

# Neoplastic Diseases of the Uterus

## Endometrial Hyperplasia, Endometrial Carcinoma, and Sarcoma: Diagnosis and Management

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Endometrial carcinoma is the most common malignancy of the lower female genital tract in the United States. Approximately 42,000 new cases develop in the United States each year, according to recent figures (2009) from the American Cancer Society. This is approximately 1.3 times the frequency of ovarian cancer and almost four times the number of new cases of cervical cancer. However, 8,000 deaths occurred annually from uterine cancer, slightly more than for cervical cancer and much less than the estimated 14,000 for ovarian cancer. Overall, approximately 3 in 100 women in the United States will develop this disease during their lives.

This chapter reviews the clinical and pathologic features of **endometrial hyperplasias** and carcinomas, factors that contribute to the development of these diseases, and appropriate treatment methods. Sarcomas of the uterus and their clinical behavior and therapy are also discussed.

### EPIDEMIOLOGY

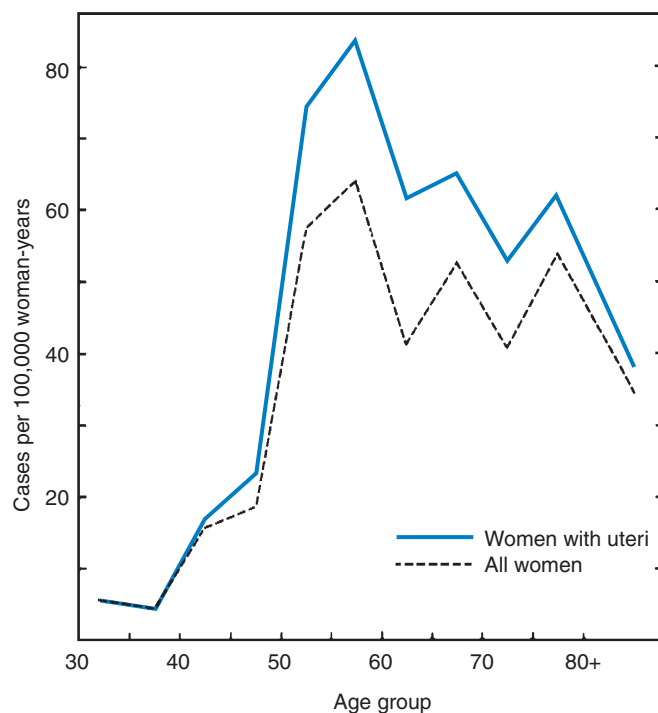
Adenocarcinoma of the endometrium affects women primarily in their perimenopausal and postmenopausal years and is most frequently diagnosed in those between the ages of 50 and 65 years. However, these cancers can also develop in young women during their reproductive years. Approximately 5% of cases are diagnosed in women younger than 40 and approximately 10% to 15% in women younger than 50. Women diagnosed under the age of 50 years are also at risk for having a synchronous ovarian cancer. [Figure 32-1](#) plots a typical age-incidence curve for cancers of the endometrium. The curve rises sharply after age 45 and peaks between 55 and 60 years; there is then a gradual decrease.

**Complex atypical hyperplasia** results from increased estrogenic stimulation of the endometrium and is a precursor to endometrioid endometrial cancer. Some endometrial cancers develop without previous hyperplasia. These non-estrogen-related carcinomas including serous histology tend to be poorly differentiated and clinically more aggressive (see later).

A number of factors increase the risk of developing endometrial carcinoma (and hyperplasia) ([Box 32-1](#)). Obesity is a strong risk factor for endometrial cancer. Women who are obese (body mass index [BMI] > 30) have a two- to threefold increased risk. The association is believed to be caused in part by increased

circulating estrogen levels that result from the conversion of androstenedione to estrone in the adipose tissue, decreased sex hormone-binding globulin, and other factors, including insulin resistance. Although more historical than clinically relevant, unopposed estrogen stimulation is strongly associated with endometrial cancer, increasing the risk by four to eight times for a woman using estrogen alone for menopausal replacement therapy. The risk increases with higher doses of estrogen (>0.625 mg conjugated estrogens), and more prolonged use but can be markedly reduced with the use of progestin (see Chapter 14, Menopause). Similarly, combination (progestin-containing) oral contraceptives decrease the risk. As noted by Grimes and Economy, combination oral contraceptives protect against endometrial cancer, with most studies showing a relative risk reduction to approximately 0.5. The protection begins after 1 year of use and lasts approximately 15 years after discontinuation. Other conditions leading to long-term estrogen stimulation of the endometrium, including the polycystic ovary syndrome (Stein-Leventhal syndrome) and the much more rare feminizing ovarian tumors, are also associated with increased risk of endometrial carcinoma.

Patients who receive the selective estrogen receptor modulator (SERM) tamoxifen are also at increased risk of developing endometrial carcinoma. In the National Surgical Adjuvant Bowel and Breast B-14 trial examining tamoxifen as adjuvant therapy in women with breast cancer, the risk of endometrial cancer was elevated 7.5-fold. This may be an overestimate because the risk of endometrial cancer in the control group was lower than expected. In the National Surgical Adjuvant Bowel and Breast P-1 trial examining tamoxifen as a chemopreventive agent, the risk of endometrial cancer was elevated 2.5-fold. Risk increased with duration of use. Most endometrial cancers that developed in tamoxifen users were of endometrioid histology and low **endometrial carcinoma grade** and **endometrial carcinoma stage**. However, high-grade endometrial cancers and sarcomas have also been reported in women taking tamoxifen. Screening strategies, including transvaginal ultrasound and office endometrial sampling, have been studied in this cohort. There is a high false-positive rate with transvaginal ultrasonography because tamoxifen causes subendometrial cyst formation, which makes the endometrial stripe appear abnormally thick. Barakat and colleagues have performed endometrial pipelle sampling on a large cohort of women taking tamoxifen.



**Figure 32-1** Incidence curve for carcinoma of the endometrium by age. (From Elwood JM, Cole P, Rothman KJ, Kaplan SD: Epidemiology of endometrial cancer. *J Natl Cancer Inst* 59:1055, 1977.)

#### Box 32-1 Endometrial Carcinoma Risk Factors

##### Increases the Risk

Unopposed estrogen stimulation  
 Unopposed menopausal estrogen replacement therapy (4-8×)  
 Menopause after 52 years (2.4×)  
 Obesity (2-5×)  
 Nulliparity (2-3×)  
 Diabetes (2.8×)  
 Feminizing ovarian tumors  
 Polycystic ovarian syndrome  
 Tamoxifen therapy for breast cancer

##### Diminishes the Risk

Ovulation  
 Progestin therapy  
 Combination oral contraceptives  
 Menopause before 49 years of age  
 Normal weight  
 Multiparity

They found very few cancers and concluded that women do not benefit from endometrial screening. Rather, women should be counseled that tamoxifen increases the risk of endometrial cancer, and all women on tamoxifen who have irregular vaginal bleeding (if premenopausal) or any vaginal bleeding (if postmenopausal) should undergo endometrial sampling or dilation and curettage (D&C).

Other factors increase the risk of endometrial cancer. Nulliparity is associated with a twofold increased risk in endometrial cancer. Diabetes increases the risk by 2.8-fold and has been found to be an independent risk factor. Hypertension

is often related to obesity and diabetes and is not considered an independent risk factor. In regard to racial factors, the incidence of endometrial cancer among white women is approximately twice the rate in black women. However, studies of Hill and coworkers have demonstrated that black women tend to develop a much higher percentage of poorly differentiated tumors. The National Cancer Database report by Partridge and colleagues has confirmed that black patients with a low income present at an advanced stage and have a poor survival compared with non-Hispanic whites. The difference in survival between blacks and non-Hispanic whites does not appear to be based solely on access to care issues, and there are likely biologic differences that account for the disparity in survival.

Lynch syndrome, or hereditary nonpolyposis colorectal cancer syndrome (HNPCC), is an autosomal dominant hereditary cancer susceptibility syndrome caused by a germline defect in a DNA mismatch repair gene (*MLH1*, *MSH2*, or *MSH6*). Women with Lynch syndrome have a 40% to 60% lifetime risk for developing endometrial cancer, a 40% to 60% lifetime risk of developing colon cancer, and a 12% lifetime risk of developing ovarian cancer. This contrasts sharply with the general population risk of 3% for endometrial cancer, 5% for colon cancer, and 1.7% risk of ovarian cancer. Endometrial cancers in Lynch syndrome can be of any histology and grade. Broaddus and Lu have reported that although most are early stage, approximately 25% are high grade, high stage, or poor histology. Given that there are few longitudinal cohort studies, screening recommendations for gynecologic cancers are based on expert opinion; these include annual endometrial biopsy and transvaginal ultrasound to evaluate the ovaries. Colonoscopy every 1 to 2 years has been shown to decrease mortality from colon cancer in Lynch syndrome. Schmeler has reported on the efficacy of prophylactic hysterectomy and salpingo-oophorectomy to decrease endometrial and ovarian cancer risk, and women with Lynch syndrome should be offered this option after childbearing is complete. Lynch syndrome is likely to account for approximately 2% of all endometrial cancers. Women with endometrial cancer and a family history of colon, endometrial, or ovarian cancer should be referred for genetic evaluation and colonoscopy. In addition, women who have a personal history of endometrial and colon cancers have a significant risk for Lynch syndrome and should be referred. Although synchronous endometrial and ovarian cancers are fairly common, Soliman and colleagues have estimated the risk of Lynch syndrome in this cohort to be less than 10%.

Investigators have begun to define the molecular alterations present in endometrial cancer. PTEN mutations are frequently seen in endometrioid endometrial cancer and have also been seen in complex endometrial hyperplasia. Microsatellite instability occurs in approximately 25% to 30% of all endometrial cancers and is the result of a germline mutation in DNA mismatch repair proteins (*MLH1*, *MSH2*, or *MSH6*) or, more frequently, from the somatic methylation of the *MLH1* promoter. In contrast to endometrioid endometrial cancers, **uterine papillary serous carcinomas** have a high frequency of p53 mutations. HER-2/neu amplification is seen in 10% to 20% of uterine papillary serous carcinomas and is likely associated with advanced stage and poor prognosis. Further studies will continue to elucidate our understanding of the molecular alterations of endometrial cancer.

## ENDOMETRIAL HYPERPLASIA

The normal morphologic changes that occur in the endometrium during the menstrual cycle are reviewed in Chapter 4, Reproductive Endocrinology. Endometrial hyperplasia is believed to result from an excess of estrogen or an excess of estrogen relative to progesterin, such as occurs with anovulation. Kurman and Norris have introduced terminology that has been adopted by the World Health Organization to describe endometrial hyperplasias and their premalignant potential. There are two important separate categories, atypical hyperplasia and hyperplasia without atypia. In these categories, two subgroups are recognized, **simple hyperplasia** and complex hyperplasia (**complex hyperplasia without atypia** and **complex atypical hyperplasia** (Table 32-1).

### CATEGORIES

#### Simple Hyperplasia

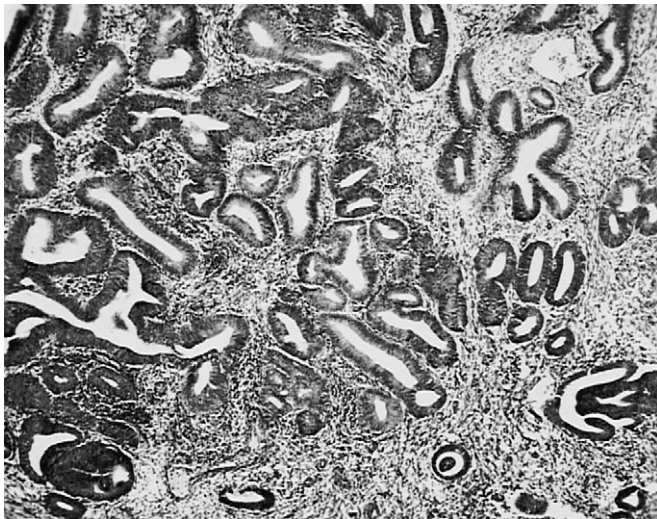
This is a term that defines an endometrium with dilated glands that may contain some outpouching and abundant endometrial stroma (Fig. 32-2). The term *cystic hyperplasia* has been used to describe dilation of the endometrial glands, which often occurs in a hyperplastic endometrium in a menopausal or postmenopausal woman (cystic atrophy). It is considered to be weakly premalignant.

#### Complex Hyperplasia (Without Atypia)

In this condition, glands are crowded, with very little endometrial stroma and a very complex gland pattern and outpouching formations (Fig. 32-3). In traditional terminology, this is a

**Table 32-1** World Health Organization Classification of Endometrial Hyperplasias

Simple hyperplasia
Complex hyperplasia
Atypical simple hyperplasia
Atypical complex hyperplasia



**Figure 32-2** Benign simple hyperplasia. (From Kurman RJ, Kaminski PF, Norris HJ: Behavior of endometrial hyperplasia: A long-term study of “untreated” hyperplasias in 170 patients. Cancer 56:403, 1985.)



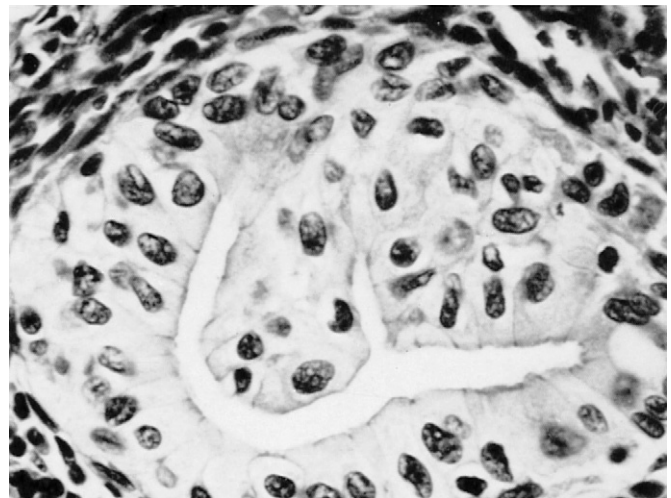
**Figure 32-3** Complex hyperplasia characterized by crowded back-to-back glands with complex outlines. (From Kurman RJ, Kaminski PF, Norris HJ: Behavior of endometrial hyperplasia: A long-term study of “untreated” hyperplasias in 170 patients. Cancer 56:403, 1985.)

variant of adenomatous hyperplasia with moderate to severe degrees of architectural atypia but with no cytologic atypia. These hyperplasias have a low malignant potential.

#### Complex Atypical Hyperplasia

This term refers to hyperplasias that contain glands with cytologic atypia and are considered premalignant. There is an increase in the nuclear-to-cytoplasmic ratio, with irregularity in the size and shape of the nuclei (Fig. 32-4). Cytologic atypia occurs primarily with complex hyperplasia. Simple hyperplasia with atypia is rarely seen. Complex atypical hyperplasia has the greatest malignant potential.

A study from the Gynecologic Oncology Group has shed light on the difficulty of making the diagnosis of complex atypical hyperplasia. In this large prospective study, one third of cases



**Figure 32-4** Severely atypical hyperplasia (complex) of the endometrium with marked irregularity of nuclei ( $\times 720$ ). (From Welch WR, Scully RE: Precancerous lesions of the endometrium. Hum Pathol 8:503, 1977.)



**Table 32-2** Endometrial Hyperplasia Follow-Up

Type	No. of Patients	Age Range (Mean)	Regressed*	Progressed to Carcinoma		Follow-Up (yr)
				No. of Cases	Mean (yr)	
Simple hyperplasia <sup>†</sup> pregnancies	93	17-71 (42)	74 (80%)	1	11	1-10
Complex hyperplasia <sup>‡</sup> pregnancies	29	20-67 (39)	23 (79%)	1	8.3	2-3
Atypical hyperplasia pregnancies	48	20-70 (40)	28 (58%)	11	4.1	1-3
Atypical simple hyperplasia	13		9	1		
Atypical complex hyperplasia	35		20	10		

\*A total of 34 patients with simple hyperplasia, 7 with complex hyperplasia, and 15 with atypical hyperplasia had no further therapy.

<sup>†</sup>Benign proliferation of the glands.

<sup>‡</sup>Greater crowding of glands, no cytologic atypia present.

Adapted from Kurman RJ, Kaminski PF, Norris HJ: The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. *Cancer* 56:403, 1985; and Kurman RJ, Norris HJ: Endometrial hyperplasia and related cellular changes. In Kurman RJ (ed): *Blaustein's Pathology of the Female Genital Tract*, 4th ed. New York, Springer-Verlag, 1994.

with a diagnosis of complex atypical hyperplasia were reproduced when evaluated by a gynecologic pathologist who was part of the study. However, one third of the cases were deemed to be less than complex atypical hyperplasia by the study pathologists and one third were greater than complex atypical hyperplasia—that is, they were considered endometrial cancers. Clinicians may benefit by consulting directly with the pathologist interpreting the endometrial histologic picture. The difficult distinction between various diagnostic categories makes this communication important.

### NATURAL HISTORY

The rate at which endometrial hyperplasia progresses to endometrial carcinoma has not been accurately determined. Studies addressing this have been retrospective, based on samples obtained from D&C specimens at a single institution, and therefore are not necessarily generalizable. Kurman and associates have studied 170 patients with endometrial hyperplasia diagnosed by D&C at least 1 year before hysterectomy. **Table 32-2** shows the results of their study. Overall, complex atypical hyperplasias had the highest risk of progression to carcinoma. Simple hyperplasia had a 1% rate of progression to cancer, complex hyperplasia without atypia had a 3% rate of progression to cancer, and complex atypical hyperplasia had a 29% rate of progression to cancer. In addition to concern about progression to cancer, a Gynecologic Oncology Group (GOG) study has shown that 40% of women with complex atypical hyperplasia have endometrial cancer in their hysterectomy specimen. This high rate of cancer suggests that complex atypical hyperplasia may frequently be present with low-grade endometrial cancer and that endometrial sampling, whether by D&C or by office endometrial biopsy, may not identify an endometrial cancer when admixed with a complex atypical hyperplasia. Clearly, there is a spectrum of histology that makes a definitive diagnosis of complex atypical hyperplasia difficult; the clinician must be aware of this when planning treatment strategies.

### DIAGNOSIS AND ENDOMETRIAL SAMPLING

Abnormal vaginal bleeding is the most frequent symptom of endometrial hyperplasia. In younger patients, hyperplasia may develop during anovulatory cycles and may even be detected after prolonged periods of oligomenorrhea or amenorrhea.

It can occur at any time during the reproductive years but is most common with abnormal bleeding in the perimenopausal period. Premenopausal women with irregular vaginal bleeding and postmenopausal women with any vaginal bleeding should be evaluated with an office endometrial sampling or a D&C. Office sampling instruments, such as a thin plastic pipelle, are introduced through the cervical os into the endometrial cavity and can provide accurate information. Many patients tolerate office endometrial sampling without an analgesic agent, but paracervical block can be an effective anesthetic aid, particularly in nulliparous women. Some patients benefit from an oral nonsteroidal anti-inflammatory drug (NSAID) taken approximately 30 minutes before biopsy.

Transvaginal ultrasonography has been evaluated as an adjunct for the diagnosis of endometrial hyperplasia and cancer. These studies have been performed in different populations, including asymptomatic postmenopausal women, women taking tamoxifen, and women presenting with postmenopausal bleeding. Langer and associates, in a study of 448 asymptomatic postmenopausal women, have found that a threshold of 5-mm endometrial thickness has only a 9% predictive value for detecting endometrial abnormalities. Its greater use was eliminating the diagnosis of neoplasia for those with thickness less than 5 mm (negative predictive value of 99%). These findings were confirmed in a literature review by Smith-Bindman and colleagues, who found that 96% of women with carcinoma had an abnormal ultrasound scan (endometrial thickness >5 mm). Conversely, 8% of postmenopausal women with an abnormal scan had no histologic abnormality, and the percentage grew to 23% for those on hormone replacement therapy. However, both these studies were conducted in postmenopausal asymptomatic women.

Cecchini and coworkers have performed biopsies on 108 postmenopausal patients on long-term tamoxifen with endometrial thickness more than 6 mm. One case of hyperplasia and one of carcinoma were found, and most patients had atrophic endometrium. The authors concluded that the false-positive rate of transvaginal ultrasonography in this population was too high to warrant its use as a screening modality; they recommended using irregular vaginal bleeding as an indication for endometrial sampling. Similarly, Love and associates have found that endometrial thickness is not necessarily a useful guide for biopsy in tamoxifen. The study by Barakat and colleagues found that routine screening with transvaginal ultrasonography was not of

value, and they concluded that sampling should be done if the patient experiences bleeding.

In postmenopausal women with any vaginal bleeding, Gull and colleagues have found that an endometrial stripe less than 4 mm has a 100% negative predictive value. A finding of endometrial thickness less than 4 mm is a reasonable predictor of lack of endometrial pathology, even in a postmenopausal woman with bleeding. However, persistent vaginal bleeding should lead to endometrial sampling, regardless of the ultrasound findings.

Endometrial ablation is sometimes undertaken to control severe uterine bleeding (see Chapter 37, Abnormal Uterine Bleeding). However, pathologic evaluation of the endometrium should be performed before ablation to rule out an underlying endometrial hyperplasia or cancer.

## TREATMENT

The therapy for endometrial hyperplasia depends on the woman's age and degree of atypia. For women with simple hyperplasia or complex hyperplasia without atypia, the risk of developing endometrial cancer is low, 1% and 3%, respectively. A diagnostic D&C can also be therapeutic, and progestins or combination oral contraceptive agents will likely be effective.

For complex atypical hyperplasia, the risk of developing endometrial cancer may be 29% and, as noted, a concurrent endometrial cancer may be present. Women who desire preservation of childbearing function are treated with high-dose progestin therapy, usually megestrol acetate 40 mg three or four times daily. The woman should have long-term follow-up and periodic sampling, the first at 3 months and at least every 6 months thereafter (Fig. 32-5A). In these patients, the risk factors that led to the development of complex atypical hyperplasia are likely to remain. Therefore, once the complex atypical hyperplasia is cleared, consideration should be given to periodic progestin treatment or oral contraception until the woman chooses to attempt pregnancy.

Studies have shown that younger patients with chronic anovulation and hyperplasia who desire children may also be treated by induction of ovulation with clomiphene citrate (Clomid) (see Chapter 41, Infertility). Weight reduction for very obese patients is also advised.

For older patients with complex atypical hyperplasia, the risk of carcinoma may be increased. Kurman and associates studied the uteri of patients after curettage had been performed, and atypical hyperplasia was found in the curettages. In their study, 11% of those younger than 35, 12% of those 36 to 54, and 28% of those older than 55 years with atypical hyperplasia were found to have carcinoma in their uterus. Thus, older patients with moderate or severe atypical hyperplasia generally require hysterectomy. In addition, those who fail progestin therapy, and especially those with severe cytologic atypia, should also be considered for hysterectomy (see Fig. 32-5B). If hysterectomy is not medically advisable, long-term high-dose progestin therapy can be used (megestrol acetate, 40 to 160 mg/day, or its equivalent, depending on the endometrial response). Current studies are being performed to evaluate the role of the progesterone-containing intrauterine device. Periodic sampling of the endometrium is also performed. Figure 32-5 displays a flow chart guide to the management of endometrial hyperplasia. It is important to emphasize that the diagnoses are not distinct; these proliferative disorders are a continuum from mild abnormalities to malignant change.

## ENDOMETRIAL CARCINOMA

### SYMPTOMS, SIGNS, AND DIAGNOSIS

Postmenopausal bleeding and abnormal premenopausal and perimenopausal bleeding are the primary symptoms of endometrial carcinoma. The diagnosis of endometrial carcinoma is established by histologic examination of the endometrium. Initial diagnosis can frequently be made on an outpatient basis, with an office endometrial biopsy. If endometrial carcinoma is found, endocervical curettage may be performed to rule out invasion of the endocervix. A routine cytologic examination (Pap smear) from the exocervix, which screens for cervical neoplasia, detects endometrial carcinoma in only approximately 50% of cases.

If adequate outpatient evaluation cannot be obtained or if the diagnosis or cause of the abnormal bleeding is not clear from the tissue obtained, a hysteroscopy and fractional D&C should be performed. The endocervix is first sampled to rule out cervical involvement by endometrial cancer, hysteroscopy is done to visualize the endometrial cavity, and then a complete uterine curettage is performed.

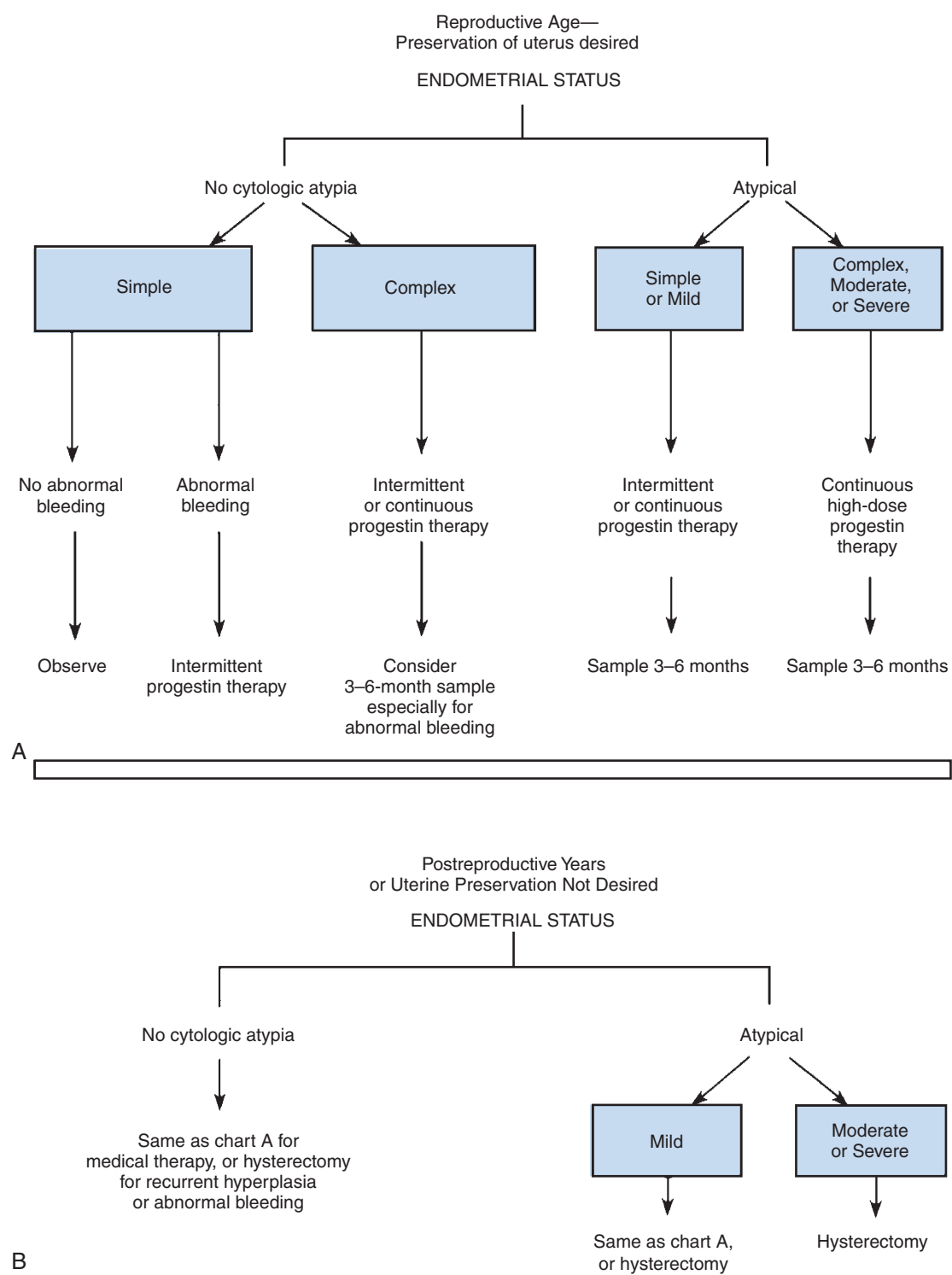
### HISTOLOGIC TYPES

The various types are listed in Box 32-2. Figure 32-6 illustrates typical adenocarcinomas of the endometrium and demonstrates varying degrees of differentiation (G1, well differentiated; G2, intermediate differentiation; G3, poorly differentiated). Grading is determined by the percentage of solid components found in the tumor; grade 1 has less than 5% solid components, grade 2 has 6% to 50% solid components, and grade 3 has more than 50% solid components.

Squamous epithelium commonly coexists with the glandular elements of endometrial carcinoma. Previously, the term *adenocanthoma* was used to describe a well-differentiated tumor and *adenosquamous carcinoma* to describe a poorly differentiated carcinoma with squamous elements. More recently, the term *adenocarcinoma with squamous elements* has been used with a description of the degree of differentiation of the glandular and squamous components. Zaino and colleagues, in a GOG study of 456 cases with squamous elements, have shown that prognosis is related to the grade of the glandular component and degree of myometrial invasion. They suggested the term *adenocarcinoma with squamous differentiation*, which has been generally adopted.

Uterine papillary serous carcinomas are a highly virulent and uncommon histologic subtype of endometrial carcinomas (5% to 10%). These tumors histologically resemble papillary serous carcinomas of the ovary (Fig. 32-7). Slomovitz and associates have evaluated 129 patients with uterine papillary serous carcinoma (UPSC) and found a high rate of extrauterine disease, even in cases without myometrial invasion. They recommended a thorough operative staging (see next section) in all cases of these tumors because of the high risk of extrauterine disease, even in cases admixed with other histologic types (endometrial and/or clear cell).

**Clear cell carcinomas** of the endometrium are less common (<5%). Histologically, they resemble clear cell adenocarcinomas of the ovary, cervix, and vagina. Clear cell tumors tend to develop in postmenopausal women and carry a prognosis much worse than typical endometrial adenocarcinomas. Survival rates



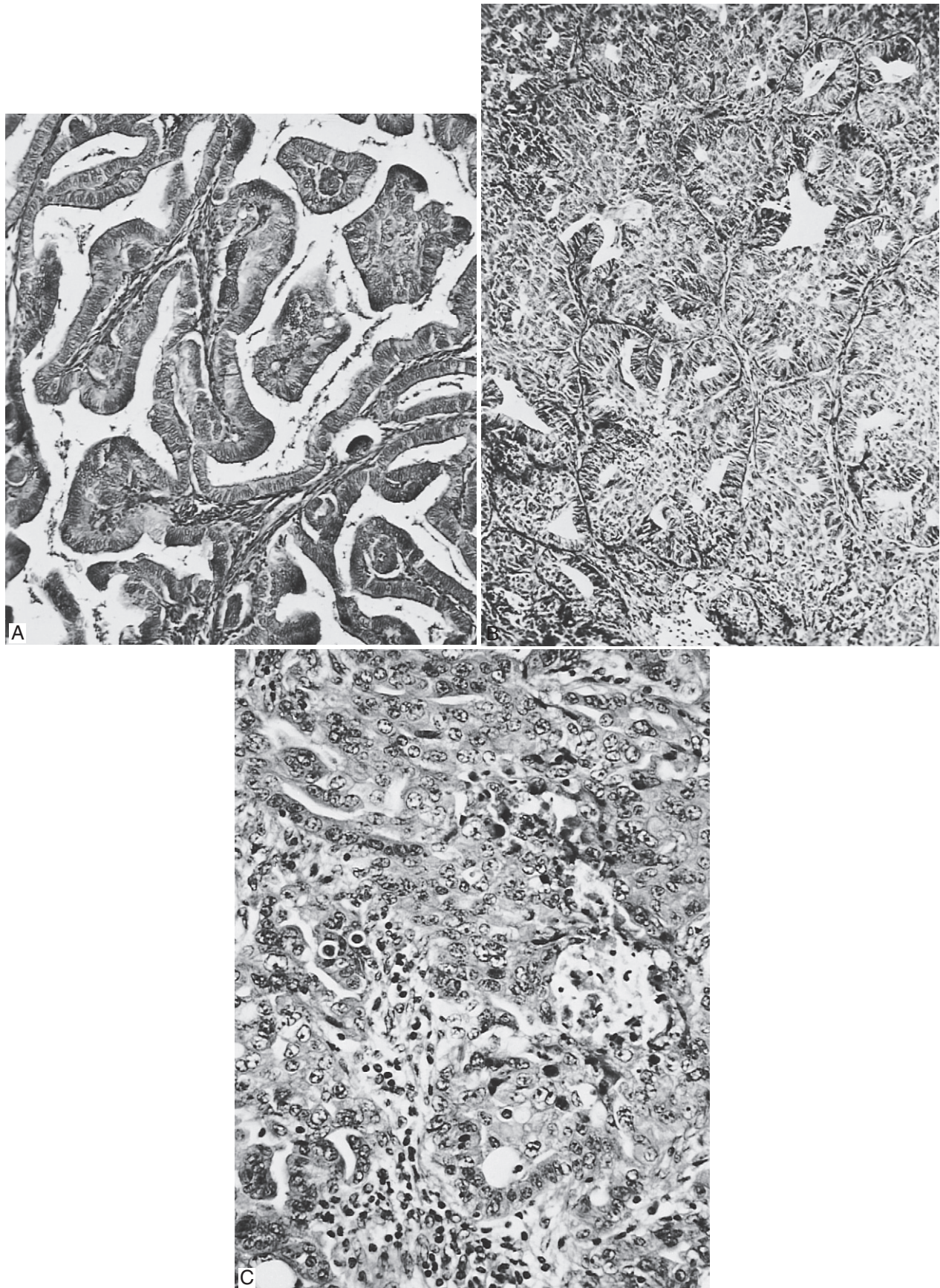
**Figure 32-5** Schematic diagram of endometrial hyperplasia management for reproductive (A) and postreproductive (B) patients.

Box 32-2 Endometrial Primary Adenocarcinomas	
Typical endometrioid adenocarcinoma	Serous carcinoma
Adenocarcinoma with squamous elements*	Secretory carcinoma
Clear cell carcinoma	Mucinous carcinoma
	Squamous carcinoma

\*Previously termed *adenocanthoma* or *adenosquamous carcinoma*.

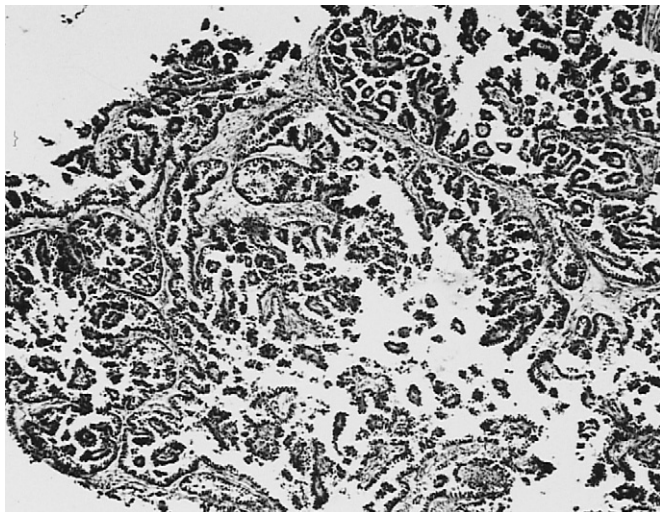
of 39% to 55% have been reported, much less than the 65% or better usually recorded for endometrial carcinoma. Abeler and Kjorstad have reviewed 97 cases and noted the best prognosis (90%) for those without myometrial invasion. Patients whose tumors had vascular invasion experienced a 15% 5-year survival. Carcangiu and Chambers have reviewed 29 cases and found 5-year survival rates for stages I and II of 72% and 59%, respectively.





**Figure 32-6** **A**, Well-differentiated adenocarcinoma of the endometrium. The glands are confluent ( $\times 130$ ). **B**, Moderately differentiated adenocarcinoma of the endometrium. The glands are more solid, but some lumens remain ( $\times 100$ ). **C**, Poorly differentiated adenocarcinoma of the endometrium. The epithelium shows solid proliferation with only a rare lumen ( $\times 100$ ). (From Kurman RJ, Norris HJ: Endometrial neoplasia: Hyperplasia and carcinoma. In Blaustein A [ed]: Pathology of the Female Genital Tract, 2nd ed. New York, Springer-Verlag, 1982.)





**Figure 32-7** Serous carcinoma characterized by a complex papillary architecture resembling serous carcinoma of the ovary. (From Kurman RJ: Blaustein's Pathology of the Female Genital Tract, 3rd ed. New York, Springer-Verlag, 1987.)

STAGING

In 2009, a revised International Federation of Gynecology and Obstetrics (FIGO) surgical staging classification was introduced (Table 32-3). The surgical staging was modified to define clinically relevant risk strata better based on the FIGO Annual Report and other supporting publications.

PROGNOSTIC FACTORS

Many variables affect the behavior of endometrial adenocarcinomas. These can be conveniently divided into clinical and pathologic factors. The clinical determinants are patient age at

diagnosis, race, and clinical tumor stage. The pathologic determinants are tumor grade, histologic type, tumor size, depth of myometrial invasion, microscopic involvement of vascular spaces in the uterus by tumor, and spread of tumor outside the uterus to the retroperitoneal lymph nodes, peritoneal cavity, or uterine adnexa.

Clinical Factors

Older patients have tumors of a higher stage and grade when compared with younger patients. White patients have a higher survival rate than black patients, a finding partially explained by higher stage and higher grade tumors in black women. In addition, black women are more likely to develop UPSC. The 10-year survival of 136 black patients in the series of Aziz and coworkers was 40% compared with 72% for 135 white patients.

Pathologic Factors

Tumor stage is a well-recognized prognostic factor for endometrial carcinoma (Table 32-4). The results reflect a combination of clinical and operative staging because it was at the midpoint of the reporting period, 1988, when staging changed from a clinical to surgical staging system. Fortunately, most cases are diagnosed in stage I, which provides a favorable prognosis.

The histologic grade of the tumor is a major determinant of prognosis. Endometrial carcinomas are divided into three grades—grade 1, well differentiated; grade 2, intermediate differentiation; and grade 3, poorly differentiated. Figure 32-8 shows the survival of 895 patients studied by the GOG that relates endometrial carcinoma survival to tumor grade and demonstrates the worsening of prognosis with advancing grade.

The histologic type of the endometrial carcinoma (Fig. 32-9) is also related to prognosis, with the best prognosis associated with endometrioid adenocarcinomas, as well as better differentiated tumors with or without squamous elements, and secretory carcinomas. Approximately 80% of all endometrial carcinomas fall into the favorable category. Poor prognostic histologic types are papillary serous carcinomas, clear cell carcinomas, and poorly differentiated carcinomas with or without squamous elements, as noted.

The degree of myometrial invasion correlates with the risk of tumor spread outside the uterus, but, in general, the higher grade and higher stage tumors have the deepest myometrial penetration (Fig. 32-10). The importance of tumor grade and myometrial invasion is also illustrated by a study of the relationship to their spread to the retroperitoneal pelvic and para-aortic lymph nodes. Studies of 142 patients by Schink and colleagues have indicated that tumor size is also prognostic. Only 4% of those with

**Table 32-3** Revised FIGO Staging for Endometrial Cancer (Adopted 2009)

Stage*	Characteristic
I	Tumor confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumor invades cervical stroma, but does not extend beyond the uterus†
III	Local and/or regional spread of the tumor
IIIA	Tumor invades serosa of the corpus uteri and/or the adnexae‡
IIIB	Vaginal and/or parametrial involvement§
IIIC	Metastases to pelvic and/or para-aortic lymph nodes†
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastasis
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal and/or inguinal lymph nodes

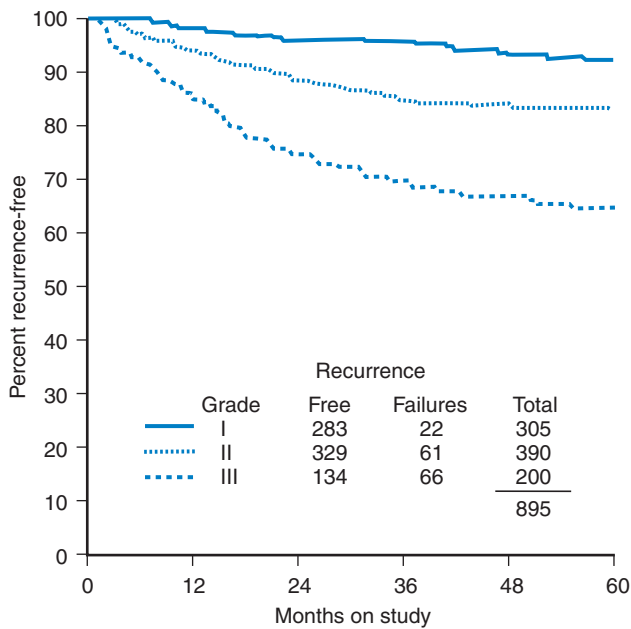
\*G1, G2, or G3.  
†Endocervical glandular involvement only should be considered as stage I and no longer as stage II.  
‡Positive cytology has to be reported separately without changing the stage.  
Adapted from Pecorelli S: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 105:103, 2009.

**Table 32-4** Carcinoma of the Corpus Uteri\*

Stage	5-Year Survival Rate (%)
IA	90.9
IB	88.2
IC	81.0
II	71.6
III	51.4
IV	8.9

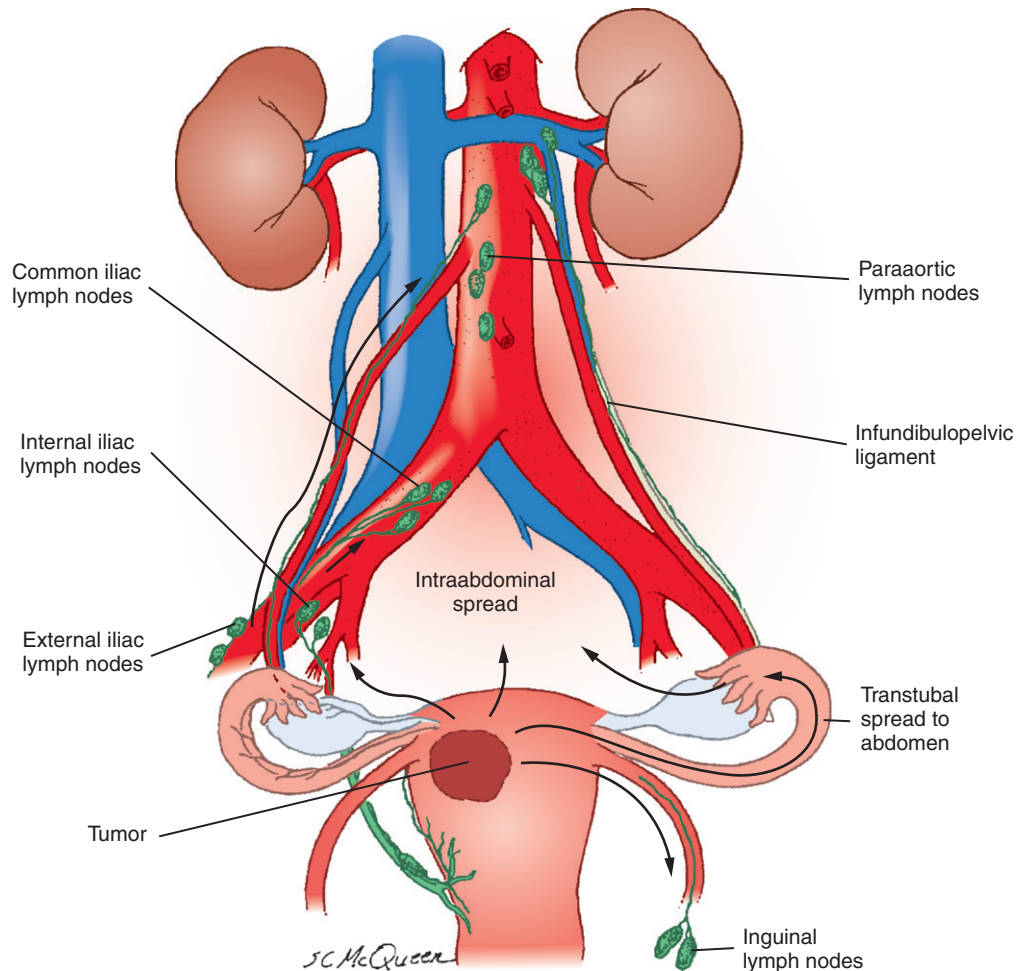
\*Patients treated in 1990-1992, survival by 1988 FIGO surgical stage, N = 5562. Adapted from Pecorelli S, Creasman WT, Pettersson F, et al: FIGO Annual Report on the Results of Treatment in Gynaecological Cancer, vol 23. Milan, Italy, International Federation of Gynecology and Obstetrics, 1998, pp 75-102.





**Figure 32-8** Recurrence-free interval by histologic grade. (Adapted from Morrow CP, Bundy BN, Kurman RJ, et al: Relationship between surgical-pathologic risk factors and outcome in clinical stage I and II carcinoma of the endometrium: A Gynecologic Oncology Group study. *Gynecol Oncol* 40:55, 1991.)

**Figure 32-9** Spread of endometrial carcinoma. The major pathways of tumor spread are illustrated (see text).

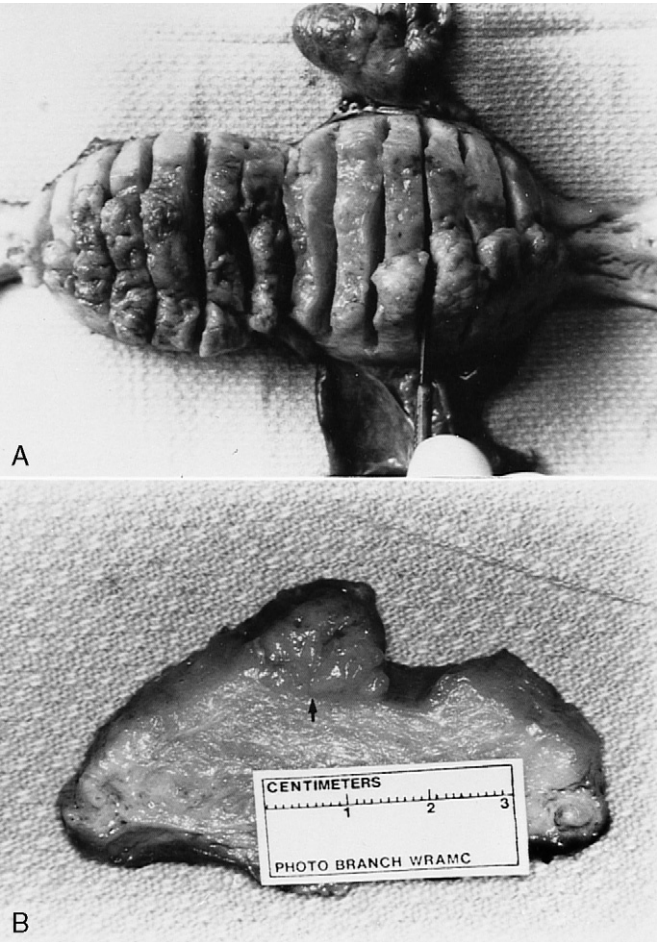


tumors 2 cm or smaller had lymph node metastases. The rate increased to 15% for those with tumors larger than 2 cm to 35% when the entire endometrial cavity was involved. [Table 32-5](#) summarizes the clinical and pathologic factors affecting outcome in early-stage tumors.

Peritoneal cytology has been studied as a prognostic factor and the results are conflicting. In a study of 567 surgical stage I cases, Turner and associates found that positive peritoneal cytology was an independent prognostic factor. In contrast, Grimshaw and coworkers evaluated 322 clinical stage I cases and found that positive peritoneal cytology was an adverse prognostic factor, but they did not find it to be an independent risk factor when other variables were considered. More recently, Kadar and associates and Lurain and colleagues have noted that positive peritoneal cytology is associated primarily with adverse features such as extrauterine disease and that therapy (see later) for positive peritoneal cytology as an isolated finding does not appear to improve survival. In the revised FIGO surgical staging (2009), positive cytology is no longer classified as stage IIIA.

#### Patterns of Spread of Endometrial Carcinoma

Plentl and Friedman have noted four major channels of lymphatic drainage from the uterus that serve as sites for extrauterine spread of tumor: (1) a small lymphatic branch along the round ligament that runs to the inguinal femoral nodes; (2) branches from the tubal and (3) ovarian pedicles (infundibulopelvic



**Figure 32-10** **A**, Technique for intraoperative assessment of the depth of myometrial invasion. **B**, Cross section of uterine wall demonstrating superficial myometrial invasion. The arrow shows the tumor-myometrial junction. (From Doering DL, Barnhill DR, Weiser EB, et al: Intraoperative evaluation of depth of myometrial invasion in stage I endometrial adenocarcinoma. *Obstet Gynecol* 74:930, 1989.)

ligaments), which are large lymphatics that drain into the para-aortic nodes; and (4) the broad ligament lymphatics that drain directly to the pelvic nodes. The pelvic and para-aortic node drainage sites (2, 3, and 4) are the most important clinically. In addition, direct peritoneal spread of tumor can occur through the uterine wall or via the lumen of the fallopian tube. Clinically, therefore, the clinician must assess the retroperitoneal nodes, peritoneal cavity, and uterine adnexa for the spread of endometrial carcinoma (see Fig. 32-9).

Extensive studies by the GOG have elucidated the frequency of lymph node metastases in endometrial carcinoma and the pathologic factors that modify this risk in stage I disease. Tumor grade, size of the uterus, and degree of myometrial invasion were studied. Table 32-6 illustrates the frequency of lymph node metastases according to uterine size and tumor grade. There are differences in the proportion of positive nodes between stages IB and IA (pre-1988 staging) cases, as well as tumor grade. Table 32-7 shows the effects of tumor grade and depth of myometrial invasion. The frequency of nodal involvement becomes much greater with higher grade tumors and with greater depth of myometrial invasion. The risk of lymph node involvement appears to be negligible

**Table 32-5** Surgical Stage I and II Tumors: Proportional Hazards Modeling of Relative Survival Time

Variable	Regression Coefficient	Relative Risk	Significance Test* (P value)
Endometrioid			
Grade 1	—	1.0	—
Grade 2	0.28	1.3	2.7 (0.1)
Grade 3	0.56	1.8	
Endometrioid with squamous differentiation			
Grade 1	0.20	1.2	
Grade 2	−0.01	1.0	0.3 (0.6)
Grade 3	0.22	0.8	
Villoglandular			
Grade 1	−4.91	0.01	
Grade 2	−0.59	0.5	10.4 (0.001)
Grade 3	3.73	41.9	
Myometrial invasion			
Endometrium only	—	1.0	
Superficial	0.39	0.5	
Middle	1.20	3.3	19.6 (0.0002)
Deep	1.53	4.6	
Age	0.17	—	
Age <sup>2</sup>	−0.000837	—	20.7 (0.0001)
45 (arbitrary reference)	—	1.0	
55	0.85	2.3	
65	1.52	4.6	
75	2.03	7.6	
Vascular space involvement	0.32	1.4	1.2 (0.3)

\*Wald  $\chi^2$  test.  
P value for grading is for overall grade within cell type.  
Modified from Zaino RJ, Kurman RJ, Diana KL, Morrow CP: Pathologic models to predict outcome for women with endometrial adenocarcinoma. *Cancer* 77:1115, 1996.

**Table 32-6** Grade, Depth of Myometrial Invasion, and Node Metastasis: Stage I

Depth of Invasion	Pelvic		
	G1 (n = 180)	G2 (n = 288)	G3 (n = 153)
<b>Pelvic</b>			
Endometrium only (n = 86)	0 (0%)	1 (3%)	0 (0%)
Inner (n = 281)	3 (3%)	7 (5%)	5 (9%)
Middle (n = 115)	0 (0%)	6 (9%)	1 (4%)
Deep (n = 139)	2 (11%)	11 (19%)	23 (34%)
<b>Aortic</b>			
Endometrium only (n = 86)	0 (0%)	1 (3%)	0 (0%)
Inner (n = 281)	1 (1%)	5 (4%)	2 (4%)
Middle (n = 115)	1 (5%)	0 (0%)	0 (0%)
Deep (n = 139)	1 (6%)	8 (14%)	15 (23%)

G, grade.  
Adapted from Creasman WT, Morrow CP, Bundy BN, et al: Surgical pathologic spread patterns of endometrial cancer. *Cancer* 60:2035, 1987.

**Table 32-7** FIGO Staging and Nodal Metastasis

Staging	Metastasis	
	Pelvic	Aortic
IA G1 ( <i>n</i> = 101)	2 (2%)	0 (0%)
G2 ( <i>n</i> = 169)	13 (8%)	6 (4%)
G3 ( <i>n</i> = 76)	8 (11%)	5 (7%)
IB G1 ( <i>n</i> = 79)	3 (4%)	3 (4%)
G2 ( <i>n</i> = 119)	12 (10%)	8 (7%)
G3 ( <i>n</i> = 77)	20 (26%)	12 (16%)

FIGO, International Federation of Gynecology and Oncology; G, grade.  
From Creasman WT, Morrow CP, Bundy BN, et al: Surgical pathologic spread patterns of endometrial cancer. *Cancer* 60:2035, 1987.

**Table 32-8** Risk Factors for Nodal Metastases: Stage I

Factor	Pelvic	Aortic
Low risk—grade 1, endometrium only, no intraperitoneal spread	0/44 (0%)	0/44 (0%)
Moderate risk, grade 2 or 3, invasion to middle third	15/268 (6%)	6/268 (2%)
High risk—invasion to outer third	21/116 (18)	17/118 (15%)

Adapted from Creasman WT, Morrow CP, Bundy BN, et al: Surgical pathologic spread patterns of endometrial cancer. *Cancer* 60:2035, 1987.

for endometrial carcinoma involving only the endometrium. With invasion of the inner third of the myometrium, there is a negligible risk of node involvement for grade 1 and 2 cases. If the outer third of the myometrium is involved, the risk of nodal metastases is greatly increased. These data emphasize the importance of myometrial invasion and tumor spread, providing the basis for the FIGO Surgical Staging System. [Table 32-8](#) summarizes the risk of nodal metastases based on the GOG studies published by Creasman and colleagues. In a more recent GOG study cited previously, Morrow and coworkers noted that for patients without metastases at operation, the greatest risk of future recurrence was grade 3 histology. Furthermore, among 48 patients with histologically documented aortic node metastases, 47 were found to have positive pelvic nodes, adnexal metastases, or tumor invasion to the outer third of the myometrium, emphasizing the poor prognostic aspects of these three findings. Mariani and colleagues at the Mayo Clinic have found that tumor size can also be incorporated into a staging paradigm to identify patients at highest risk for nodal spread. They found that in grades 1 and 2 tumors with less than 50% invasion and tumor size smaller than 2 cm, the risk of lymph node involvement is almost zero.

### Steroid Hormone Receptors

Steroid hormones affect the growth of target cells by binding with steroid receptors in the cell. The receptor steroid complex then interacts with DNA in the cell nucleus, stimulating the synthesis of messenger RNA, which acts in the cytoplasm to stimulate protein synthesis.

The steroid receptor level in endometrial carcinoma is lower than in normal endometrium. The highest levels of estrogen and progesterone receptors in tumors have been found in the well-differentiated (grade 1) tumors and the lowest in grade 3 tumors. Despite extensive research in this area, receptor status in endometrial carcinoma does not appear to have the same clinically relevant role as it does in cases of breast carcinoma.

## EVALUATION

In addition to the usual routine preoperative evaluation, the woman should have a chest radiographic examination, and/or a chest and abdominal pelvic computed tomography (CT). However, a study by Connor and associates has noted that preoperative CT has only a 50% positive predictive value for nodal disease. Furthermore, postoperative CT monitoring did not appear to improve survival. The measurement of cancer antigen 125 (CA-125), generally used in cases of ovarian carcinoma, may occasionally be useful. Preoperatively, an elevated CA-125 level can often indicate extrauterine disease. It may be a particularly useful marker for those with serous carcinoma of the endometrium.

## TREATMENT

### Stage I

Surgery is the primary treatment modality for patients with endometrial carcinoma, except in patients with significant medical comorbidities. Complete surgical staging includes hysterectomy, bilateral salpingo-oophorectomy, pelvic cytology (washings), and pelvic and para-aortic lymph nodes. According to Orr and Chamberlin, the exceptions include women with significant medical comorbidities and young premenopausal women who desire future fertility, with grade 1 endometrial adenocarcinoma associated with endometrial hyperplasia.

Surgical staging allows accurate surgical and histologic assessment of the following: (1) tumor spread within the uterus; (2) degree of penetration into the myometrium; and (3) extrauterine spread to retroperitoneal nodes, adnexa, and/or the peritoneal cavity. This approach is used for cases that are staged according to the 2009 FIGO system (see [Table 32-3](#)).

The use of minimally invasive surgery in the treatment of early-stage endometrial cancer has continued to grow. The GOG has recently published a phase III randomized trial of surgical staging for endometrial carcinoma comparing the laparoscopic approach with the more traditional abdominal approach. The pathologic outcomes were the same and most patients in the laparoscopy arm were able to have the surgery completed. There were some benefits in the minimally invasive arm, including shorter hospital stay and improved quality of life in the postoperative period. Minimally invasive surgery can be used particularly for patients who are incompletely staged at the time of initial operation and require a second staging procedure.

For patients with significant medical comorbidities, radiation therapy alone can be used. However, radiation as the sole method of therapy yields inferior results, as Bickenbach and colleagues noted, with an 87% 5-year survival rate for patients with stage I carcinoma treated by surgery alone, in comparison with a 69% survival rate for those treated with radiation therapy alone. For those who cannot tolerate surgery or external beam therapy, treatment by intracavitary radiation alone offers some benefit. Lehoczyk and associates have reported on 170 older patients treated with brachytherapy alone with uncorrected 5-year survival rates for stages IA and IB of 46% and 30%, respectively. For patients with grade 1 cancers, progesterone therapy could also be considered if patients are not medically fit for surgery or radiation therapy.

Occasionally, morbidly obese patients are encountered for whom an abdominal operation is very risky. Sood and coworkers



have noted that for stage I patients with a preoperative CA-125 level less than 20 U/mL, the risk of extrauterine disease is only 3%, making vaginal hysterectomy a therapeutic option. Dotters has reported that a CA-125 level more than 35 U/mL usually predicts extrauterine disease, although approximately one third of patients needing full operative staging are not identified by an elevated CA-125 level for grade 1 or 2 cases, whereas for grade 3, the sensitivity increases to 88%. However, a few false-positive cases were noted, making the results a useful guide but not sufficiently precise to be the sole criterion for performing lymphadenectomy.

Stage I, Grade 1

The risk of spread of a grade 1 tumor to the pelvic nodes is extremely small (see Table 32-7). At the time of surgery, the abdomen is explored, peritoneal cytology is carried out, and an extrafascial total abdominal hysterectomy with bilateral salpingo-oophorectomy is performed. Pelvic and para-aortic lymph node dissection should be considered in cases with deep myometrial invasion. In patients with stage I, grade 1 tumors, postoperative radiation (vaginal brachytherapy and/or external beam irradiation) may be considered if there is deep myometrial invasion.

Stage I, Grades 2 and 3

Regardless of the surgeon's preference for the extent of surgical staging, all patients with grade 2 or 3 lesions should undergo complete surgical staging. Mariani and coworkers reported improved survival in patients at high risk of nodal disease who underwent para-aortic lymphadenectomy compared with those who did not have this procedure. The use of postoperative irradiation depends on the pathologic findings.

Three phase III randomized trials evaluating the use of adjuvant radiotherapy in patients with high-risk stage I endometrial cancer have shown no improvement in overall survival (see Table 32-9). In a Norwegian study comparing brachytherapy with brachytherapy plus pelvic radiation, local recurrences were decreased in the group of patients receiving pelvic radiation. In the PORTEC trial from The Netherlands, Creutzberg and colleagues reported on 714 patients with presumed stage I disease. Patients received full pelvic radiotherapy or observation. Although locoregional control was better in the treatment arm, there was no difference in overall survival. In a GOG trial, Keys and associates randomized almost 400 patients who underwent complete surgical staging to whole-pelvis radiation versus observation. Similar to the PORTEC trial, there was a decrease in local recurrences in the radiation arm, with no difference in overall survival. An ongoing GOG study is evaluating the role of vaginal brachytherapy and chemotherapy as adjuvant treatment in patients with high intermediate-risk disease.

Stage II

Three therapeutic options have been used for the treatment of stage II carcinoma of the endometrium that also involves the endocervix: (1) primary operation (radical hysterectomy and pelvic and para-aortic lymph node dissection); (2) primary radiation (intrauterine and vaginal implant and external irradiation), followed by an operation (extrafascial hysterectomy); and (3) simple hysterectomy, followed by external beam irradiation.

Radical hysterectomy and pelvic dissection have been used as effective therapy. Mariani and colleagues have reported on 57 patients with endocervical involvement at the time of diagnosis. Of these, 61% underwent radical hysterectomy and staging. There were no recurrences in the radical hysterectomy group if their nodes were negative at the time of surgery. Five year disease-related survival and recurrence-free survival in the radical hysterectomy patients was 76% and 71%, respectively.

Another option for patients with stage II carcinoma of the endometrium is treatment with a combination of radiation and extrafascial hysterectomy. The protocol includes external radiation (45 Gy) and a single brachytherapy implant, usually followed by extrafascial total abdominal hysterectomy, bilateral salpingo-oophorectomy, and para-aortic node sampling. Podczaski and coworkers have noted that those with gross cervical tumor have a poor prognosis and are likely to have extrauterine disease at operation. For patients with cervical involvement on biopsy but no gross tumor, Trimble and Jones have found radiation treatment by a single implant alone followed by a hysterectomy to be effective; they added external therapy depending on the nodal findings and myometrial invasion. Andersen has reported on 54 patients with stage II tumors and found a 70.6% survival rate in patients treated by abdominal hysterectomy followed by radiation.

Comparable outcomes have recently been reported using high dose rate brachytherapy approaches in stages I and II patients unable to undergo surgery. Nguyen and coworkers have reported a 3-year disease-free survival rate of 85% in 36 stage I patients treated with definitive radiation therapy. Nineteen patients were considered inoperable because of morbid obesity, and the remainder had significant medical problems precluding anesthesia. All patients were treated as outpatients with five weekly brachytherapy applications performed under conscious sedation. At a median follow-up of 32 months, the 3-year actuarial uterine control rate was 88%.

Adjuvant Systemic Therapy for Early-Stage Endometrioid Endometrial Cancer

In addition to radiation therapy, adjuvant chemotherapy is being explored for patients with endometrial cancer and high-risk features. Although the addition of postoperative radiation to high-risk patients reduces the local recurrence rate, distant metastasis

Table 32-9 Summary of Randomized Trials of Adjuvant Radiotherapy in Stage I Endometrial Carcinoma

Trial	Surgery	Randomization	Locoregional Recurrences	Survival
Norwegian, 1968-1974	TAH-BSO	Brachytherapy versus brachytherapy and pelvic RT	7% versus 2% at 5 yr; $P < .01$	89% versus 91% at 5 yr; $P = NS$
PORTEC	TAH-BSO	Obs versus pelvic RT	14% versus 4% at 5 yr; $P < .001$	85% versus 81% at 5 yr; $P = .31$
GOG	TAH-BSO, nodes	Obs versus pelvic RT	12% versus 3% at 2 yr; $P < .01$	86% versus 92% at 4 yr; $P = .56$

continues to be problematic. In approximately 25% of patients with low-stage grade 3 lesions, the disease recurs at a distant site. In addition, 20% of clinical stage II patients and at least 30% of patients who present with extrauterine disease recur at distant sites, even after patients have received adjuvant pelvic radiation.

Adjuvant chemotherapy may also be useful in this group of patients. The Japanese GOG compared pelvic radiation with combination chemotherapy in high-risk, early-stage patients and found an improvement in progression-free and overall survival in the chemotherapy arm.

### **Stage I or II Uterine Papillary Serous Carcinoma**

Several academic centers have tried to determine the best treatment for patients with early-stage UPSC. Even with minimal disease within the uterus, patients with UPSC often have extrauterine spread of disease. In a retrospective, multi-institutional study, Huh and associates reported on 60 patients with stage I UPSC who underwent comprehensive surgical staging. They found that recurrence rates were lower than previously reported and inferred that complete staging may provide a potential benefit. In their study, none of 7 patients who received chemotherapy had a recurrence. In a multi-institutional retrospective study of early-stage UPSC, Dietrich and colleagues have found that the combination of carboplatin and paclitaxel in the adjuvant setting is effective in improving survival and limiting recurrences. Further investigation is necessary.

Combined chemotherapy and radiation therapy may play a role in the management of patients with early-stage disease. Turner and associates have reported the application of vaginal irradiation at a high dose rate in combination with chemotherapy in surgical stage I patients. The 5-year survival rate was 94%, which is higher than that seen in most other studies for patients with stage I disease.

### **Stage III or IV Recurrent Endometrial Cancer**

Because of the hematogenous and lymphatic spread of endometrial cancer, patients with recurrent or advanced disease often present with tumor outside the pelvis. Systemic therapy, therefore, plays an important role in the treatment of these patients. Hormonal and cytotoxic agents have activity in patients with advanced or recurrent endometrial cancer. In addition, there continues to be a role for radiation therapy to obtain local control or treat disease in the pelvis.

In stage III carcinoma, the disease has spread outside the uterus but remains confined to the pelvis or the retroperitoneal nodes. These tumors do not involve the mucosa of the rectum or bladder. They account for approximately 7% of all endometrial carcinomas and occur in women older than those with lower stage tumors and often medically less able to undergo an operation.

Patients with stage IIIA disease include those with disease spread to the adnexa and/or the serosa of the uterus. Stage IIIB involves the vagina and stage IIIC includes spread to the retroperitoneal lymph nodes. In the revised FIGO staging, stage IIIC has been further divided into those with positive pelvic nodes only (stage IIIC1) and those with positive para-aortic nodes (stage IIIC2). Patients with nonendometrioid histology or spread to the serosa or adnexa require adjuvant therapy (radiation, chemotherapy, or both). Approximately 3% of endometrial carcinomas are at stage IV, and many of these patients have tumor metastases outside the pelvis. If it is possible to carry out, optimal surgical debulking can be associated with prolonged

survival. Bristow and coworkers have reported that the amount of residual disease after cytoreductive surgery, age, and performance status appear to be important determinants of survival in patients with stage IVB endometrial carcinoma.

Several chemotherapeutic agents or combinations have demonstrated activity in patients with endometrial cancer. Combination therapy is more effective than single-agent therapy in treating this disease. The challenge has been to combine agents to maximize efficacy while attempting to limit toxicity.

Doxorubicin was one of the first drugs identified with good activity against endometrial cancer. Single-agent doxorubicin has a response rate of approximately 25%, with a median duration of response of less than 1 year. Single-agent cisplatin also has demonstrated response rates between 20% and 42% when used as a first-line agent. The duration of response was again short (3 to 5 months). In several phase II studies, adding cisplatin to doxorubicin has resulted in response rates between 45% and 60%. In a GOG randomized phase III study, cisplatin and doxorubicin in combination had a higher response rate compared with single-agent doxorubicin (45% versus 27%), but there was no difference in overall survival. The European Organisation for Research and Treatment of Cancer (EORTC) has performed a similar trial comparing the same two regimens. Again, the combination arm had a higher response rate than the doxorubicin-alone treatment group. In this study, there was a modest survival advantage in those patients who received the combination regimen. The median overall survival in cisplatin- and doxorubicin-treated patients was 9 months compared with 7 months in patients who received doxorubicin alone ( $P = 0.065$ ).

More recently, phase II studies of paclitaxel have found significant activity in chemotherapy-naïve patients with recurrent endometrial cancer, with a response rate of 36%. In patients who failed previous chemotherapy, paclitaxel also demonstrated activity, with a response rate up to 27%. The antitumor effect of single-agent paclitaxel has led to the incorporation of paclitaxel into combination therapy regimens. In a phase II study, the combination of cisplatin and paclitaxel demonstrated a 67% response rate. In a phase III study, the GOG found similar activity between the combination of cisplatin and doxorubicin versus doxorubicin and paclitaxel. Following this study, the GOG performed a phase III trial evaluating doxorubicin and cisplatin compared with doxorubicin, cisplatin, and paclitaxel (TAP) with granulocyte colony-stimulating factor. The TAP regimen yielded a superior response rate (57% versus 34%;  $P < .001$ ), longer progression-free survival (8.3 versus 5.3 months;  $P < .001$ ), and longer overall survival (15.3 versus 12.3 months;  $P = .037$ ). The results of this study have set the TAP regimen as the standard of care for the first-line treatment of advanced or recurrent endometrial cancer.

In an attempt to decrease the toxicity related to cisplatin therapy, carboplatin has been investigated. Single-agent carboplatin demonstrates modest activity in chemotherapy-naïve patients, with little or no activity in patients pretreated with chemotherapy. In a phase II study, the combination of paclitaxel and carboplatin was evaluated in patients with advanced and recurrent disease. In patients with advanced endometrioid endometrial cancer, there was a 78% response rate to this combination. The median failure-free survival time was 23 months and the 3-year overall survival rate was 62%. In patients with recurrent disease, the response rate was 56% and the median failure-free interval was 6 months.

The combination of carboplatin and paclitaxel has a more favorable toxicity profile than cisplatin and paclitaxel. Thus, many community physicians prefer this combination in the setting of advanced or recurrent endometrial cancer rather than the TAP regimen. The GOG recently completed accrual to a phase III randomized study comparing TAP with carboplatin and paclitaxel to address this question. In a phase III randomized trial, the GOG has recently reported that the combination of doxorubicin and cisplatin demonstrates improved progression-free and overall survival compared with whole-abdomen irradiation in patients with advanced disease.

Despite higher response rates, more effective cytotoxic agents with longer durations of response are needed. The alkylating agent ifosfamide has demonstrated a response rate of 24% in chemotherapy-naïve patients and a 0% to 15% response rate in patients pretreated with platinum agents. 5-Fluorouracil has demonstrated activity as a single agent and in combination with melphalan in the phase II setting. Oral etoposide has been shown to have some activity against chemotherapy-naïve patients with a tolerable toxicity profile, but this was not seen in patients who had received previous chemotherapy.

The prognosis is poor for patients who fail first-line chemotherapy. The response rates for second- and third-line agents are often less than 10% and the overall survival is less than 9 months. Paclitaxel may have better activity than other agents in this setting. In patients who have failed previous chemotherapy, paclitaxel has response rates up to 27%. In particular, in a cohort of patients who were refractory to platinum, paclitaxel was shown to have a 22% response rate. Preliminary data suggest that retreatment with a platinum-paclitaxel-based regimen may be effective for patients who previously responded to these agents.

For patients with an isolated recurrence in the pelvis, radiotherapy can be useful. Ackerman and coworkers have treated 21 patients with pelvic relapse and found that radiation achieved pelvic control of disease in 14 (67%). The best results were with recurrences in the vaginal mucosa. Similarly, Sears and colleagues have treated 45 patients with vaginal recurrence of endometrial cancer with radiation and achieved a 44% 5-year survival rate. As noted, Carey and associates salvaged 15 of 17 patients with vaginal recurrence initially treated by operation alone. The addition of chemotherapy at the time of radiation is currently being evaluated. In patients who have had previous irradiation, pelvic exenteration can be considered for those with an isolated central recurrence.

### **Chemotherapy for Advanced and Recurrent Uterine Papillary Serous Carcinoma**

Most information available for patients with UPSC is from retrospective, nonrandomized case series. In addition, response rates to therapy often come from subset analyses of studies of all types of advanced or recurrent endometrial cancer, including phase III GOG studies. Levenback and associates have reported 20 patients with recurrent or advanced UPSC treated with cyclophosphamide, doxorubicin, and cisplatin. Of these patients, 58% were alive without disease after 24 months. However, this regimen was highly toxic. Price and coworkers have also evaluated cyclophosphamide, doxorubicin, and cisplatin in 19 patients with advanced disease and 11 patients with recurrent disease. Of the patients treated in the adjuvant setting for advanced disease, 58% were alive without evidence of disease, with a median follow-up of 24 months. In the patients with recurrent disease, the response rate was 27%.

In addition, all patients developed treatment-related toxicities. Most of these toxicities were hematologic. One treatment-related death was due to caused by cardiotoxicity.

Recently, more favorable results using paclitaxel with and without carboplatin have been demonstrated. In a phase II study evaluating carboplatin and paclitaxel, the response rate was 60% in 20 patients with high-stage UPSC. The progression-free survival time was 18 months and the 3-year overall survival rate was 39%. Two of 4 patients with recurrent UPSC demonstrated a response to carboplatin and paclitaxel. Zanotti and colleagues have evaluated 24 patients with measurable disease (progressive disease after initial surgery or recurrent disease). There was an 89% response rate in patients treated after initial surgery and a 64% response rate for patients with recurrent disease. At the University of Texas M.D. Anderson Cancer Center, single-agent paclitaxel demonstrated a 77% response rate in patients with recurrent disease. Despite this activity, the duration of response in these studies was less than 1 year. Other agents are under investigation for the treatment of UPSC.

## **HORMONE THERAPY**

### **Progestins for Advanced or Recurrent Disease**

For the past 50 years, progestational agents have been valuable in the armamentarium against endometrial cancer, particularly in patients with recurrent disease. Progestins are generally well tolerated. Side effects are usually minor and include weight gain, edema, thrombophlebitis, headache, and occasional hypertension. In patients with medical comorbidities, the use of hormonal agents may be preferable to cytotoxic chemotherapy. Initial clinical trials in patients with advanced or recurrent endometrial cancer have demonstrated response rates of 30% to 50%. Larger studies with more specific response criteria have demonstrated more modest response rates, usually between 11% and 24%. Podratz and colleagues have treated 155 patients with advanced or recurrent endometrial cancer with progestational agents. The objective response rate was 11%. Overall survival after the initiation of hormone therapy was 40% at 1 year, 19% at 2 years, and 8% at 5 years. In a GOG phase II study, patients who had no previous exposure to chemotherapy or hormonal agents were treated with megestrol acetate (800 mg/day). The overall response rate was 24%. Progression-free and overall survival were 2.5 and 7.6 months, respectively.

Current recommendations for progestin therapy include oral medroxyprogesterone acetate (Provera), IM medroxyprogesterone acetate (Depo-Provera), and megestrol acetate (Megace). Although there are no randomized studies that have directly compared different formulations of progestins, response rates are similar. In addition, although a dose-response effect of progestin therapy has been reported in breast cancer, there is no evidence of this effect in patients with endometrial cancer. In a randomized trial of oral medroxyprogesterone acetate, patients receiving the low-dose regimen (200 mg/day) had a higher response to therapy than those receiving the high-dose regimen (1000 mg/day).

There are a number of tumor characteristics that increase the likelihood of response to hormone therapy. These include low-grade tumors, the presence of steroid hormone receptors (i.e., progesterone receptor [PR] and estrogen receptor [ER]-positive), and a longer disease-free interval. The GOG has demonstrated a response rate of 8% in women whose tumors were PR-negative and 37% for women whose tumors were PR-positive. In addition,



there was a 7% response rate in women with ER-negative tumors compared with a 26% response rate in women with ER-positive tumors. Patients with poorly differentiated tumors or hormone receptor-negative tumors have significantly lower response rates to progestin therapy.

Because of the low toxicity profile and modest efficacy, progestins should be considered for patients with recurrent endometrial cancer. In particular, all patients not eligible for clinical trials with well-differentiated hormone receptor-positive recurrent or advanced disease can be given a trial of progestin therapy. If the woman has an objective response, the progestin may be continued indefinitely until there is disease progression.

### Selective Estrogen Receptor Modulators and Aromatase Inhibitors

SERMs with antiestrogenic effects in the uterus have been used to treat women with recurrent endometrial cancer. First-generation SERMs such as tamoxifen have mixed estrogenic agonist and antagonist activity. Early response rates for tamoxifen in advanced or recurrent endometrial cancer were between 20% and 36%. However, in a GOG phase II study of tamoxifen given at a dose of 20 mg twice daily, only 10% of patients demonstrated an objective response. Grade 1 and 2 tumors were more likely to respond to tamoxifen than grade 3 tumors.

Short-term administration of tamoxifen can cause an increase in PR levels in postmenopausal women with endometrial cancer. Studies with alternating tamoxifen and progestins have been performed to determine whether this upregulation increases the response to progestin therapy. Phase II trials of tamoxifen plus alternating cycles of progestin have demonstrated a 27% to 33% response rate. The Eastern Cooperative Oncology Group has found no difference in response rates between patients treated with progestin alone and those treated with progestin combined with tamoxifen.

Anastrozole, an oral nonsteroidal aromatase inhibitor, has been approved by the U.S. Food and Drug Administration (FDA) for postmenopausal women with progressive breast cancer following tamoxifen therapy. The aromatase level is elevated in the stroma of endometrial cancer. In a phase II trial by the GOG, anastrozole was found to have minimal activity (9% response rate) in an unselected population of patients with advanced or recurrent endometrial cancer. More than 25% of the patients in this study had nonendometrioid histologic subtypes, and only 22% of the patients had ER- and PR-positive tumors or demonstrated a response to previous therapy. In the subset of women with FIGO grades 1 and 2 tumors with endometrioid histology, the response rate was 30%.

## SARCOMAS

Sarcomas comprise less than 5% of uterine malignancies and are much less frequent than endometrial carcinomas, particularly in Western countries. Numerous terms have been used to describe the many histologic types. One useful classification is based on determination of the resemblance of the sarcomatous elements to mesenchymal tissue normally found in the uterus (**homologous uterine sarcomas**) in contrast to tissues foreign to the uterus (**heterologous uterine sarcomas**). Homologous types include **leiomyosarcoma**, endometrial stromal sarcoma (ESS) and, rarely, angiosarcoma. Heterologous types include

### Box 32-3 Modified Classification of Uterine Sarcomas

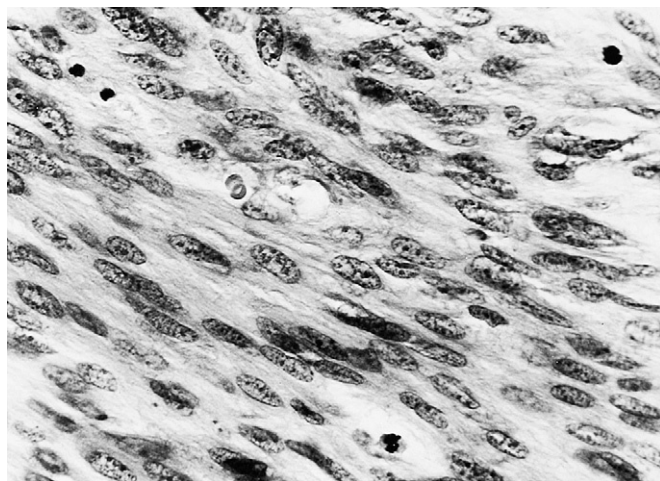
- I. Pure sarcoma
  - A. Homologous
    1. Smooth muscle tumors
      - a. Leiomyosarcoma
      - b. Leiomyoblastoma
      - c. Metastasizing tumors with benign histologic appearance
        - i. IV leiomyomatosis
        - ii. Metastasizing uterine leiomyoma
        - iii. Leiomyomatosis peritonealis disseminata
    2. Endometrial stromal sarcomas
      - a. Low grade: Endolymphatic stromal myosis
      - b. High grade: Endometrial stromal sarcoma
  - B. Heterologous
    1. Rhabdomyosarcoma
    2. Chondrosarcoma
    3. Osteosarcoma
    4. Liposarcoma
  - C. Other sarcomas
- II. Carcinosarcoma—malignant mixed müllerian tumors
  - A. Homologous (carcinosarcoma): Carcinoma + homologous sarcoma
  - B. Heterologous: Carcinoma + heterologous sarcoma
- III. Müllerian adenosarcoma
- IV. Lymphoma

Adapted from Clement P, Scully RE: Pathology of uterine sarcomas. In Coppleston M (ed): Gynecologic Oncology. New York, Churchill Livingstone, 1981, p 591.

rhabdomyosarcoma, chondrosarcoma, osteosarcoma, and liposarcoma. These sarcomas may exist exclusively or may be admixed with epithelial adenocarcinoma, in which case the term **carcinosarcoma (malignant mixed müllerian tumor)** is applied. Box 32-3 shows a morphologic classification for uterine sarcomas. A study by Zelmanowicz and colleagues has suggested that risk factors for these tumors are similar to those of endometrial carcinoma—that is, estrogens and obesity increase the risk and oral contraceptive use decreases the risk. No uniformly defined staging criteria exist for these tumors and the most widely used definitions are similar to those for endometrial carcinoma—stage I, confined to the corpus; stage II, corpus and cervix involved; stage III, spread outside the uterus but confined to the pelvis or retroperitoneal lymph nodes; and stage IV, spread outside the true pelvis or into the mucosa of the bladder or rectum. Similar to endometrial adenocarcinoma, operative stage is the most important predictor of survival.

### LEIOMYOSARCOMA

Leiomyosarcomas represent 1% to 2% of uterine malignancies and approximately one third of uterine sarcomas (Fig. 32-11). Although the exact cause is unknown, leiomyosarcomas are not thought to arise from benign leiomyomas. Leibsohn and co-workers have noted that of 1423 patients who had hysterectomies for presumed leiomyomas with a uterine size comparable with a 12-week pregnancy or larger, the risk of sarcoma increased with age, from 0.4% for those in their 30s to 1.4% for those in their 50s. The determination of malignancy is made in part by ascertaining the number of mitoses/10 HPF (high-powered field) as well as the presence of cytologic atypia, abnormal mitotic figures, and nuclear pleomorphism (see Fig. 32-11). Vascular invasion and extrauterine spread of tumor are associated



**Figure 32-11** Leiomyosarcoma. Nuclear hyperchromatism and mitotic figures are present ( $\times 660$ ), respectively. (From Clement PB, Scully RE: Pathology of uterine sarcomas. In Coppleston M [ed]: Gynecologic Oncology. Edinburgh, Churchill Livingstone, 1981.)

with worse prognoses. A finding of more than 5 mitoses/10 HPF with cytologic atypia leads to a diagnosis of leiomyosarcoma; when there are four or fewer mitoses/10 HPF, the tumors usually have a more benign clinical course. The prognosis worsens for tumors with more than 10 mitoses/10 HPF. The presence of bizarre cells may not necessarily establish the diagnosis because they can occasionally be seen in benign leiomyomas and in patients receiving progestational agents. Furthermore, it is important to note that an increase in mitotic count in leiomyomas occurs in pregnancy and during oral contraceptive use. This can occasionally cause confusion in the histologic diagnosis.

Usually, the woman has an enlarged pelvic mass, occasionally accompanied by pain or vaginal bleeding. Leiomyosarcomas are suspected if the uterus undergoes rapid enlargement, particularly in patients in the perimenopausal or postmenopausal age group. Approximately 85% of women diagnosed with a leiomyosarcoma have clinical stage I or II disease (i.e., disease limited to the uterus and cervix). The risk of lymph node involvement is very low. Primary treatment includes total hysterectomy, bilateral salpingo-oophorectomy, and staging. Despite the low incidence of high-stage disease, approximately 50% of patients will have a recurrence within 2 years. The recurrence in most of these patients is outside the pelvis.

The GOG has evaluated the role of adjuvant radiation therapy in patients ( $n = 48$ ) with clinical stages I and II disease (Table 32-9). There was no difference in the progression-free interval, absolute 2-year survival rate, or site of first recurrence between patients who received pelvic radiation ( $n = 11$ ) and those that did not ( $n = 37$ ). This is not surprising, because most recurrences were outside the pelvis (83%). There was recurrence in 48% of patients and most of them had a recurrence within 17 months of diagnosis. In the adjuvant chemotherapy trial by the GOG, patients treated with doxorubicin (Adriamycin) had a recurrence less frequently than those in the observation arm (44% versus 61%); however, this difference was not statistically significant. There is no known benefit to adjuvant radiation or chemotherapy in women with leiomyosarcoma limited to the uterus.

Several studies have evaluated the treatment of advanced or recurrent leiomyosarcoma. Hannigan and colleagues used vincristine, actinomycin D, and cyclophosphamide (Cytoxan, VAC protocol) and noted a 13% complete response rate and 16% partial response rate in 74 patients with advanced metastatic uterine sarcomas. A large collaborative trial was conducted by the GOG and reported by Omura and associates. The best responses were obtained for patients with lung metastases who received doxorubicin and dacarbazine (DTIC). Current evidence suggests that a multidrug program offers the greatest response for these patients. Cisplatin, doxorubicin, paclitaxel (Taxol), ifosfamide, and etoposide (VP-16) all appear to have some effectiveness. Most recently, gemcitabine and docetaxel have been evaluated in a phase II study for patients with recurrent leiomyosarcoma. In this study, 34 patients with leiomyosarcoma were treated. The overall response rate was 53%; however, the duration of response was only 5.6 months.

### ENDOMETRIAL STROMAL SARCOMA

Overall, stromal tumors comprise approximately 10% of uterine sarcomas. Their behavior correlates primarily with mitotic rate. Although these tumors were once divided into low grade and high grade, all ESSs are now considered low grade. If high-grade elements are present, these tumors would be classified as undifferentiated high-grade sarcomas. Undifferentiated sarcomas have a greater degree of anaplasia and lack the branching vasculature characteristic of ESSs. ESSs have a peak incidence in the fifth decade of life. There is no association with previous radiation nor are risk factors of endometrial carcinoma associated with the development of ESS. Histologically, ESS most resembles proliferative endometrial stroma. Prognosis depends on the extent of disease and ability to remove the entire tumor at the time of surgery. In general, ESSs are indolent, slowly progressing tumors.

Recurrent disease may be diagnosed as long as 30 years after diagnosis. ESS tends to recur locally in the pelvis or peritoneal cavity and frequently spreads to the lungs. In treating metastatic disease, it should be remembered that these tumors contain estrogen and progesterone steroid hormone receptors and are often sensitive to hormone therapy. Complete resolution has been reported with megestrol acetate (Megace), medroxyprogesterone (Provera), letrozole (Femara), tamoxifen, and 17 $\alpha$ -hydroxyprogesterone caproate (Delalutin).

There are reports of radiation in the treatment of pelvic recurrence, with resolution of all residual tumors, but extensive experience with radiation therapy is not available. Systemic chemotherapy with cytotoxic agents has not been reported to be effective, although good responses to doxorubicin have been seen.

### UNDIFFERENTIATED SARCOMAS

These high-grade tumors behave aggressively and have a poor prognosis. They must be evaluated carefully because they are often confused with other large cell undifferentiated tumors (e.g., lymphoma, leukemia, high-grade endometrial cancer, carcinosarcoma).

Microscopically, more than 10 mitoses/10 HPF are present, and frequently 20 or more mitoses/10 HPF are present. Some series have reported 100% fatalities, although Vongtama and

coworkers have reported survival of more than 60% for 24 patients with stage I and 1 patient with stage II disease. Recurrences are common in the pelvis, lung, and abdomen. If there has been no previous radiation treatment and the recurrence is confined to the pelvis, pelvic irradiation is usually prescribed. If there is disseminated disease, multiagent chemotherapy is used.

### **CARCINOSARCOMA (MALIGNANT MIXED MÜLLERIAN TUMORS)**

As shown in **Box 32-3**, these tumors consist of carcinoma and sarcoma elements native to the uterus that may resemble the endometrial stroma of smooth muscle (homologous) or of sarcomatous tissues foreign to the uterus (heterologous). Spanos and colleagues have reviewed 188 patients with mixed mesodermal tumor and found the prognosis and pattern of survival to be similar for homologous and heterologous tumors. George and coworkers have shown that patients with these tumors have a markedly worse prognosis than patients with high-grade endometrial carcinomas. Unlike patients with endometrial stromal sarcoma or leiomyosarcoma, those with carcinosarcoma tend to be older and primarily postmenopausal, usually older than 62 years. Previous pelvic irradiation has been identified as an occasional predisposing factor and was experienced by 17 of 136 patients reviewed by Norris and Taylor. Heterologous and homologous tumors occur with approximately equivalent frequency. These tumors can spread locally into the myometrium and pelvis, or distally to the abdominal cavity, lungs and pleura, a pattern similar to the spread of endometrial carcinoma.

A common symptom is postmenopausal bleeding, often accompanied by an enlarged uterus. Occasionally, the diagnosis is made in tissue removed with D&C and the tumor may appear to be a polypoid excrescence from the cervix; diagnosis may also be made by vaginal ultrasound examination.

As is true for other sarcomas, the primary treatment is surgical removal of the uterus. The extent of the tumor and depth of myometrial invasion are important prognostic factors. Women with deep myometrial invasion are more likely to have spread to pelvic or para-aortic nodes. Patients with tumors confined to the uterus and little or no myometrial spread have the best prognosis. A comprehensive surgical staging procedure is recommended for all patients with this diagnosis. Nielsen and coworkers have reported a 5-year survival rate of 58% for these patients when the disease is confined to the uterus.

In a phase I and II study of ifosfamide and cisplatin as adjuvant therapy in patients with high-stage carcinosarcoma, the GOG found this combination to be tolerable. Progression-free and overall survival rates at 2 years were 69% and 82%, respectively. This study lacked appropriate controls so the impact of this regimen on improving survival could not be evaluated. For patients with advanced or recurrent disease, the GOG has evaluated ifosfamide versus ifosfamide and cisplatin in a phase III randomized study. The response rate to the combination therapy was superior (54% versus 36%); however, the toxicity was significantly higher. In addition, no significant difference in overall survival was seen. A follow-up study compared ifosfamide with ifosfamide plus paclitaxel in a phase III randomized study. Response rates in the combination arm were superior (45% versus 29%) but, more importantly, there was a significant difference in overall survival (13 versus 8 months).

### **MÜLLERIAN ADENOSARCOMA**

Müllerian adenosarcoma is a rare low-grade malignancy composed of a sarcomatous stroma (homologous) and a proliferation of benign glandular elements that are intimately associated. It occurs predominantly in women older than 60 years. Total abdominal hysterectomy with bilateral salpingo-oophorectomy is the treatment of choice. Mitotic index and sarcomatous overgrowth are related to prognosis.

### **KEY POINTS**

- Endometrial carcinoma is the most common malignancy of the female genital tract. In the United States, the lifetime risk of endometrial cancer is 3%.
- Most women who develop endometrial cancer are between 50 and 65 years of age.
- Women with Lynch syndrome (HNPCC syndrome) have a 40% to 60% lifetime risk of endometrial cancer, which is similar to their lifetime risk of colon cancer.
- Chronic unopposed estrogen stimulation of the endometrium leads to endometrial hyperplasia and, in some cases, adenocarcinoma. Other important predisposing factors include obesity, nulliparity, late menopause, and diabetes.
- The risk of a woman developing endometrial carcinoma is increased threefold if her BMI is greater than 30 kg/m<sup>2</sup>.
- Tamoxifen use increases the risk of endometrial neoplasia two- to threefold.
- The primary symptom of endometrial carcinoma is postmenopausal bleeding. Women with abnormal bleeding should undergo endometrial sampling to rule out endometrial pathology.
- Cytologic atypia in endometrial hyperplasia is the most important factor in determining malignant potential.
- Simple hyperplasia will develop into endometrial cancer in 1% of patients, whereas complex hyperplasia will develop into cancer in 29% of patients.
- Studies have found that there is a 40% concurrent rate of endometrial cancer in patients with a preoperative diagnosis of complex atypical hyperplasia.
- Prognosis in endometrial carcinoma is related to tumor grade, tumor stage, histologic type, and degree of myometrial invasion.
- Older patients with atypical hyperplasia are at increased risk of malignant progression compared with younger patients.
- CT may miss as many as 50% of patients with nodal disease.
- A key determinant of the risk of nodal spread of endometrial carcinoma is the depth of myometrial invasion, which is often related to tumor grade.
- Well-differentiated (grade 1) endometrial carcinomas usually express steroid hormone receptors, whereas poorly differentiated (grade 3) tumors usually do not express these receptors.



**KEY POINTS—CONTINUED**

- Uterine papillary serous carcinoma is an aggressive histologic subtype associated with metastatic disease even in the absence of myometrial invasion.
- Of recurrences of adenocarcinoma of the endometrium, 90% occur within 5 years.
- Overall survival rates for patients with adenocarcinoma of the endometrium by stage are as follows: stage I, 86%; stage II, 66%; stage III, 44%; stage IV, 16% (overall 72.7% 5-year survival rate combining clinical and operative staging systems).
- Histologic variants of endometrial carcinoma with a poor prognosis include uterine papillary serous carcinoma and clear cell carcinoma.
- Patients with uterine papillary serous or clear cell carcinoma of the endometrium should have a full staging laparotomy similar to that for ovarian carcinoma.
- The most frequent sites of distant metastasis of adenocarcinoma of the endometrium are the lung, retroperitoneal nodes, and abdomen.
- Primary treatment of endometrial cancer includes hysterectomy, bilateral salpingo-oophorectomy, pelvic cytology, bilateral pelvic and para-aortic lymphadenectomy, and resection of all disease. The exceptions include young premenopausal women with stage I, grade 1 endometrial carcinoma associated with endometrial hyperplasia and women with increased risk of mortality secondary to medical comorbidities.
- Postoperative adjuvant radiation has not been shown to improve overall survival.
- Patients with high-stage or recurrent disease should be treated with a multimodality approach, including chemotherapy, radiation, and/or hormone therapy.
- Uterine sarcomas comprise less than 5% of uterine malignancies.
- Uterine sarcomas are treated primarily by surgery, including removal of the uterus, tubes, and ovaries.
- Endometrial stromal sarcomas are low-grade sarcomas with an indolent course.
- Multiagent chemotherapeutic regimens are usually prescribed for metastatic sarcomas; complete responses are rare and usually temporary.

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