were in the hospital an average of 2.1 days (79). In many cases, the ovaries are not removed to decrease the risk of requiring laparotomy. Conversion to laparotomy is advised when a) the uterus is too large to remove intact, b) adhesions or obesity impair visualization, and c) metastatic disease is encountered, to facilitate optimal surgical resection. Vaginal hysterectomy usually can be accomplished in even nulliparous obese patients by experienced surgeons (80).

▶ *What is the appropriate follow-up for women after treatment of endometrial cancer?*

The pattern of recurrent disease depends on the original sites of metastasis in patients with advanced stage disease, as well as the treatment received. In women in whom the disease is confined to the uterus, the types of recurrence depend on histologic cell type, lymph–vascular invasion, depth of invasion, and the use of radiation therapy. Investigators reported on 379 patients in whom recurrence sites were local in 50%, distant in 29%, and combined in 21% (81). The median time to detection of recurrence was 14 months for vaginal disease and 19 months for distant disease. Thirty-four percent of recurrences were diagnosed in the first year of follow-up, 76% were found within 3 years, and 10% did not recur until more than 5 years of follow-up. The recurrent disease was found on physical examination in 32% of cases, when the patients were asymptomatic. Only 37% reported vaginal bleeding. The patients who received postoperative radiotherapy had a decreased risk of vaginal recurrence (2–4%). In addition, they have few therapeutic options to treat recurrence and, therefore, would benefit less from frequent surveillance with cervical cytology screening and pelvic examinations for detection of recurrent disease.

The follow-up strategy in the nonirradiated patient is based on the knowledge that recurrent disease in the pelvis, particularly in the vaginal cuff, can be treated successfully with radiotherapy (37, 38, 82). Vaginal or pelvic recurrence can be detected and treated successfully in 68–88% of women who have not received radiation therapy (38, 82). Most studies cited monitored patients every 3–4 months for 2–3 years, then twice yearly with a speculum and rectovaginal examination at each visit. The use of cervical cytology testing for detection of recurrent disease is mostly anecdotal. The identification of asymptomatic distant recurrence is unlikely to have a survival benefit; treatment is primarily palliative chemotherapy. The use of periodic chest radiographic evaluation cannot be supported outside a research setting.

▶ *Which patients may benefit from referral to a gynecologic oncologist?*

Physicians with advanced training and expertise in the treatment of women with endometrial cancer, such as gynecologic oncologists, understand the nuances of uter-

ine cancer management, including the selection and sequencing of treatment modalities likely to benefit the individual patient. When it is practical and feasible, preoperative consultation with a physician with advanced training and demonstrated competence such as a gynecologic oncologist may be recommended. Consultation may be particularly beneficial in the following situations:

- The ability to completely and adequately surgically stage the patient is not readily available at the time of her initial procedure.
- Preoperative histology (grade 3, papillary serous, clear cell, carcinosarcoma) suggests a high risk for extrauterine spread.
- The final pathology test result reveals an unexpected endometrial cancer following hysterectomy performed for other indications.
- There is evidence of cervical or extrauterine disease.
- The pelvic washings are positive for malignant cells.
- Recurrent disease is diagnosed or suspected.
- Nonoperative therapy is contemplated.

Summary of Recommendations and Conclusions

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Most women with endometrial cancer should undergo systematic surgical staging, including pelvic washings, bilateral pelvic and paraaortic lymphadenectomy, and complete resection of all disease. Exceptions to this include young or perimenopausal women with grade 1 endometrioid adenocarcinoma associated with atypical endometrial hyperplasia and those at increased risk of mortality secondary to comorbidities.
- Women with atypical endometrial hyperplasia and endometrial cancer who desire to maintain their fertility may be treated with progestin therapy. Following therapy they should undergo serial complete intrauterine evaluation approximately every 3 months to document response. Hysterectomy should be recommended for women who do not desire future fertility.
- Patients with surgical stage I disease may be counseled that postoperative radiation therapy can reduce the risk of local recurrence, but the cost and toxicity should be balanced with the evidence that it does not improve survival or reduce distant metastasis.
- For those women who have not received radiation therapy, pelvic examinations every 3–4 months for 2–3 years, then twice yearly following surgical treatment of endometrial cancer are recommended for detection and treatment of recurrent disease.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Women who cannot undergo systematic surgical staging because of comorbidities may be candidates for vaginal hysterectomy.
- Only a physical examination and a chest radiograph are required for preoperative staging of the usual (type I endometrioid grade 1) histology, clinical stage I patient. All other preoperative testing should be directed toward optimizing the surgical outcome.

References

1. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30. (Level II-3)
2. Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, Heintz AP, et al. Carcinoma of the corpus uteri. Int J Gynaecol Obstet 2003;83(Suppl 1):79–118. (Level II-3)
3. Ries LA, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al, editors. SEER Cancer Statistics Review, 1975–2001, National Cancer Institute. Bethesda (MD): 2004. Available at: http://seer.cancer.gov/csr/1975_2001/. Retrieved November 9, 2004. (Level II-3)
4. Gershenson DM, McGuire WP, Gore M, Quinn MA, Thomas G, editors. Gynecologic cancer: controversies in management. Philadephia (PA): Elsevier; 2004. (Level III)
5. Boyd J. Hereditary gynecology cancer syndromes. In: Gershenson DM, McGuire WP, Gore M, Quinn MA, Thomas G, editors. Gynecologic cancer: controversies in management. Philadephia (PA): Elsevier; 2004. p. 833–45. (Level III)
6. Alberhasky RC, Connelly PJ, Christopherson WM. Carcinoma of the endometrium. IV. Mixed adenosquamous carcinoma. A clinical-pathological study of 68 cases with long-term follow-up. Am J Clin Pathol 1982;77: 655–64. (Level III)
7. Pekin T, Yildizhan B, Eren F, Pekin O, Yildizhan R. Adenocarcinoma, adenoacanthoma, and mixed adenosquamous carcinoma of the endometrium. Eur J Gynaecol Oncol 2001;22:151–3. (Level III)
8. Zaino RJ, Kurman R, Herbold D, Gliedman J, Bundy BN, Voet R, et al. The significance of squamous differentiation in endometrial carcinoma. Data from a Gynecologic Oncology Group study. Cancer 1991;68:2293–302. (Level II-2)
9. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. Cancer 1985;56:403–12. (Level III)

10. Trimble CL. Atypical endometrial hyperplasia: a tough call. Int J Gynecol Cancer 2005;15:401.

11. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst 2000;92:924–30. (Level III)

12. Maxwell GL, Risinger JI, Gumbs C, Shaw H, Bentley RC, Barrett JC, et al. Mutation of the PTEN tumor suppressor gene in endometrial hyperplasias. Cancer Res 1998;58: 2500–3. (Level III)

13. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol 1982;6:93–108. (Level III)

14. Christopherson WM, Alberhasky RC, Connelly PJ. Carcinoma of the endometrium: I. A clinicopathologic study of clear-cell carcinoma and secretory carcinoma. Cancer 1982;49:1511–23. (Level III)

15. Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 1991;40:55–65. (Level II-2)

16. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987;60(Suppl 8):2035–41. (Level II-2)

17. Boronow RC, Morrow CP, Creasman WT, Disaia PJ, Silverberg SG, Miller A, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. Obstet Gynecol 1984;63:825–32. (Level III)

18. Kodama S, Kase H, Tanaka K, Matsui K. Multivariate analysis of prognostic factors in patients with endometrial cancer. Int J Gynaecol Obstet 1996;53:23–30. (Level II-3)

19. Baak JP, Snijders WP, Van Diest PJ, Armee-Horvath E, Kenemans P. Confirmation of the prognostic value of the ECPI-1 score (myometrial invasion, DNA-ploidy and mean shortest nuclear axis) in FIGO stage I endometrial cancer patients with long follow-up. Int J Gynecol Cancer 1995;5:112–6. (Level II-2)

20. Ambros RA, Kurman RJ. Identification of patients with stage I uterine endometrioid adenocarcinoma at high risk of recurrence by DNA ploidy, myometrial invasion, and vascular invasion. Gynecol Oncol 1992;45:235–9. (Level II-3)

21. Gal D, Recio FO, Zamurovic D, Tancer ML. Lymphvascular space involvement—a prognostic indicator in endometrial adenocarcinoma. Gynecol Oncol 1991; 42:142–5. (Level II-3)

22. American Joint Committee on Cancer. AJCC cancer staging manual. 6th ed. New York (NY): Springer-Verlag; 2002. (Level III)

23. Patsner B, Tenhoppen DJ, Mann WJ. Use of serum CA-125 levels to monitor therapy of patients with advanced or recurrent endometrial carcinoma. Eur J Gynaecol Oncol 1989;10:322–5. (Level III)

24. Patsner B, Orr JW Jr, Mann WJ Jr. Use of serum CA 125 measurement in posttreatment surveillance of early-stage endometrial carcinoma. Am J Obstet Gynecol 1990;162: 427–9. (Level II-2)

25. Kilgore LC, Partridge EE, Alvarez RD, Austin JM, Shingleton HM, Noojin F 3rd, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol 1995; 56:29–33. (Level II-3)

26. Giradi F, Petru E, Heydarfadai M, Haas J, Winter R. Pelvic lymphadenectomy in the surgical treatment of endometrial cancer. Gynecol Oncol 1993;49:177–80. (Level III)

27. Chuang L, Burke TW, Tornos C, Marino BD, Mitchell MF, Tortolero-Luna G, et al. Staging laparotomy for endometrial carcinoma: assessment of retroperitoneal lymph nodes. Gynecol Oncol 1995;58:189–93. (Level II-3)

28. Arango HA, Hoffman MS, Roberts WS, DeCesare SL, Fiorica JV, Drake J. Accuracy of lymph node palpation to determine need for lymphadenectomy in gynecologic malignancies. Obstet Gynecol 2000;95:553–6. (Level II-3)

29. McMeekin DS, Lashbrook D, Gold M, Johnson G, Walker JL, Mannel R. Analysis of FIGO Stage III endometrial cancer patients. Gynecol Oncol 2001;81:273–8. (Level II-3)

30. Geisler JP, Geisler HE, Melton ME, Wiemann MC. What staging surgery should be performed on patients with uterine papillary serous carcinoma? Gynecol Oncol 1999;74:465–7. (Level II-3)

31. Orr JW Jr, Orr PF, Taylor PT. Surgical staging endometrial cancer. Clin Obstet Gynecol 1996;39:656–68. (Level III)

32. Kennedy AW, Austin JM Jr, Look KY, Munger CB. The Society of Gynecologic Oncologists Outcomes Task Force. Study of endometrial cancer: initial experiences. Gynecol Oncol 2000;79:379–98. (Level III)

33. Holub Z, Jabor A, Bartos P, Eim J, Urbanek S, Pivovarnikova R. Laparoscopic surgery for endometrial cancer: long-term results of a multicentric study. Eur J Gynaecol Oncol 2002;23:305–10. (Level II-2)

34. Eltabbakh GH, Shamonki MI, Moody JM, Garafano LL. Laparoscopy as the primary modality for the treatment of women with endometrial carcinoma. Cancer 2001;91: 378–87. (Level II-2)

35. Malur S, Possover M, Michels W, Schneider A. Laparoscopic-assisted vaginal versus abdominal surgery in patients with endometrial cancer—a prospective randomized trial. Gynecol Oncol 2001;80:239–44. (Level I)

36. Fanning J, Hoffman ML, Andrews SJ, Harrah AW, Feldmeier JJ. Cost-effectiveness analysis of the treatment for intermediate risk endometrial cancer: postoperative brachytherapy vs. observation. Gynecol Oncol 2004; 93:632–6. (Level III)

37. Straughn JM, Huh WK, Orr JW Jr, Kelly FJ, Roland PY, Gold MA, et al. Stage IC adenocarcinoma of the endometrium: survival comparisons of surgically staged patients with and without adjuvant radiation therapy. Gynecol Oncol 2003;89:295–300. (Level II-3)

38. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355:1404–11. (Level I)

39. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980;56:419–27. (Level II-2)

40. Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, van den Bergh AC, de Winter KA, Koper PC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. J Clin Oncol 2004;22:1234–41. (Level II-2)

41. Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC. Predictors of lymphatic failure in endometrial cancer. Gynecol Oncol 2002;84:437–42. (Level II-3)

42. Nelson G, Randall M, Sutton G, Moore D, Hurteau J, Look K. FIGO stage IIIC endometrial carcinoma with metastases confined to pelvic lymph nodes: analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy. Gynecol Oncol 1999;75:211–4. (Level II-3)

43. Fanning J. Treatment for early endometrial cancer. Cost-effectiveness analysis. J Reprod Med 1999;44:719–23. (Level III)

44. Childers JM, Spirtos NM, Brainard P, Surwit EA. Laparoscopic staging of the patient with incompletely staged early adenocarcinoma of the endometrium. Obstet Gynecol 1994;83:597–600. (Level III)

45. Mundt AJ, McBride R, Rotmensch J, Waggoner SE, Yamada SD, Connell PP. Significant pelvic recurrence in high-risk pathologic stage I–IV endometrial carcinoma patients after adjuvant chemotherapy alone: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 2001;50:1145–53. (Level II-3)

46. Ayhan A, Taskiran C, Celik C, Aksu T, Yuce K. Surgical stage III endometrial cancer: analysis of treatment outcomes, prognostic factors and failure patterns. Eur J Gynaecol Oncol 2002;23:553–6. (Level II-3)

47. Bristow RE, Zahurak ML, Alexander CJ, Zellars RC, Montz FJ. FIGO stage IIIC endometrial carcinoma: resection of macroscopic nodal disease and other determinants of survival. Int J Gynecol Cancer 2003;13:664–72. (Level II-3)

48. Rose PG, Cha SD, Tak WK, Fitzgerald T, Reale F, Hunter RE. Radiation therapy for surgically proven para-arotic node metastasis in endometrial carcinoma. Int J Radiat Oncol Biol Phys 1992;24:229–33. (Level II-3)

49. Husseinzadeh N, Shrake P, DeEulis T, Rowley K, Aron B. Chemotherapy and extended-field radiation therapy to para-aortic area in patients with histologically proven metastatic cervical cancer to para-artic nodes: a phase II pilot study. Gynecol Oncol 1994;52:326–31. (Level I)

50. Katz LA, Andrews SJ, Fanning J. Survival after multimodality treatment for stage IIIC endometrial cancer. Am J Obstet Gynecol 2001;184:1071–3. (Level II-2)

51. McMeekin DS, Tillmanns T. Endometrial cancer: treatment of nodal metastases. Curr Treat Options Oncol 2003;4:121–30. (Level III)

52. Memarzadeh S, Holschneider CH, Bristow RE, Jones NL, Fu YS, Karlan BY, et al. FIGO stage III and IV uterine papillary serous carcinoma: impact of residual disease on survival. Int J Gynecol Cancer 2002;12:454–8. (Level II-3)

53. Ayhan A, Taskiran C, Celik C, Yuce K, Kucukali T. The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer. Int J Gynecol Cancer 2002;12:448–53. (Level II-3)

54. Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol 2000;78:85–91. (Level II-3)

55. Chi DS, Welshinger M, Venkatraman ES, Barakat RR. The role of surgical cytoreduction in Stage IV endometrial carcinoma. Gynecol Oncol 1997;67:56–60. (Level II-3)

56. Goff BA, Goodman A, Muntz HG, Fuller AF Jr, Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol 1994;52:237–40. (Level II-3)

57. Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 2004;22:2159–66. (Level I)

58. Leminen A, Forss M, Lehtovirta P. Endometrial adenocarcinoma with clinical evidence of cervical involvement: accuracy of diagnostic procedures, clinical course, and prognostic factors. Acta Obstet Gynecol Scand 1995;74:61–6. (Level II-3)

59. Boente MP, Orandi YA, Yordan EL, Miller A, Graham JE, Kirshner C, et al. Recurrence patterns and complications in endometrial adenocarcinoma with cervical involvement. Ann Surg Oncol 1995;2:138–44. (Level II-3)

60. Maggino T, Romagnolo C, Landoni F, Sartori E, Zola P, Gadducci A. An analysis of approaches to the management of endometrial cancer in North America: a CTF study. Gynecol Oncol 1998;68:274–9. (Level III)

61. Mariani A, Webb MJ, Kenney GL, Calori G, Podratz KC. Role of wide/radical hysterectomy and pelvic lymph node dissection in endometrial cancer with cervical involvement. Gynecol Oncol 2001;83:72–80. (Level II-3)

62. Sartori E, Gadducci A, Landoni F, Lissoni A, Maggino T, Zola P, et al. Clinical behavior of 203 stage II endometrial cancer cases: the impact of primary surgical approach and of adjuvant radiation therapy. Int J Gynecol Cancer 2001;11:430–7. (Level II-3)

63. Reisinger SA, Staros EB, Mohiuddin M. Survival and failure analysis in stage II endometrial cancer using the revised 1988 FIGO staging system. Int J Radiat Oncol Biol Phys 1991;21:1027–32. (Level II-3)

64. Maingon P, Horiot JC, Fraisse J, Salas S, Collin F, Bone-Lepinoy MC, et al. Preoperative radiotherapy in stage I/II endometrial adenocarcinoma. Radiother Oncol 1996;39:201–8. (Level II-3)

65. Eltabbakh GH, Moore AD. Survival of women with surgical stage II endometrial cancer. Gynecol Oncol 1999; 74:80–5. (Level II-3)

66. Calvin DP, Connell PP, Rotmensch J, Waggoner S, Mundt AJ. Surgery and postoperative radiation therapy in stage II endometrial carcinoma. Am J Clin Oncol 1999;22: 338–43. (Level II-3)

67. Fishman DA, Roberts KB, Chambers JT, Kohorn EI, Schwartz PE, Chambers SK. Radiation therapy as exclusive treatment for medically inoperable patients with stage I and II endometrioid carcinoma with endometrium. Gynecol Oncol 1996;61:189–96. (Level II-2)

68. Kucera H, Knocke TH, Kucera E, Potter R. Treatment of endometrial carcinoma with high-dose-rate brachytherapy alone in medically inoperable stage I patients. Acta Obstet Gynecol Scand 1998;77:1008–12. (Level II-3)

69. Rouanet P, Dubois JB, Gely S, Pourquier H. Exclusive radiation therapy in endometrial carcinoma. Int J Radiat Oncol Biol Phys 1993;26:223–8. (Level II-3)

70. Knocke TH, Kucera H, Weidinger B, Holler W, Potter R. Primary treatment of endometrial carcinoma with high-dose rate brachytherapy: results of 12 years of experience with 280 patients. Int J Radiat Oncol Biol Phys 1997; 37:359–65. (Level II-3)

71. Kupelian PA, Eifel PJ, Tornos C, Burke TW, Delclos L, Oswald MJ. Treatment of endometrial carcinoma with radiation therapy alone. Int J Radiat Oncol Biol Phys 1993;27:817–24. (Level II-3)

72. Montz FJ, Bristow RE, Bovicelli A, Tomacruz R, Kurman RJ. Intrauterine progesterone treatment of early endometrial cancer. Am J Obstet Gynecol 2002;186:651–7. (Level III)

73. Gotlieb WH, Beiner ME, Shalmon B, Korach Y, Segal Y, Zmira N, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol 2003;102:718–25. (Level III)

74. Imai M, Jobo T, Sato R, Kawaguchi M, Kuramoto H. Medroxyprogesterone acetate therapy for patients with adenocarcinoma of the endometrium who wish to preserve the uterus—usefulness and limitations. Eur J Gynaecol Oncol 2001;22:217–20. (Level III)

75. Kaku T, Yoshikawa H, Tsuda H, Sakamoto A, Fukunaga M, Kuwabara Y, et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. Cancer Lett 2001;167:39–48. (Level III)

76. Wang CB, Wang CJ, Huang HJ, Hsueh S, Chou HH, Soong YK, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer 2002; 94:2192–8. (Level III)

77. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol 2004;95:133–8. (Level III)

78. Tillmanns TD, Kamelle SA, Abudayyeh I, McMeekin SD, Gold MA, Korkos TG, et al. Panniculectomy with simultaneous gynecologic oncology surgery. Gynecol Oncol 2001;83:518–22. (Level III)

79. Scribner DR Jr, Walker JL, Johnson GA, McMeekin SD, Gold MA, Mannel RS. Surgical management of early-stage endometrial cancer in the elderly: is laparoscopy feasible? Gynecol Oncol 2001;83:563–8. (Level II-3)

80. Bloss JD, Berman ML, Bloss LP, Buller RE. Use of vaginal hysterectomy for the management of stage I endometrial cancer in the medically compromised patient. Gynecol Oncol 1991;40:74–7. (Level II-3)

81. Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. Gynecol Oncol 1984;17:85–103. (Level II-2)

82. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study [published erratum appears in Gynecol Oncol 2004;94:241–2]. Gynecol Oncol 2004;92:744–51. (Level I)

The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and April 2005. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

ISSN 1099-3630

The American College of Obstetricians and Gynecologists
409 12th Street, SW
PO Box 96920
Washington, DC 20090-6920

12345/98765

Management of endometrial cancer. ACOG Practice Bulletin No. 65. American College of Obstetricians and Gynecologists. Obstet Gynecol 2005;106:413–25.