Endometrial Carcinoma

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Epidemiology

Endometrial carcinoma is the most common invasive neoplasm of the female reproductive tract and the fourth most frequently diagnosed cancer in women in the United States. In 2017, it was estimated there were 61,380 new cases and 10,920 deaths resulting from this neoplasm. Worldwide, approximately 319,600 cases are diagnosed each year, making endometrial carcinoma the sixth most common cancer in women (Torre et al. 2015). The incidence of endometrial cancer varies widely throughout the world. The highest rates occur in North America and Europe, whereas rates in developing countries are four to five times lower. The incidence of endometrial cancer in Japan has been steadily increasing since 1978 and is now the most common gynecologic malignancy in Japan (Yamagami et al. 2017). In 2012 in the United States, the age-adjusted incidence rates of endometrial carcinoma in black and white women were similar, however since 1990 the incidence has been increasing in black women who have an 80% higher mortality rate than white women (Eheman et al. 2012; Jamison et al. 2013). Although the reason for this is not completely understood, it has been shown in a number of studies that an increase in aggressive histologic subtypes and advanced stage are contributing factors and that discrepancies in access to and quality of health care as well as genetics are also likely to play a role.

Classification

Historically, endometrial carcinoma, like most other tumors, has been classified based on its light microscopic features on hematoxylin and eosin (H&E) stained tissue sections. Although molecular

investigation has expanded our understanding of the molecular basis of endometrial cancer, it has not, to date, been used to change the classification of endometrial carcinoma. Recent studies using high throughput analyses of DNA and RNA have suggested a molecular-based classification system. At the time of preparation of this chapter it has not been fully implemented, but many aspects of the classification system have been incorporated into diagnostic reports based on previous molecular studies. Given the speed at which molecular pathology is advancing, much of what is contained within this portion of the chapter must be viewed from the perspective of the time it was prepared.

Since a landmark clinicopathological study in 1983, endometrial carcinoma has been broadly divided into two major categories, referred to as type I and type II (Bokhman 1983). It is important to recognize that these are not diagnostic categories but rather a framework for understanding the pathogenesis of endometrial carcinoma. As discussed below, factors associated with unopposed estrogenic stimulation, such as obesity and exogenous hormone use, as well as the presence of endometrial hyperplasia, are related to the development of the most common form of endometrial carcinoma, the endometrioid subtype, which is the prototype of type I carcinoma (Bokhman 1983). More recent studies have confirmed this association by demonstrating elevated serum estrogen levels in patients with endometrioid carcinoma (Lukanova et al. 2004). It also has been recognized that some forms of endometrial carcinoma appear to be largely unrelated to hormonal factors and hyperplasia (Sherman et al. 1997). Serous carcinoma is the most common form of endometrial carcinoma that is not usually related to estrogenic stimulation and is the prototypic type II carcinoma.

Molecular genetic studies, as discussed below, have provided further support for the dualistic categorization by identifying significant molecular genetic differences between the two most common types, endometrioid and serous carcinoma. Most of the other histologic subtypes of endometrial carcinoma, with exceptions as discussed below, can be classified as variants of either type I or II on the basis of clinicopathologic, immunohistochemical, and molecular features. Thus, other low-grade carcinomas, which are associated with endometrial hyperplasia and estrogenic stimulation, such as secretory, villoglandular, or low-grade endometrioid with squamous differentiation, are type I carcinomas. The exceptions to this are clear cell carcinoma and some International Federation of Gynecology and Obstetrics (FIGO) grade 3 endometrioid tumors. Over the years, clinicopathological studies of clear cell carcinoma have produced variable results. While most studies found that clear cell carcinomas were aggressive tumors, other studies demonstrated a more indolent behavior. Although most clear cell carcinomas have distinctive features, it has been recognized that in some instances the morphologic features are ambiguous. An early molecular study suggested that the genetic alterations of clear cell carcinoma were heterogenous with some sharing alterations with serous carcinoma, others with endometrioid tumors, and another group which did not overlap with either (An et al. 2004). More recent next-generation studies have confirmed the molecular heterogeneity of clear cell carcinoma (discussed in more detail in the section on "Clear Cell Carcinoma") (DeLair et al. 2017). In addition, early molecular and clinicopathological studies suggested that grade 3 endometrioid tumors might be best categorized as type II tumors. This is an area under current investigation and at present it seems that, like clear cell carcinoma, they are a heterogenous group of tumors (Bosse et al. 2018). This categorization of endometrial carcinoma has been challenged by some based on the recent high-throughput molecular studies. However, the broad categorization takes into account additional etiologic factors of endometrial carcinoma that have not yet been thoroughly addressed with molecular analyses alone. In the future, high throughput RNA analyses, proteomics, and metabolomics integrated with DNA analysis will undoubtedly provide more comprehensive information about additional etiologic factors. Presently, however, the recent next-generation sequence analyses have suggested that endometrioid and serous endometrial carcinomas can be divided into four distinct molecular subtypes (Kandoth et al. 2013). Interestingly, the subtypes correspond to a large extent with type I and II tumors, as is discussed in detail below.

Table 1 Classification of endometrial carcinoma[a]

Endometrioid adenocarcinoma
Squamous differentiation
Villoglandular
Secretory
Mucinous carcinoma
Serous carcinoma
Clear cell carcinoma
Neuroendocrine tumors
Low-grade neuroendocrine tumor
Carcinoid tumor
High-grade neuroendocrine carcinoma
Small cell neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Mixed cell adenocarcinoma
Undifferentiated carcinoma
Dedifferentiated carcinoma

[a]Modified World Health Organization and International Society of Gynecological Pathologists Histologic Classification of Endometrial Carcinoma.

A modified version of the recent World Health Organization (WHO) and International Society of Gynecological Pathologists (ISGYP) classification of endometrial carcinoma is shown in Table 1.

Etiology

Hormonal Stimulation

The strong association between replacement estrogen therapy and the development of endometrial cancer was demonstrated in a number of case-control studies in the late 1970s that have been supported by more recent studies (Gray et al. 1977; Greenwald et al. 1977; Mack et al. 1976; McDonald et al. 1977; Shapiro et al. 1980; Smith et al. 1975; Ziel and Finkle 1975). A study of endogenous hormones and endometrial cancer demonstrated that the risk associated with elevated levels of unopposed estrogen varies according to menopausal status (Potischman et al. 1996). In particular, high estrone and albumin-bound estradiol levels were associated with increased risk in postmenopausal women, but high levels of total, free, and albumin-bound estradiol were unrelated to increased risk in premenopausal women. In addition, high circulating levels of androstenedione were identified as a risk factor in both pre- and postmenopausal women. Factors that lower the risk of endometrial cancer include the addition of progestin to hormone replacement regimens, the use of oral contraceptives, and smoking (Jama 1987; Austin et al. 1993; Beral et al. 1999; Franks et al. 1987; Kaufman et al. 1980; Lesko et al. 1985; Pickar et al. 1998; Weir et al. 1994; Brinton and Felix 2014). It has been shown that women using unopposed estrogen for more than 2 years have a two- to three-fold increase in the risk of endometrial cancer, whereas women receiving progestins in conjunction with estrogen have no increased risk (Persson et al. 1989). One large case-control study demonstrated that the use of oral contraceptives for at least 1 year reduces the risk of endometrial carcinoma by 50% and that protection persists at least 15 years after discontinuation (Jama 1987). The risk of endometrial carcinoma may also be affected by polymorphisms in the estrogen receptor (ER) genes, however, the mechanism responsible is not currently understood (Ashton et al. 2009).

Tamoxifen is a nonsteroidal compound that acts by competing with estrogen for ER. In reproductive age women it has an antiestrogenic effect, but in postmenopausal (hypoestrogenic) women it has weak estrogenic effects and as a result significantly increases the risk of endometrial cancer (Andersson et al. 1991; Boccardo et al. 1992; Cook et al. 1995; Fisher et al. 1994, 1998; Fornander et al. 1989; Katase et al. 1998; Ribeiro and Swindell 1992; Rutqvist et al. 1995; Ryden et al. 1992; van Leeuwen et al. 1994; Stewart 1992). In addition, some studies have reported a higher proportion of high-risk types of carcinomas in tamoxifen-treated women whereas others have found predominantly low-grade carcinomas (Fisher et al. 1998; Barakat et al. 1994; Silva et al. 1994; Curtis et al. 2004). Despite the risk of endometrial carcinoma, tamoxifen remains a mainstay of treatment for prevention of breast cancer recurrence. Conversely, although it has been recently reported that oral contraceptives increase the risk of breast

carcinoma, their beneficial effects in substantially reducing the risk of endometrial and ovarian cancer, not to mention their value as highly effective contraceptive agents, merit their continued use (Morch et al. 2017).

Constitutional Factors

Obesity, like estrogen replacement therapy, is a well-defined risk factor for endometrial cancer, (Voskuil et al. 2007) with reported relative risks ranging from 2 to 10 (Parazzini et al. 1991; Parazzini et al. 1997; Onstad et al. 2016). The worldwide increase in obesity is thought to be related to the increase in endometrial carcinoma, as greater than half of the cases of endometrial carcinoma are associated with obesity. The risk can be explained by the increase of estrogens from aromatization of androgens to estrogens in adipose tissue and lower concentrations of sex hormone-binding globulins in obese women (Enriori and Reforzo-Membrives 1984). Diabetes is associated with an increased risk of endometrial cancer, ranging from 1.2 to 2.1, and this risk appears to be independent of other frequently associated variables such as obesity (Parazzini et al. 1991; Parazzini et al. 1997; Brinton et al. 1992). Other factors that have been associated with an increased risk of endometrial cancer include early age of menarche, later age of menopause, and nulliparity. The association with nulliparity appears to be primarily on the basis of infertility due to chronic anovulation in which unopposed estrogenic stimulation occurs (Brinton et al. 1992). The protective effect of pregnancy appears to be related and restricted to the first full-term pregnancy because abortions and increasing numbers of births do not influence the risk.

Diet

Endometrial cancer risk is correlated with total caloric intake, total protein intake, and frequency of consumption of meat, eggs, milk, fats, and oils. These dietary factors, as well as decreased energy expenditure and physical exercise associated with a sedentary lifestyle, are major determinants of obesity, which is an established risk factor. The independent contribution of specific dietary factors to endometrial cancer risk has not been clearly established (Parazzini et al. 1991; Levi et al. 1993). More recent studies suggest that activity decreases the risk of endometrial cancer independent of body weight (Voskuil et al. 2007).

Molecular Genetics

Advances in the field of molecular biology and bioinformatics have provided novel information on the mutational landscape of endometrial carcinoma. This information is critical to our understanding of endometrial carcinoma and, thus, to improvements in diagnosis, patient management, and prevention. Although many of the common tumor suppressor genes, oncogenes, and mutator genes involved in the pathogenesis of endometrial carcinoma were identified prior to next-generation sequencing, the vast amount of data being generated and analyzed will not only affect our understanding of endometrial cancer but will undoubtedly have a significant impact on the classification of endometrial carcinoma. The most recent next-generation sequencing studies suggest that endometrioid and serous carcinoma can be classified into four major molecular subtypes. Studies on the more uncommon types of endometrial carcinoma are ongoing and will determine if they also fall into these molecular subtypes. The integration of these subgroups into diagnostic practice is currently under investigation. However, there are a number of molecular studies in routine use that place tumors into one of these molecular subtypes. Given the pace of personalized medicine, it is possible that in the not too distant future classification systems may become obsolete as each individual's tumor will be classified based on its unique molecular alterations. Below, the four molecular subgroups will be described and the diagnostic aspects of the molecular studies will be presented in the subsequent sections on each specific WHO-classified tumor type.

Ultramutated Subtype

This subtype of carcinoma is defined by an extremely high mutation rate, among the highest rates reported for any tumor type, with individual tumors typically demonstrating greater than 10,000 mutations. The high mutation rate is caused by mutations in the exonuclease domain of the *POLE* gene that encodes the central catalytic subunit of DNA polymerase epsilon. The mutations lead to a dysfunctional holoenzyme that results in lack of DNA repair during replication. Mutations in *POLE* have been described in approximately 5.6–6.5% of endometrial carcinomas (Kandoth et al. 2013; Billingsley et al. 2015). Although the majority of endometrial carcinomas exhibiting *POLE* mutations demonstrate endometrioid histology, the mutations have been found in undifferentiated and dedifferentiated carcinomas, and in tumors with ambiguous histology (Haruma et al. 2018) (Espinosa et al. 2017) (Hoang et al. 2017). The clinical importance of this molecular subtype stems from a number of studies that have shown an association with improved survival (Bosse et al. 2018; Kandoth et al. 2013). However, the majority of the studies have not shown statistically significant associations and one study did not show an association with favorable outcome (Billingsley et al. 2015). Given the lack of a clear association with reproducible histology, identification of tumors with *POLE* mutations requires molecular analysis and definitive recommendations for altering patient management await larger studies.

Hypermutated/Microsatellite Instability (MSI) Subtype

This group of tumors is also characterized by an elevated mutation rate, albeit not as high as that of the ultramutated subtype. It was initially detected due to the presence of alterations in the length of microsatellite DNA sequences, hence the designation as the MSI subtype. The underlying molecular abnormality is loss of DNA mismatch repair (MMR), a post-replicative repair mechanism that predominately repairs mismatched base-pairs due to strand slippage in areas of nucleotide repeats. The loss of this repair mechanism results in base-pair substitutions and small insertions and deletions that are characteristic of loss of DNA MMR. With the advent of high-throughput DNA sequence analysis, a number of target genes in endometrial cancer have been discovered due to the characteristic type of mutations. In addition, there are a number of genes, although not clearly a target of mismatch repair, commonly mutated in this subtype as is discussed below. This subtype consists of endometrioid carcinoma and is found in approximately 20–25% of sporadic cases. In addition, it is a molecular phenotype found in tumors arising in the setting of Lynch Syndrome. This is discussed in more detail in other sections of the chapter.

Copy Number Low/Microsatellite Stable (MSS) Subtype

This subtype, as the name implies, lacks abnormalities in DNA MMR and significant copy number alterations. It does, however, have frequent mutations in *PTEN*, *PIK3CA*, *PIK3R1*, *ARID1A*, and *CTNNB1* (beta-catenin) similar to the MSI subtype, although the frequency of *CTNNB1* mutations is higher in this subtype. Like the MSI subtype, this group is composed entirely of endometrioid tumors.

Copy Number High/Serous-Like Subtype

One of the main characteristics of this subtype beyond the high level of copy number abnormalities is the extremely high frequency of *TP53* mutations. These occur in over 90% of tumors in this subtype. As expected, this subtype consists predominately of serous tumors along with some grade 3 endometrioid carcinomas but also includes some clear cell carcinomas and carcinosarcomas.

Hereditary Syndromes

Lynch Syndrome

Lynch syndrome is the most common cause of familial endometrial carcinoma. It is due to germline transmission of defective DNA

MMR genes (*MSH2*, *MLH1*, *MSH6*, and *PMS2*) resulting in an autosomal dominant inheritance pattern. As described above, mutations in DNA MMR genes result in the molecular phenotype of MSI, which results in an increased rate of mutations in cancer-causing genes, thus predisposing affected individuals to the development of various cancers. Endometrial carcinoma is an integral part of Lynch syndrome, and women with endometrial carcinoma may be probands for affected families.

Up to one-third of endometrioid carcinomas demonstrate abnormal DNA MMR protein expression (Modica et al. 2007; Vasen et al. 2004; Peiro et al. 2002; de Leeuw et al. 2000). This results from *MLH1* promoter hypermethylation in most cases or mutation of *MLH1, MSH2*, *MSH6, or PMS2* in the remaining. Mutation, but not loss of expression alone, of one of these genes indicates that the affected patient may be part of a Lynch syndrome kindred. Therefore, DNA MMR protein immunohistochemistry serves as a screen for Lynch syndrome; it is not a diagnostic test. For practical purposes, loss of expression of MSH2 and/or MSH6 or PMS2 is considered a surrogate for the presence of a somatic or germline (signifying Lynch syndrome) mutation involving one of the corresponding genes, whereas loss of expression of MLH1 and PMS2 is more likely associated with an epigenetic (promoter methylation of *MLH1*) etiology unassociated with Lynch syndrome.

Presently, it is recommended that all newly diagnosed cases of endometrial carcinoma be screened for loss of DNA MMR using an immunohistochemical approach (Anagnostopoulos et al. 2017; Watkins et al. 2017; Mills and Longacre 2016). However, there remains some controversy on whether MSI analysis should accompany the immunohistochemical screening as some studies have shown that immunohistochemistry alone may miss a small fraction of cases with microsatellite instability (Mills and Longacre 2016). Carcinomas which demonstrate loss of expression of MLH1 and PMS2 are submitted for *MLH1* methylation analysis. If methylation is identified, the MSI phenotype is considered the result of a somatic alteration resulting in loss of MLH1. However, if methylation is absent or there is loss of MSH2 and/or MSH6 or PMS2 alone, the patients should be referred for a comprehensive genetic evaluation for Lynch syndrome.

Loss of expression tends to occur in couplets (MLH1 with PMS2 and MSH2 with MSH6), although examples of isolated PMS2 loss (without MLH1) or MSH6 loss (without MSH2) are on record. Only complete loss of expression in the setting of a valid positive internal control is considered interpretable. Valid internal controls include non-neoplastic endometrial stroma and glands with reproducibly stained nuclei. Care should be taken to ensure that the lesion being assessed is carcinoma, not hyperplasia. It is also extremely important that the immunohistochemical methodology and interpretation of stains be performed using the strictest guidelines, as performing and interpreting the MLH1 stain, in particular, can be very problematic. Inappropriately interpreting an MLH1 stain as negative rather than as technically unsatisfactory in the absence of a valid positive internal control is a rather common occurrence.

Cowden Syndrome

Cowden syndrome is an autosomal dominant disorder caused by mutations in the *PTEN* tumor suppressor gene and is defined by a number of benign conditions and an increase in the risk of malignancies of the breast, thyroid, and endometrium. The lifetime risk of endometrial carcinoma in women with Cowden syndrome is estimated to be between 5–10% versus 2.6% in the general population. The syndrome is recognized in approximately 1 in 200,000 individuals and the histologic type of endometrial carcinoma has not been described (Nelen et al. 1999). As discussed above, given the increase in lifetime risk, it is currently recommended that women with Cowden syndrome be screened for endometrial carcinoma with blind biopsies annually starting at 35–40 years of age or 5 years prior to the earliest diagnosis of endometrial carcinoma in the family and with annual endometrial ultrasound in postmenopausal women.

Clinical and Pathologic Features of Specific Types of Carcinomas

Endometrioid Carcinoma

Endometrioid carcinoma is the most common form of endometrial carcinoma, accounting for more than three-fourths of all cases. These tumors are referred to as endometrioid because they resemble proliferative-phase endometrium and to maintain consistency with the terminology used for describing tumors with the same histologic appearance in the cervix, ovary, and fallopian tube.

Clinical Features

Patients with endometrioid carcinoma range in age from the second to the eighth decade, with a mean age of 59 years. Most women are postmenopausal, as the disease is relatively uncommon in young women. Only 1–8% of endometrial carcinomas occur in women under 40 years (Crissman et al. 1981; Dockerty et al. 1951; Gitsch et al. 1995a; Ross et al. 1983; Peterson 1968). A small number of cases have been reported in women under the age of 30 years, the youngest being 14 years with Cowden syndrome (Farhi et al. 1986; Lee and Scully 1989; Baker et al. 2013). In young women, the tumor is generally low grade and minimally invasive. In most series, the majority of patients have had clinical evidence of polycystic ovary syndrome (irregular menses, infertility, obesity, or hirsutism) but in some reports the patients lacked these features. Rarely, endometrioid carcinoma occurs during pregnancy (Hoffman et al. 1989). In pregnant women, endometrial carcinomas are nearly always low grade, superficially invasive or noninvasive, and have an excellent prognosis.

The initial manifestation of endometrial carcinoma is typically abnormal vaginal bleeding, although rarely the patient is asymptomatic and the diagnosis is made fortuitously. In one study, 24 asymptomatic women with unsuspected endometrial carcinoma were detected among 8998 women dying of unrelated causes who were autopsied at the Yale–New Haven and Massachusetts General Hospitals (Horwitz et al. 1981). The estimated rates of undetected endometrial carcinoma were 22 and 31 per 10,000, respectively. These rates were four to five times higher than the diagnosis of endometrial carcinoma recorded by the Connecticut State Tumor Registry, indicating that a number of endometrial carcinomas may be asymptomatic and are undetected during life.

A number of studies have evaluated cytologic screening of endometrial cancer. The most recent studies support that the finding of atypical glandular cells on Pap test should trigger endocervical and endometrial sampling, especially in women over 50 years of age. One recent study of 554 women with endometrial carcinoma and a liquid-based Pap test within 36 months prior to the histologic diagnosis found that 38% had abnormal glandular cells on Pap and 6.2% had only benign endometrial cells in women 40 years or older. The detection of abnormal glandular cells correlated with tumor size, tumor type, higher FIGO stage, and lymph-vascular invasion (Serdy et al. 2016). However, the study did not comment on whether the women had vaginal bleeding (i.e., were symptomatic) at the time of the Pap test. In sum, the Pap test remains an insensitive method for the detection of endometrial carcinoma and cytologic detection methods in symptomatic women are of little value as women with abnormal vaginal bleeding are evaluated by either endometrial biopsy or curettage, which yields a more easily interpreted specimen. More recently, molecular analyses to detect endometrial and ovarian cancer have been applied to DNA isolated from thin-prep Pap samples and this is an active area of current research (Wang et al. 2018).

Gross Findings

The gross appearance of endometrioid carcinoma is similar to the various other types of endometrial carcinoma with the possible exception of serous carcinoma or carcinosarcoma (see "Serous Carcinoma" and "Carcinosarcoma" (Malignant Mixed Mullerian Tumor). The endometrial surface is shaggy, glistening, and tan and may be focally hemorrhagic. Endometrioid carcinoma is almost uniformly exophytic even when deeply invasive. The neoplasm may be focal or diffuse but at times

may be composed of separate polypoid masses. Necrosis usually is not evident macroscopically in well-differentiated carcinomas but may be seen in poorly differentiated tumors, sometimes in association with ulcerated or firm areas. Myometrial invasion by carcinoma may result in enlargement of the uterus, but a small atrophic uterus may harbor carcinoma diffusely invading the myometrium. Myometrial invasion usually appears as well-demarcated, firm, gray-white tissue with linear extensions beneath an exophytic mass or as multiple, white nodules with yellow areas of necrosis within the uterine wall. However, some cases of well differentiated carcinoma may show extensive myometrial invasion in the absence of a grossly identifiable invasive component. Extension into the lower uterine segment is common, whereas involvement of the cervix occurs in approximately 20% of cases.

Microscopic Findings: Grading

The grade of endometrioid carcinoma is determined by the microscopic appearance of the tumor. It is based on the architectural pattern, nuclear features, or both (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, and 16). The architectural grade is determined by the extent to which the tumor is composed of solid masses of cells as compared with well-defined glands (Table 2) (Figs. 1, 3, 4, 5, 6, and 7, 10, 12, 13, 15). In endometrioid carcinomas with squamous differentiation, it is important to exclude masses of squamous epithelium in determining the amount of solid growth. If the areas of squamous differentiation are non-keratinizing, it may not be possible to distinguish them from solid growth. It has been suggested that if the nuclear features in the solid areas are similar to those seen in the glandular component of the tumor they are best considered non-squamous, solid tumor growth. The nuclear grade is determined by the variation in nuclear size and shape, chromatin distribution, and size of the nucleoli. Grade 1 nuclei are oval, mildly enlarged, and have evenly dispersed chromatin (Figs. 2 and 8). Grade 3 nuclei are markedly enlarged and pleomorphic, with irregular, coarse chromatin and prominent eosinophilic nucleoli (Fig. 14). Grade 2 nuclei have features intermediate to grades 1 and 3 (Figs. 11 and 16). Mitotic activity is an independent histologic variable, but it is generally increased with increasing nuclear grade, as are abnormal mitotic figures.

The most recent revision of the FIGO Staging System (Table 3) and the WHO Histopathologic Classification of uterine carcinoma recommend that tumors be graded using both architectural and nuclear criteria (Scully et al. 1994; Creasman 1989). The grade of tumors that are architecturally grade 1 or 2 should be increased by one grade in the presence of

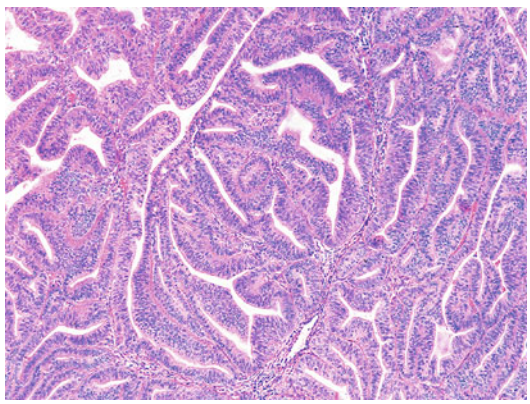

Fig. 1 Endometrioid carcinoma, FIGO grade 1 (architectural grade 1, nuclear grade 1). Well-differentiated endometrioid glands are interconnected in a confluent glandular pattern with surrounding desmoplastic stroma; these features indicate endometrial stromal invasion by carcinoma

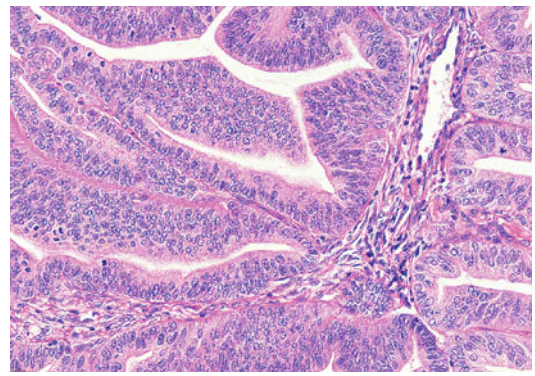

Fig. 2 Endometrioid carcinoma, FIGO grade 1 (architectural grade 1, nuclear grade 1). Well-formed endometrioid glands have small, round to oval nuclei with uniform chromatin

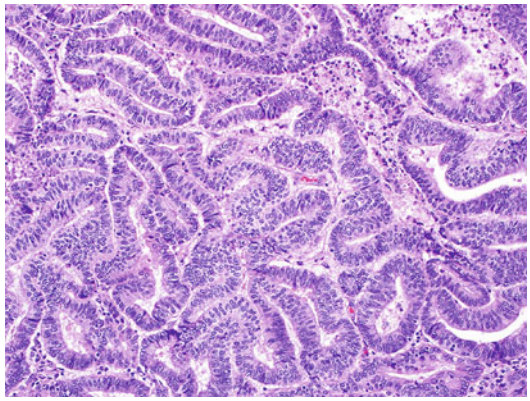

Fig. 3 Endometrioid carcinoma, FIGO grade 1 (architectural grade 1, nuclear grade 1). Endometrioid glandular epithelium is interconnected in a confluent glandular fashion, a pattern indicating endometrial stromal invasion by carcinoma

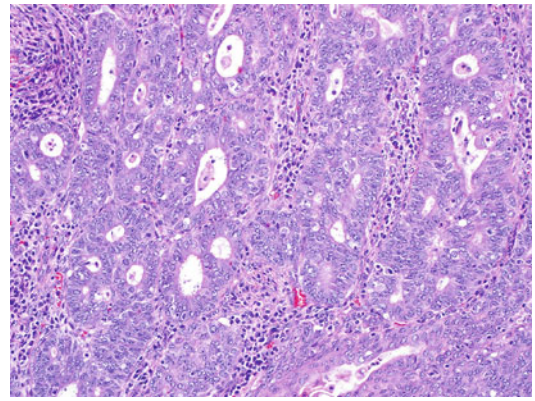

Fig. 5 Endometrioid carcinoma, FIGO grade 1 (architectural grade 1, nuclear grade 2). Well-differentiated endometrioid glands exhibit cribriform growth, a pattern indicating endometrial stromal invasion by carcinoma

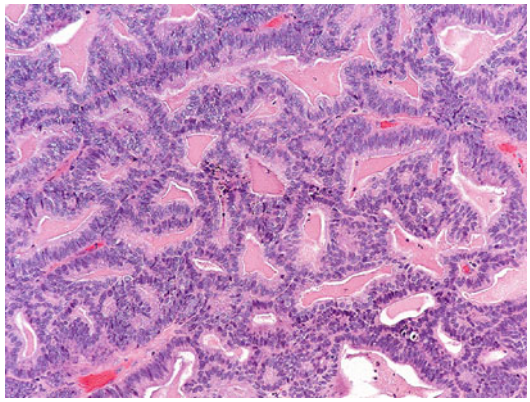

Fig. 4 Endometrioid carcinoma, FIGO grade 1 (architectural grade 1, nuclear grade 1). Well-differentiated endometrioid glands are back-to-back with foci of gland fusion. The latter is indicative of carcinoma

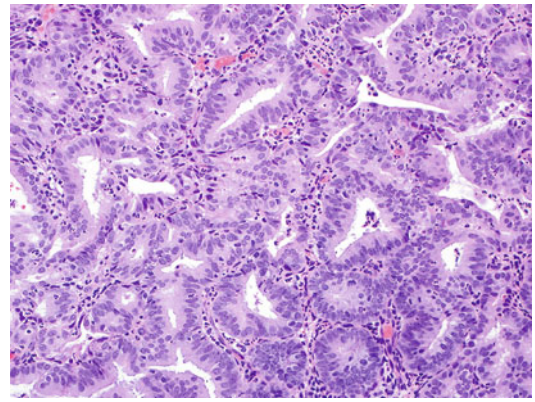

Fig. 6 Endometrioid carcinoma, FIGO grade 1 (architectural grade 1, nuclear grade 1). Back-to-back and fused glands are consistent with carcinoma

"notable" nuclear atypia (grade 3 nuclei) involving greater than 50% of the tumor (Zaino et al. 1995). For example, a tumor that is grade 2 by architecture but in which there is marked nuclear atypia (nuclear grade 3) should be upgraded to grade 3. Thus, tumors are graded primarily by their architecture, with the overall grade modified by the nuclear grade when there is discordance. Marked discordance between nuclear and architectural grade is unusual in endometrioid carcinoma and should raise suspicion that the tumor is a serous carcinoma (see "Serous Carcinoma").

Given the importance of tumor grading in patient outcome, and consequently its significant role in clinical decision making, appropriate interobserver reproducibility is necessary in utilized grading schemes. Multiple studies have shown that the interobserver reproducibility of the FIGO grading method for endometrioid carcinomas based on architecture is acceptable, but have shown poor reproducibility when grading is based on nuclear features (Lax et al. 2000a; Nielsen et al. 1991). Nonetheless, it has been shown that upgrading architecturally grade 1 or 2 tumors based on nuclear features resulted in their reclassification into a higher grade category with similar risk of recurrence and

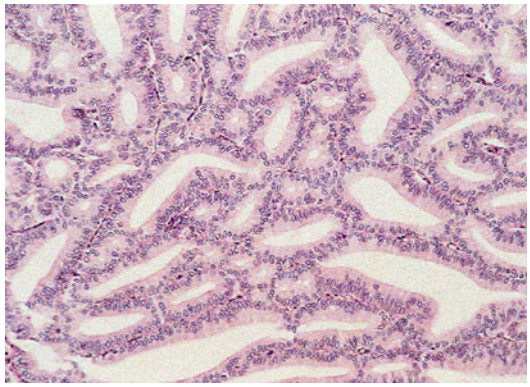

Fig. 7 Endometrioid carcinoma, FIGO grade 1 (architectural grade 1, nuclear grade 1). Back-to-back and fused well-differentiated glands have mucinous features

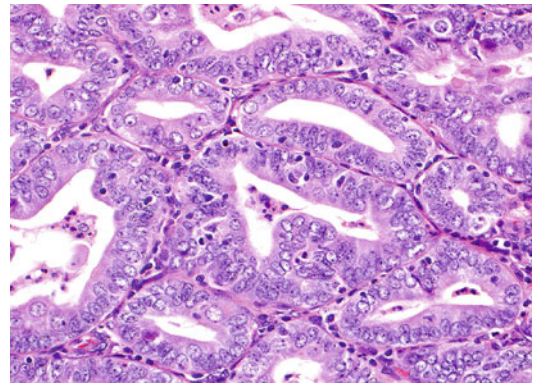

Fig. 9 Endometrioid carcinoma, FIGO grade 1 (architectural grade 1, nuclear grade 2). Nuclei are somewhat enlarged, rounded, and have granular to vesicular chromatin with occasional small nucleoli

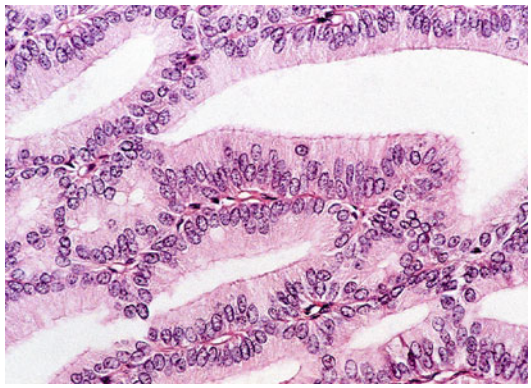

Fig. 8 Endometrioid carcinoma, FIGO grade 1 (architectural grade 1, nuclear grade 1). Nuclei are round to oval with uniform chromatin

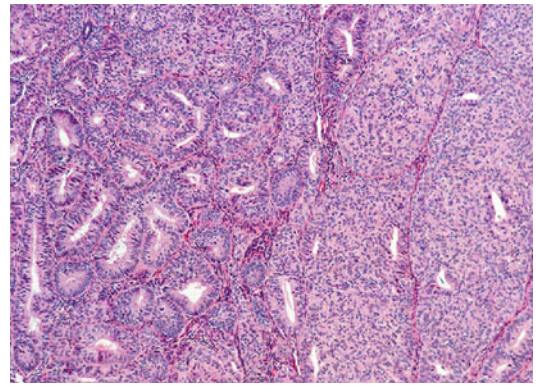

Fig. 10 Endometrioid carcinoma, FIGO grade 2 (architectural grade 2, nuclear grade 1). Well-formed glands are admixed with solid non-squamous nests of tumor, with the latter comprising more than 5% but less than 50% of the overall tumor

death, reinforcing the need for a uniform definition of nuclear atypia (Zaino et al. 1995).

Marked differences in architectural grade can be seen within a tumor. It is not unusual to see well-formed glandular elements immediately adjacent to solid endometrioid areas. When a tumor displays this type of heterogeneity, the architectural grade should be based on the overall appearance. The heterogeneity in differentiation accounts for the differences in grade that can be observed between the endometrial curettings and the hysterectomy specimen. Discordance between the curettage and hysterectomy specimens occurs in 15–25% of cases (Daniel and Peters 1988; Larson et al. 1995; Obermair et al. 1999).

Myoinvasion

Endometrial carcinoma may manifest different forms of myometrial invasion (Figs. 17 and 18). It can invade along a broad pushing front or it can infiltrate the myometrium diffusely as masses, cords, or clusters of cells and individual glands. When it invades along a broad front it may be difficult to determine whether invasion is, in fact, present unless it can be compared to the adjacent uninvolved endomyometrium. When the tumor diffusely invades the myometrium, the neoplastic glands usually elicit a reactive stromal response characterized by loose fibrous tissue accompanied

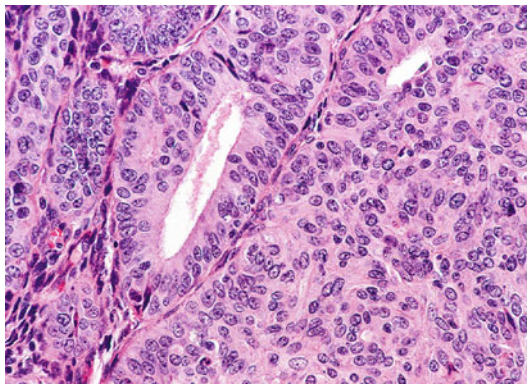

Fig. 11 Endometrioid carcinoma, FIGO grade 2 (architectural grade 2, nuclear grade 1). Glandular and solid areas have generally uniform small, round to oval nuclei with granular chromatin

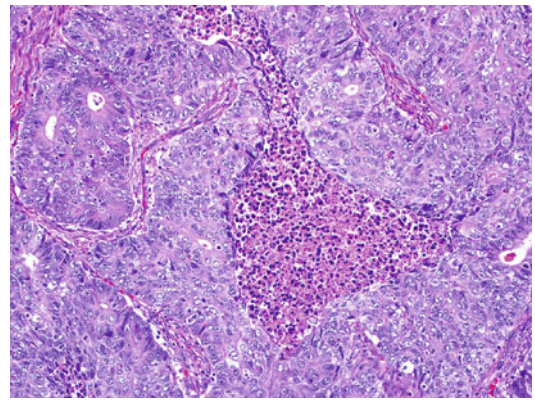

Fig. 13 Endometrioid carcinoma, FIGO grade 3 (architectural grade 3, nuclear grade 3). A few residual glandular structures are present within an otherwise solid non-squamous (>50%) tumor with areas of necrosis

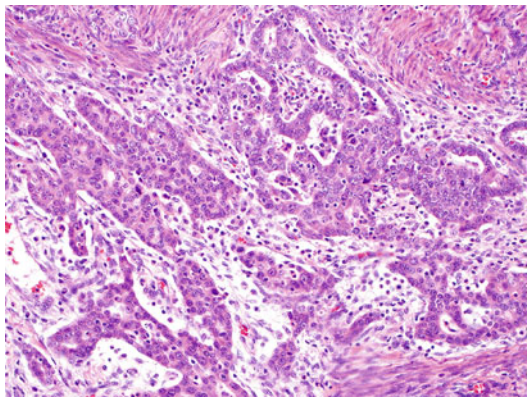

Fig. 12 Endometrioid carcinoma, FIGO grade 2 (architectural grade 2, nuclear grade 2). Tumor is composed of intimately admixed glandular and solid non-squamous epithelium within an edematous and inflamed altered stroma

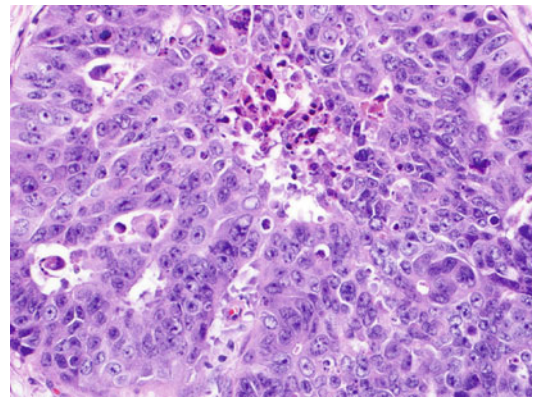

Fig. 14 Endometrioid carcinoma, FIGO grade 3 (architectural grade 3, nuclear grade 3). Solid non-squamous tumor with foci of necrosis and rare residual glandular lumens displays notable nuclear atypia characterized by nuclear enlargement and pleomorphism with vesicular chromatin and prominent nucleoli

by a chronic inflammatory infiltrate that surrounds the glands. Occasionally, well-differentiated carcinomas may be deeply invasive with glands directly in contact with surrounding myometrium in the absence of a stromal response (diffusely infiltrative or adenoma malignum pattern of invasion) (Mai et al. 2002) (Longacre and Hendrickson 1999). In these cases, when myometrial invasion is superficial the presence of invasion can be identified if a haphazard glandular arrangement is present. Usually this pattern of invasion is found in deeply invasive tumors, however, and therefore recognizing myometrial invasion is not a problem. Endometrioid carcinomas with the diffusely infiltrative pattern of invasion share the same prognostic indicators of clinically aggressive disease as those having the more conventional pattern of myometrial invasion (Longacre and Hendrickson 1999). An unusual form of myoinvasion has been described that consists of outpouching of neoplastic glands that become detached and may be lined by flattened epithelium sometimes appearing as microcysts which is associated with a fibromyxoid stromal reaction (Fig. 18). This type of invasion has been

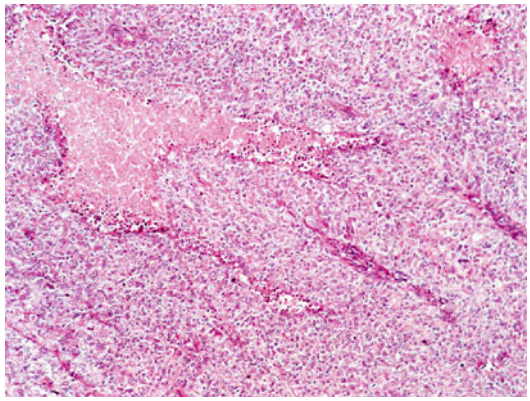

Fig. 15 Endometrioid carcinoma, FIGO grade 3 (architectural grade 3, nuclear grade 2). Tumor is composed of solid non-squamous epithelium with areas of necrosis

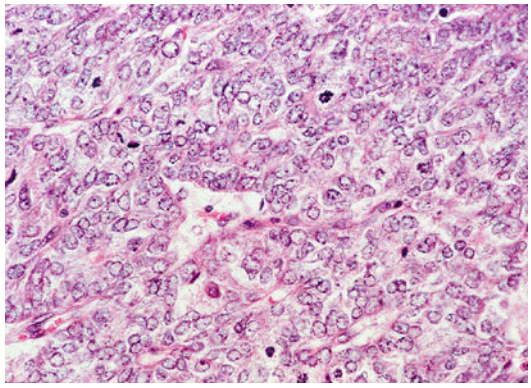

Fig. 16 Endometrioid carcinoma, FIGO grade 3 (architectural grade 3, nuclear grade 2). Nuclei are only modestly pleomorphic, with vesicular chromatin and numerous mitotic figures. Spaces consistent with residual gland lumens favor endometrioid rather than undifferentiated carcinoma and clear cytoplasmic change in the absence of any other characteristic features of clear cell carcinoma is insufficient to diagnose the latter

Table 2 Architectural grading of endometrial carcinoma

Grade 1	No more than 5% of the tumor is composed of solid masses
Grade 2	6–50% of the tumor is composed of solid masses
Grade 3	More than 50% of the tumor is composed of solid masses

Table 3 International Federation of Gynecology and Obstetrics Staging of Endometrial Cancer, 2009

IA	G123	Tumor limited to the endometrium or the inner half of myometrium
IB	G123	Tumor invasion into the outer half of myometrium
II	G123	Tumor invades cervical stroma[a]
IIIA	G123	Tumor invades serosa and/or adnexa[b]
IIIB	G123	Vaginal and/or parametrial invasion
IIIC1	G123	Metastases to pelvic lymph nodes
IIIC2	G123	Metastases to para-aortic lymph nodes
IVA	G123	Tumor invasion of bladder and/or bowel mucosa
IVB	G123	Distant metastases including intra-abdominal and/or inguinal lymph nodes

G1, 5% or less of a non-squamous or nonmorular solid growth pattern; G2, 6–50% of a non-squamous or nonmorular solid growth pattern; G3, more than 50% of a non-squamous or nonmorular solid growth pattern

Rules on staging: 1. Corpus cancer is now surgically staged. Those patients who do not undergo a surgical procedure should be staged according to the 1971 FIGO clinical staging. 2. Ideally, the thickness of the myometrium should be measured along with the depth of tumor invasion

Notes on grading: 1. Notable nuclear atypia, inappropriate for the architectural grade, raises a grade 1 or grade 2 tumor by one. 2. In serous adenocarcinomas, clear cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence. 3. Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component

[a]Endocervical gland involvement should be considered Stage I

[b]Positive peritoneal fluid cytology should be reported separately, but does not affect the stage

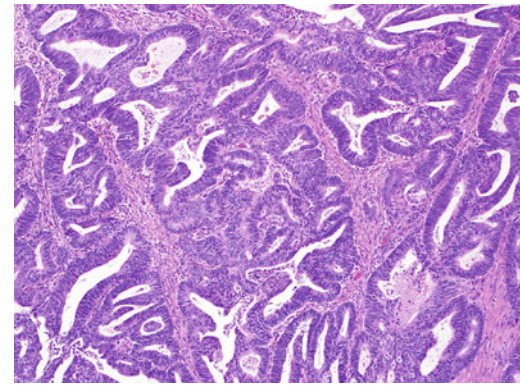

Fig. 17 Endometrioid carcinoma, FIGO grade 1, myoinvasive. Myometrial invasion by carcinoma is characterized by islands of well-differentiated glands surrounded by smooth muscle

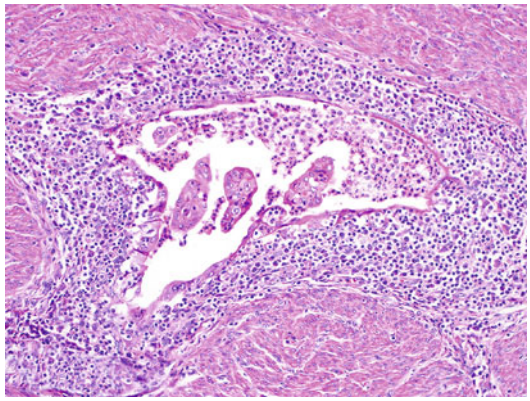

Fig. 18 Endometrioid carcinoma, FIGO grade 1, myoinvasive. Some endometrioid carcinomas lose their characteristic columnar endometrioid features and invade myometrium insidiously as attenuated and dilated glands, often intimately associated with an inflammatory reaction

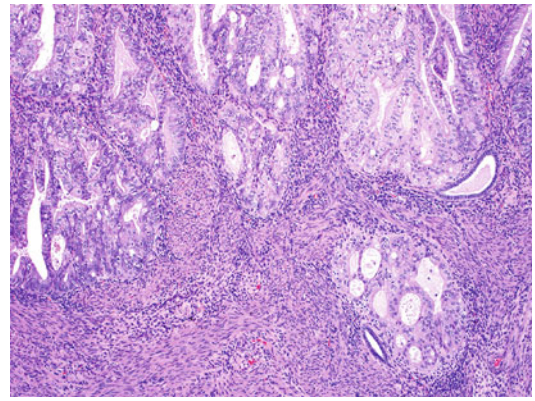

Fig. 20 Endometrioid carcinoma, FIGO grade 1, noninvasive. Nests of carcinoma along an irregular endomyometrial junction suggest superficial myometrial invasion but preserved benign endometrial glands at the periphery of two nests indicate the tumor is still confined to the endometrium

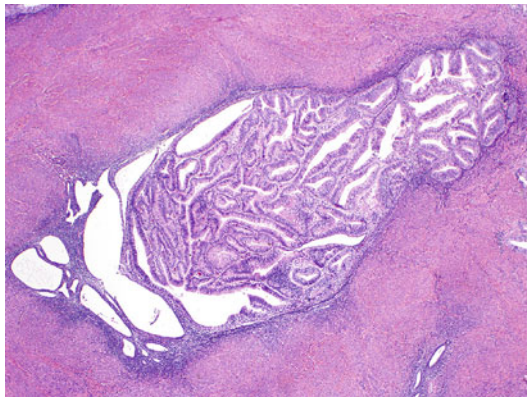

Fig. 19 Endometrioid carcinoma involving adenomyosis. FIGO grade 1 carcinoma is present within an island of adenomyosis, identified by the residual benign endometrial glands and stroma along the periphery of the island. Uninvolved adenomyosis is also present

termed "microcystic, elongated, and fragmented (MELF)" (Murray et al. 2003). MELF invasion is associated with lymph-vascular invasion, but not with poor prognosis in a multivariate analysis (Euscher et al. 2013).

It may be difficult to distinguish myometrial invasion from extension of the carcinoma into adenomyosis (Fig. 19). The distinction, however, is important because the presence of carcinoma in adenomyosis deeper than the maximum depth of true tumor invasion does not worsen the prognosis (Hall et al. 1984; Hernandez and Woodruff 1980; Jacques and Lawrence 1990; Mittal and Barwick 1993). When the carcinoma is surrounded by endometrial stroma and residual benign glands are present in these foci, the diagnosis of carcinoma extending into adenomyosis is straightforward. At times, however, the distinction from myometrial invasion may be extremely difficult, particularly in older women in whom adenomyosis may have very minimal stroma as a result of fibrosis and atrophy. In these cases, it is necessary to evaluate additional features such as the presence of desmoplasia, surrounding edema and inflammation, and the shape of the glands (Jacques and Lawrence 1990). In contrast to carcinoma involving adenomyosis, true myometrial invasion is usually characterized by desmoplasia or loosening of the myometrium surrounding the glands. Often there is accompanying chronic inflammation and the glandular outline is jagged and irregular, as compared to carcinoma involving adenomyosis in which the glands have a smooth, rounded outline and desmoplasia and inflammation are lacking (Fig. 20). Since CD10 is normally expressed by endometrial stromal cells but not smooth muscle of the myometrium, it would seem that the presence of CD10 in the cells around an adenocarcinoma in the myometrium would indicate its presence in adenomyosis. Unfortunately, CD10 is

also often (52% of cases) expressed focally in the cells surrounding clusters of tumor in the myometrium of women in whom adenomyosis is absent, thus eliminating its utility (Nascimento et al. 2003; Srodon et al. 2003). A diagnosis of carcinoma involving adenomyosis should be made only when there is evidence of adenomyosis uninvolved by carcinoma or residual adenomyosis within foci involved by carcinoma in the uterus because some endometrioid carcinomas invade the myometrium without eliciting a stromal response. A recent study noted that adenocarcinoma involving adenomyosis frequently is associated with preceding estrogen use, low tumor grade, and an excellent prognosis (Mittal and Barwick 1993).

Diagnosis of superficial myometrial invasion is often problematic due to irregularity of the normal endomyometrial junction, particularly in older women. The presence of residual non-neoplastic endometrial glands and stroma along the deep or peripheral aspect of rounded nests of carcinoma situated at the irregular endomyometrial junction is evidence that these nests are still within the endometrium proper and have not invaded superficial myometrium (Fig. 20). Fortunately, the 2009 FIGO staging eliminated the need to distinguish between superficially invasive and noninvasive tumors as they are both considered stage IA.

Differential Diagnosis

The main problem in the differential diagnosis of low-grade endometrioid carcinoma is the distinction from atypical hyperplasia, atypical polypoid adenomyoma, hyperplasia with various types of cytoplasmic alterations (metaplasias), Arias-Stella reaction, and menstrual endometrium. The distinction from the first three conditions is discussed in ▶ Chap. 8, "Precursors of Endometrial Carcinoma." At times, an extremely atypical Arias-Stella reaction may simulate adenocarcinoma. In the reproductive age group, Arias–Stella reaction is much more likely than carcinoma, especially if the clinical history indicates a recent pregnancy. Nonetheless, carcinoma can occur in young women and also in pregnancy. In contrast to a carcinoma, the Arias–Stella reaction tends to be multifocal and is admixed with secretory glands and decidua. The glands in the Arias–Stella reaction may be complex and tortuous but lack confluent or papillary patterns. The stroma does not show a desmoplastic response. The nuclei in the glandular epithelium of the Arias–Stella reaction may be markedly enlarged, but the chromatin appears degenerated and smudged and mitotic figures are very unusual.

Menstrual endometrium can be confused with adenocarcinoma because of the extensive tissue breakdown characterized by tissue fragmentation and hemorrhage. The pattern of stromal breakdown results in fragmented glands of varying size and compact clusters of stromal cells haphazardly mixed with blood, which can appear ominous. The glandular epithelium, however, is bland and shows evidence of secretory activity. Adjacent intact fragments of endometrium with associated predecidual change usually can be identified and assist in the differential diagnosis.

Another problem in differential diagnosis is the distinction of primary endometrial carcinoma from endocervical adenocarcinoma. This is problematic because these carcinomas share morphologic features (endometrioid and mucinous differentiation). Distinction can be difficult even in hysterectomy specimens when the tumor involves both the lower uterine segment and endocervix, and precursor lesions are lacking or obscured by carcinoma. The distinction is important because surgical management of these tumors often differs (see "Immunohistochemical Findings" for further discussion of markers that assist in this distinction).

A related problem is the distinction of a primary endometrial carcinoma from a metastasis from an extrauterine site, discussed in "Tumors Metastatic to the Endometrium." A high-grade endometrioid carcinoma at times may be difficult to distinguish from a carcinosarcoma (discussed in that section below).

Immunohistochemical Findings

Endometrioid carcinoma expresses PAX8, pan-cytokeratins, epithelial membrane antigen (EMA), and the glycoprotein associated markers CA125, Ber EP4, and B72.3, among others. Expression of carcinoembryonic antigen (CEA), which is uncommon, is almost always limited to apical membranes, although tumors showing extensive mucinous differentiation may express

this antigen more diffusely. Nearly all endometrioid carcinomas are cytokeratin 7 positive and cytokeratin 20 negative (Wang et al. 1995; Castrillon et al. 2002). Occasionally, endometrioid tumors in areas of mucinous and squamous morular metaplasia express CDX2 (Wani et al. 2008; Park et al. 2008). Unlike many other adenocarcinomas, endometrioid tumors frequently display strong staining for vimentin.

Studies of the molecular pathogenesis of endometrioid carcinoma have led to a better understanding of its immunophenotype. The preponderance of FIGO grade 1 and 2 endometrioid carcinomas express ER and progesterone receptor (PR) and approximately one-half of FIGO grade 3 endometrioid carcinomas without serous, clear cell, or undifferentiated features are ER/PR positive (Koshiyama et al. 1993; Reid-Nicholson et al. 2006; Soslow et al. 2000a; Lax et al. 1998a; Vang et al. 2001; Darvishian et al. 2004). p53 overexpression resulting from *TP53* mutation and accumulation of mutant p53 protein is extremely rare in FIGO grade 1 adenocarcinomas and only in a minority of FIGO grade 2 adenocarcinomas but is present in a significant number of FIGO grade 3 adenocarcinomas. However, when p53 staining is prominent, serous, clear cell, or undifferentiated tumors should be considered (Lax et al. 1998a; Darvishian et al. 2004; Tashiro et al. 1997a; Soslow et al. 1998; Lax et al. 2000b; Lax et al. 1998b; Sherman et al. 1995; Zheng et al. 1998). Overexpression is defined as diffuse and strong expression in more than 80% of tumor cell nuclei. This should be distinguished from low-level expression of p53 in less than 50% of tumor cell nuclei, which is commonly found in endometrioid adenocarcinomas.

PTEN is frequently mutated in endometrioid carcinomas (Darvishian et al. 2004; Obata et al. 1998; Risinger et al. 1997; Simpkins et al. 1998; Tashiro et al. 1997b; Yokoyama et al. 2000; Bussaglia et al. 2000) and expression of this gene is sometimes silenced via hypermethylation of its promoter. Detecting loss of PTEN with immunohistochemistry, however, is challenging (Darvishian et al. 2004; Pallares et al. 2005).

DNA MMR proteins are found to be lacking in tumor cell nuclei using immunohistochemistry in one-fifth to one-third of endometrioid carcinomas (Modica et al. 2007; Vasen et al. 2004; Peiro et al. 2002; de Leeuw et al. 2000). In sporadic cases, this most often results from *MLH1* promoter hypermethylation. Those that arise in the setting of Lynch syndrome are due to mutations of *MSH6, MSH2, MLH1,* or *PMS2,* listed in descending order of prevalence. Interpreting DNA MMR protein immunohistochemistry relies on complete loss of expression in the setting of a valid positive internal control (Fig. 21). Valid internal controls include non-neoplastic endometrial stroma and glands with reproducibly stained nuclei. Expression loss, when present, usually occurs in couplets (MLH1 with PMS2 and MSH2 with MSH6) due to the fact that these form protein–protein complexes and loss of one of the proteins leads to destabilization of the other protein in the complex.

For the distinction of endometrial and endocervical adenocarcinomas, the most useful marker panel depends on which subtypes of endometrial and endocervical adenocarcinomas are being considered in the differential diagnosis. For the most common situation of distinguishing endometrial endometrioid carcinomas from high-risk HPV-related endocervical adenocarcinomas, a panel of immunohistochemical markers comprised of p16, ER, and PR has been shown to be useful (Yemelyanova et al. 2009a; Staebler et al. 2002; Missaoui et al. 2006; McCluggage and Jenkins 2003; Ansari-Lari et al. 2004). The vast majority of endocervical adenocarcinomas (~90%) are human papillomavirus (HPV)-related and exhibit diffuse/moderate-strong p16 expression due to complex molecular mechanisms by which high-risk HPV transforming proteins (E6, E7) interact with cell cycle regulatory proteins (p53, pRb) to generate a futile feedback loop resulting in p16 over-expression (see ▶ Chap. 6, "Carcinoma and Other Tumors of the Cervix" on Cervical Cancer). Interestingly, these HPV-related endocervical adenocarcinomas also often lack hormone receptor expression (ER and PR receptors) (Staebler et al. 2002; McCluggage et al. 2002; Yemelyanova et al. 2009b; Ronnett et al. 2008). In contrast, endometrial endometrioid carcinomas are considered

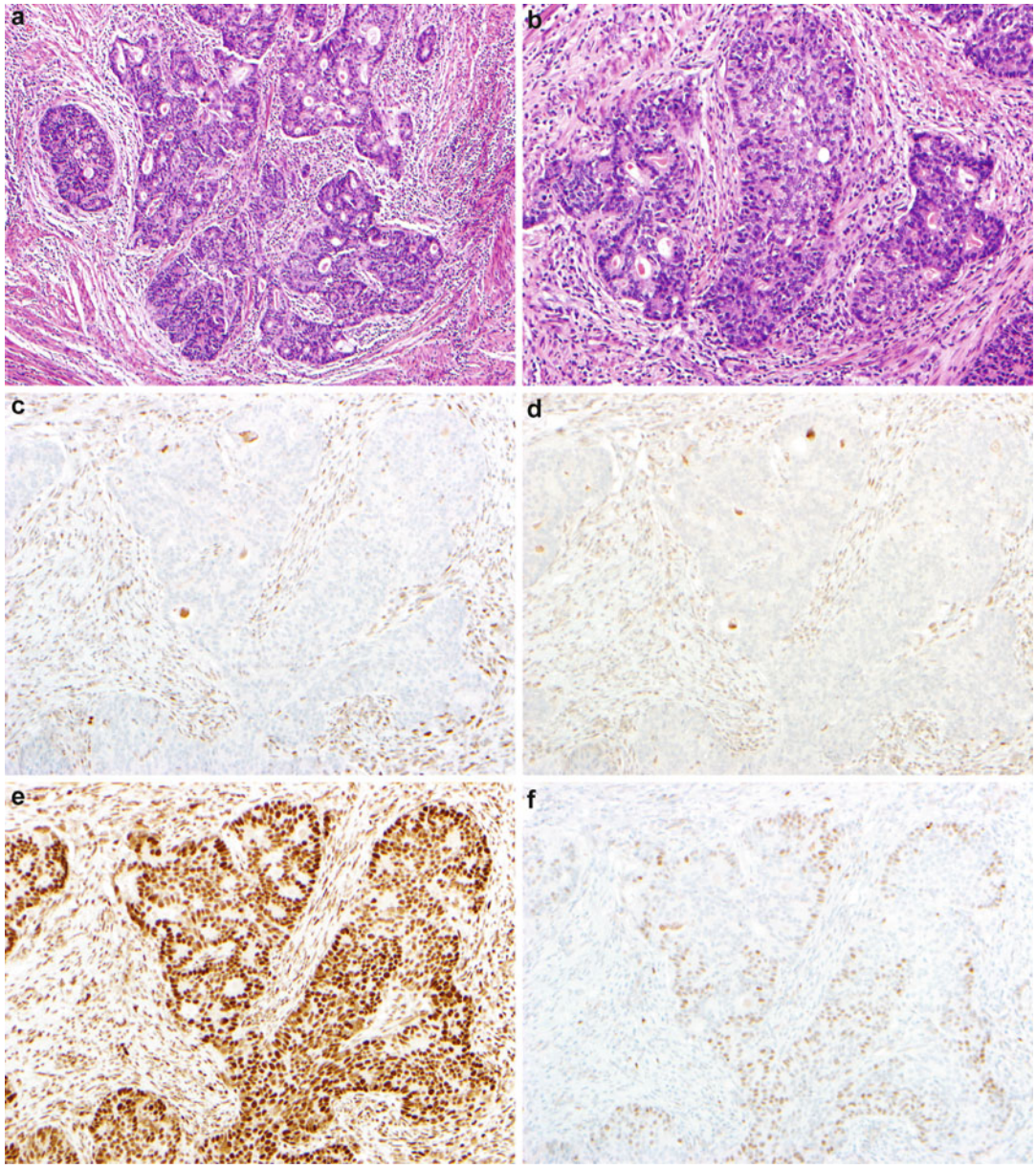

Fig. 21 Immunohistochemistry for DNA MMR proteins in endometrioid carcinoma. (**a**, **b**) Endometrioid carcinoma, FIGO grade 2 has predominantly glandular and focal solid growth. (**c**) Loss of expression of MLH1 in the tumor cells. (**d**) Loss of expression of PMS2 in the tumors cells. (**e**) Retention of MSH2 expression in the tumor cells. (**f**) Retention of MSH6 expression (despite a small number of positive tumor cells, this is interpreted as retention)

etiologically unrelated to HPV. They have been shown to exhibit generally patchy p16 expression of variable intensity, with mean/median extent of expression in 30–40% of tumor cells across all FIGO grades and only rare tumors exhibiting diffuse/strong expression (Fig. 22) (Yemelyanova et al. 2009a). This patchy pattern, even when extensive, is distinct from the completely diffuse expression characteristic of high-risk HPV-related endocervical adenocarcinomas. In addition, most endometrial endometrioid carcinomas, particularly FIGO grade 1 and 2 tumors but also many

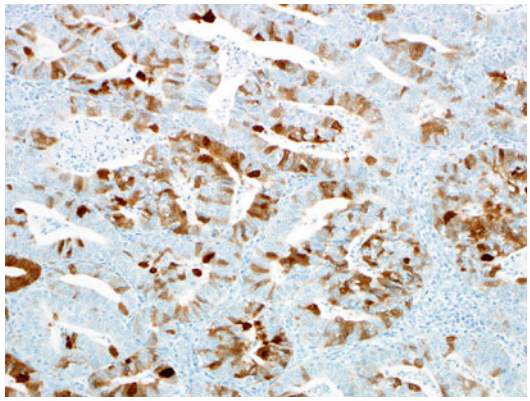

Fig. 22 Endometrioid carcinoma, FIGO grade 1. Tumor exhibits patchy expression of p16

FIGO grade 3 tumors, express hormone receptors (Lax et al. 1998a; Staebler et al. 2002; McCluggage et al. 2002). In practice, p16 alone usually suffices for this particular differential diagnosis. If hormone receptor expression is assessed, we specifically recommend the use of PR in conjunction with ER based on our published (Yemelyanova et al. 2009a; Staebler et al. 2002; Ronnett et al. 2008) and unpublished experiences indicating that the subset of endocervical carcinomas that retains some expression of hormone receptors most often retains ER expression to some degree (often focal/weak-moderate) with loss of PR expression; thus, PR is often the more discriminatory marker of the two for this differential diagnosis. Of note, a subset (minority) of high-risk HPV-related endocervical adenocarcinomas will retain expression of both ER and PR, so retained hormone receptor expression should not necessarily be used to refute a diagnosis of high-risk HPV-related endocervical adenocarcinoma. Detection of high-risk HPV DNA or RNA is definitive for diagnosing high-risk HPV-related endocervical adenocarcinoma but it should be noted that in situ hybridization assays are not 100% sensitive.

Molecular Genetics

Over the past three decades, a number of cancer-causing genes have been analyzed in endometrial carcinoma. Recently, a number of studies have shown that the most frequently altered gene in endometrioid carcinoma is the *PTEN* tumor suppressor gene, which is mutated in 30–54% of cases (Risinger et al. 1997; Tashiro et al. 1997b). *PTEN* is located on chromosome 10q23.3 and encodes a dual-specificity phosphatase (Li et al. 1997). The primary target is the lipid molecule phosphatidylinositol 3,4,5-triphosphate (PIP3) that is involved in a signal transduction pathway that regulates cell growth and apoptosis. The dephosphorylation of PIP3 counteracts the activity of a protein complex called PI3K (phosphoinositol 3 kinase) that leads to the conversion of PIP2 (phosphatidylinositol 4,5-diphosphate) to PIP3. Consequently, the inactivating mutations in *PTEN* result in increased levels of PIP3, which activates downstream molecules including phosphorylation of protein kinase B (AKT). AKT is a central regulator of numerous pathways involved in cell proliferation, cell growth, and apoptosis that are altered in cancer development. Although the specific consequences of *PTEN* mutation have not been completely elucidated in endometrial carcinoma development, it has been noted that the frequency of *PTEN* mutation is similar in all three grades of endometrioid carcinoma. In addition, it is mutated in approximately 20–48% of atypical and non-atypical hyperplasias (Levine et al. 1998; Maxwell et al. 1998). These findings suggest that inactivation of this gene is important early in the pathogenesis of endometrioid carcinoma. Genetic mouse models with germline heterozygous deletion of *PTEN* spontaneously develop endometrial hyperplasia in 100% of female mice with 20% of female mice showing progression to carcinoma supporting an early role of *PTEN* in endometrial tumorigenesis (Podsypanina et al. 1999). Furthermore, one epidemiologic study found that the presence of *PTEN* mutations in complex atypical hyperplasia did not predict progression to carcinoma (Lacey et al. 2008). In sum, these findings suggest that *PTEN* mutations may be central to the development of hyperplasia, but may not play a role in the transition to carcinoma.

Of further interest, mutations in the *PIK3CA* oncogene, the catalytic subunit of PI3K, are common in endometrioid carcinoma (Oda et al. 2005; Hayes et al. 2006). Mutations in *PIK3CA* are

activating mutations and, like *PTEN* mutations, lead to activation of the PI3K pathway. The mutations are found in endometrioid carcinoma with and without *PTEN* mutations but are more common in tumors with *PTEN* mutations. An additional study showed that while *PTEN* mutations occur in a similar frequency in complex atypical hyperplasia and carcinoma, *PIK3CA* mutations are rare in complex atypical hyperplasia and occur in approximately 39% of carcinoma, and are present in all three tumor grades (Hayes et al. 2006). These studies suggest that inactivation of *PTEN* and activation of *PIK3CA* have different roles in the development of endometrioid carcinoma. While *PTEN* is important in the development of hyperplasia, mutations in *PIK3CA* may play a role in the transition of complex atypical hyperplasia to carcinoma. Although the biologic basis of this has not yet been elucidated, understanding *PTEN* and *PIK3CA* mutations and their roles in the development of endometrial hyperplasia and carcinoma may provide targets for therapeutic intervention before the development of invasive disease.

ARID1A mutations are common in endometrioid carcinoma occurring in about 40% of tumors. The vast majority are truncation mutations resulting in loss of expression of the protein. *ARID1A* is a tumor suppressor gene and is a member of the SWI/SNF family that has both helicase and ATPase activity. This family of genes is thought to control transcription of specific genes through their role in regulating chromatin structure.

The *TP53* tumor suppressor gene has been extensively studied in endometrial cancer, as in other tumors. *TP53* encodes a DNA-binding phosphoprotein that is involved in cell cycle control and apoptosis. Mutations in *TP53* are found in approximately 10% of all endometrioid carcinomas, with most occurring in grade 3, and occasionally in grade 2 tumors. Overall, *TP53* mutations occur in approximately 50% of grade 3 tumors, and they have rarely been identified in grade 1 tumors or endometrial hyperplasia (Lax et al. 2000b). This finding is consistent with a role for *TP53* in the progression, but not the initiation, of endometrioid carcinoma.

As discussed in the section on Lynch syndrome, another common molecular alteration in endometrioid carcinoma is the molecular phenotype of MSI. MSI is defined as alterations in the length of short, repetitive DNA sequences, called microsatellites, in tumor DNA compared to DNA isolated from the same patient's normal tissue. This molecular phenotype is detected in tumors that lack an intact DNA MMR system, a fundamental cellular mechanism for preventing DNA alterations that are created largely during DNA replication. In tumors that display MSI, the DNA MMR system has been inactivated either through mutation or "silencing" by promoter hypermethylation of one of the DNA MMR genes (Esteller et al. 1998). The consequence of inactivating the DNA MMR system is an increase in the rate at which mutations occur, a factor that clearly contributes to tumorigenesis. Microsatellite instability is found in tumors from patients affected by Lynch syndrome in which endometrial carcinoma is the most common noncolorectal malignancy, as discussed above in the section on Lynch syndrome (Eshleman and Markowitz 1995). MSI also is present in approximately 20–30% of sporadic endometrial cancers and can be found in complex atypical hyperplasias that are associated with cancers that demonstrate instability (Levine et al. 1998; Mutter et al. 1996; Duggan et al. 1994). It remains unclear exactly when in the development of endometrial neoplasia the DNA MMR system becomes inactivated. Further studies of endometrial hyperplasia are warranted to address this important biologic and potentially clinically relevant question. Recent studies indicate that MMR deficiency is associated with a more aggressive tumor phenotype, despite the fact that patients with MMR deficient tumors have a similar overall survival to patients with intact MMR tumors. The underlying mechanisms responsible for this seemingly antithetical finding is unclear at present but may be due, at least in part, to the immunological response to the production of neoantigens resulting from the hypermutable state. A recent study reports that patients with MMR deficient

tumors due to methylation of *MLH1* had reduced recurrence free survival (Cosgrove et al. 2017). Clearly, future studies are necessary to better define the prognostic significance of MMR deficiency, recognizing that the cause of the deficiency, the specific mutational profile, and the patient's immune response, as well as response to therapy may all play a role in determining tumor behavior.

As mentioned above, next generation sequencing studies found that approximately 5–7% of endometrioid carcinomas have mutations in *POLE*, a component of DNA polymerase epsilon, that results in an ultramutated phenotype. Although there have been associations of *POLE* mutations with certain morphologic features, they are not robust enough to allow for recognition of this underlying molecular abnormality. Since *POLE* mutations are associated with a good prognosis and eligibility for immune checkpoint inhibitor treatment, these tumors may be important to identify. However, at the present time, assessment of *POLE* mutations is not routinely performed as it requires DNA sequence analysis. However, in cases with ambiguous or unclassifiable morphology and unusual immunohistochemical features, mutational analyses should be considered.

A number of oncogenes have been studied in endometrioid carcinomas, but only a few are altered in a significant number of cases. Mutations in the *KRAS* proto-oncogene have been identified consistently in 10–30% of endometrial cancers in several studies (Lax et al. 2000b; Boyd and Risinger 1991; Enomoto et al. 1993). The mutations have been found in all grades of endometrioid carcinoma and have been reported in complex atypical hyperplasia, suggesting a relatively early role for *KRAS* mutations in this tumor type. *KRAS* encodes a guanine nucleotide-binding protein of 21 kDa that plays a role in the regulation of cell growth and differentiation by transducing signals from activated transmembrane receptors. In the mutant form, *KRAS* is constitutively "on" even in the absence of an activated receptor. Mutations in *FGFR2* (fibroblast growth factor receptor 2) have been identified in 16% of endometrioid carcinomas and it has been shown that *KRAS* and *FGFR2* mutations are mutually exclusive (Byron et al. 2008; Pollock et al. 2007). *CTNNB1* is the gene that encodes β-catenin, an integral component of the Wnt signaling pathway, involved in regulation and coordination of cell-cell adhesion and gene transcription. In endometrial carcinomas, mutations of *CTNNB1* leading to nuclear overexpression of β-catenin can be seen in a subset of low-grade endometrioid carcinomas and significantly less so in either higher grade endometrioid carcinomas or endometrial carcinomas with non-endometrioid histologies (Scholten et al. 2003). However, *CTNNB1* mutations and subsequent Wnt pathway activation are only present in a subset of low-grade endometrioid endometrial carcinomas. Multivariate analysis of prognostic factors in low-grade and early stage endometrioid carcinomas has shown that *CTNNB1* mutations (in particular activating exon 3 mutations) are strongly associated with increased risk of recurrence and overall worse prognosis (Heckl et al. 2018; Kurnit et al. 2017; Liu et al. 2014). L1-cell adhesion molecule (L1CAM) is a transmembrane protein of the immunoglobulin family initially identified in the nervous system, which has been associated with invasive tumor growth and aggressive tumor behavior in various malignancies, by acting as a proangiogenic factor (Friedli et al. 2009; Kiefel et al. 2012; Kommoss et al. 2017; Raveh et al. 2009). In endometrial carcinoma, L1CAM appears to contribute to alterations in the Wnt signaling pathway and epithelial-mesenchymal transition (EMT) (Kommoss et al. 2017; Colas et al. 2012; Heuberger and Birchmeier 2010). Studies have shown a significant association between L1CAM expression and worse clinical outcome in endometrioid histology, and have also established correlations between L1CAM expression and high risk factors such as non-endometrioid histology, vascular invasion, and high-grade tumors (Kommoss et al. 2017; Bosse et al. 2014; Dellinger et al. 2016; Geels et al. 2016; Smogeli et al. 2016; van der Putten et al. 2016; Zeimet et al. 2013). When looking at L1CAM expression in low grade, early stage endometrial endometrioid carcinomas, which would otherwise be considered as "low-risk" tumors, increased expression of L1CAM by

immunohistochemistry was associated with a significant decrease in 5-year survival (71.8% versus 100% in L1CAM negative tumors), suggesting a potential role of L1CAM in management algorithms for these patients (Kommoss et al. 2017).

Other oncogenes that have been found to be overexpressed or amplified are EGFR, CMYC, HER-2/neu, BCL2, and CFMS (Borst et al. 1990; Hetzel et al. 1992; Leiserowitz et al. 1993; Taskin et al. 1997). Additional studies on these genes are needed to more definitively determine their role in endometrial cancer.

Behavior and Treatment

Endometrioid adenocarcinoma spreads by lymphatic and vascular dissemination, direct extension to contiguous organs, and transperitoneal and transtubal seeding. Lymphatic metastasis is more common than hematogenous spread, but involvement of the lungs without metastasis to mediastinal lymph nodes suggests that hematogenous spread may occur early in the course of disease. Endometrial carcinoma tends to spread to the pelvic lymph nodes before involving paraaortic lymph nodes; however, rare examples of isolated para-aortic metastases have been reported. The relative frequency of metastasis to lymph node groups and various organs is shown in Tables 4 and 5, respectively.

The standard treatment for endometrial carcinoma is hysterectomy and bilateral salpingo-oophorectomy. Over the years, preoperative or postoperative radiotherapy and chemotherapy have been used in addition to hysterectomy. The current approach is to treat all patients, when feasible, by hysterectomy supplemented by surgical staging and to administer postoperative radiation to patients with poor prognostic factors that put them at high risk of recurrence. Postoperative estrogen replacement therapy has been advocated for patients with early stage disease and no significant poor prognostic factors (Creasman et al. 1986). One study showed that survival is not compromised in patients with low tumor grade (grades 1 and 2), less than 50% myometrial invasion, and no metastases to lymph nodes or other organs (Lee et al. 1990). Given the prognostic significance of pelvic and paraaortic lymph node status, these nodes should be sampled or dissected in patients when any of the following is present: greater than 50% myometrial invasion, grade 3 tumor, cervical involvement, extrauterine spread, serous, clear cell, or undifferentiated carcinoma, or palpably enlarged lymph nodes. In a Gynecologic Oncology Group (GOG) study, only a quarter of patients had these findings, but they accounted for the majority of patients with positive aortic lymph nodes (Morrow et al. 1991). Recently, evaluation of sentinel lymph nodes has become common, as several studies have suggested that it is both sensitive

Table 4 Sites of lymph node metastasis from endometrial carcinomas at autopsy (From Hendrickson 1975)

Lymph nodes	Relative frequency (%)
Para-aortic	64
Hypogastric	61
External iliac	48
Common iliac	40
Obturator	37
Sacral	22
Mediastinal	18
Inguinal	16
Supraclavicular	12

Table 5 Sites of metastasis from endometrial carcinoma at autopsy (From Hendrickson 1975)

Organ site	Relative frequency (%)
Lung	41
Peritoneum and omentum	39
Ovary	34
Liver	29
Bowel	29
Vagina	25
Bladder	23
Vertebra	20
Spleen	14
Adrenal	14
Ureter	8
Brain or skull	5
Vulva	4
Breast	4
Hand	
Femur	
Tibia	Rare
Pubic bone	
Skin	

and specific, and reduces the morbidity associated with lymph node dissection. However, the significance of micrometastases and isolated tumor cells on prognosis remains unclear (Holloway et al. 2017). Several studies have shown that the depth of myometrial invasion can be assessed by gross inspection and intraoperative frozen section (Noumoff et al. 1991; Shim et al. 1992; Egle et al. 2008). However, other studies have suggested that intraoperative assessments are not reproducible with discrepancies of up to 38% with the final diagnosis and that random sections in the absence of a gross lesion are not warranted (Desouki et al. 2017).

Postoperatively, patients are classified as low, intermediate, or high risk based on surgical pathologic staging. Patients with grade 1 or 2 tumors that are confined to the endometrium or are minimally invasive are defined as low risk and require no further therapy. Patients with pelvic or paraaortic lymph node metastases, or involvement of the adnexa or intraperitoneal sites, are high risk and receive postoperative radiation (vaginal cuff, pelvis, paraaortic area, or whole abdominal). Radiation appears to be of benefit because the 5-year survival rate for women with positive aortic lymph nodes who were treated with postoperative radiation is nearly 40% (Morrow et al. 1991). Despite treatment with surgery and radiotherapy, 50% of stage III tumors recur. Half of these patients die with distant metastasis, although local control is also a major problem. About 4% of patients with endometrial carcinoma have stage IV disease. Spread to the lungs occurs in 36% of patients with stage IV disease. Patients who do not qualify as low or high risk are intermediate in risk. A decision as to whether or not these patients should receive postoperative radiation should be individualized because there are no conclusive data demonstrating a survival benefit for these patients treated with postoperative radiotherapy. Studies evaluating the use of adjuvant hormonal or cytotoxic chemotherapy have shown no improvement in survival over surgery and radiation, and consequently these methods currently are not recommended as standard treatment. In contrast, radiation, hormone, and cytotoxic chemotherapy are used for management of patients with recurrent tumor; 50% of patients with isolated vaginal vault recurrence treated by irradiation are alive at 3 years (Podczaski et al. 1992).

Histologic Effects of Treatment

Radiation

The histologic changes in neoplastic tissues after intracavitary radiation are nonspecific and variable, showing minor to major alterations from their pre-irradiated state. Similarly, nonneoplastic endometrial or endocervical glands may be affected only minimally or show nuclear and cytoplasmic changes that are indistinguishable from those found in neoplastic cells. Because the cytologic changes in both neoplastic and nonneoplastic tissue are similar, identification of carcinoma depends largely on the recognition of histologic patterns and signs of invasion. Irradiated carcinoma generally retains a haphazard glandular pattern, but nonirradiated, nonneoplastic glands tend to maintain their normal architectural arrangement despite radiation effects in the endometrial stroma and myometrium. When radiation effect is evident, nuclei tend to be enlarged, highly pleomorphic, and hyperchromatic, with coarsely clumped chromatin. The cytoplasm often is granular and swollen. Vacuolation can be present in both the nucleus and the cytoplasm. The nuclear changes result from replication of DNA without cell division.

Cytoplasmic vacuolation results from dilatation of various organelles and possible lysis caused by damaged lysosomal membranes. In some instances, radiation may enhance cellular differentiation. Occasionally, poorly differentiated carcinomas without squamous differentiation in the curettings may have nests of squamous epithelium in the resected uterus after radiation. It is in mitosis and the S phase of the cell cycle that a cell is most susceptible to radiation injury. Thus, the difference in radiosensitivity of tumor cells and benign cells is due largely to the increased mitotic activity of the neoplastic cells and the better reparative capacity of nonneoplastic cells. In view of the variable morphologic response to irradiation, it is often difficult to determine whether irradiated tumor cells are viable. On a practical basis, if tumor cells are

evident after irradiation, it should be assumed that some retain the capacity to persist however abnormal they appear.

Radiation changes in the endometrial stroma and myometrium are greatest in the vicinity of the radiation source. The stromal cells are first converted to giant fibroblasts. Early vascular effects include damage to endothelial cells, resulting in thrombosis. The stroma undergoes progressive hyalinization, resulting in a collagenous scar. Elastic tissue often is fragmented and frayed, and blood vessels are thickened and sclerotic. Occasionally, changes similar to those found in atherosclerosis may be present in the intima of blood vessels. Foam cells occur in the intima, and myometrial cells may appear granular and swollen, especially in areas close to the radium source. Scarring, atrophy, and sclerosis of vessels characterize long-standing radiation effects. The endometrium is thin and easily traumatized, and small blood vessels in the stroma are thin walled and ectatic. Some blood vessels form plaques of lipid-filled clear cells in the media.

Progestins

Progestin-induced changes include secretory differentiation of glandular cells, mitotic arrest, conversion of spindle-shaped stromal cells to decidual cells, decrease in estrogen-related cellular changes such as ciliogenesis, and development or enlargement of squamous areas (Richart and Ferenczy 1974; Saegusa and Okayasu 1998). The earliest evidence of progestin effect is subnuclear vacuolization, observed within 2–3 days of treatment. The vacuoles are a manifestation of glycoprotein synthesis, which is followed by an apocrine-type secretion in which the apical portion of the cytoplasm of the cell is discharged into the gland lumen, with reduction in the size of the cell. Longer term therapy aimed at eliminating the disease, at least until patients can become pregnant, results in a number of morphologic changes that can predict response to therapy. These include decreased glandular-to-stroma ratio, decreased to absent mitotic activity, decreased glandular cellularity, loss of cytologic atypia, and a variety of cytoplasmic changes including mucinous, secretory, squamous, and eosinophilic metaplasia. Persistent architectural abnormalities and/or cytologic atypia were predictive of treatment failure (Mentrikoski et al. 2012). Some architectural changes (cribriform and papillary patterns) induced by progestin treatment, are noteworthy as they may be confused with progression (Wheeler et al. 2007; Gunderson et al. 2014). Importantly, biopsies taken after the initiation of treatment require a comparison to the pre-treatment sample for correct interpretation and determination of treatment response.

Squamous Differentiation

Many endometrioid adenocarcinomas contain squamous epithelium, but the amount of squamous epithelium can vary widely. In a well-sampled neoplasm, the squamous element should constitute at least 10% of a tumor to qualify as an adenocarcinoma with squamous differentiation. Endometrioid carcinomas with squamous epithelium should be classified simply as endometrioid carcinoma with squamous differentiation (not "with squamous metaplasia") and graded on the basis of the glandular component as well, moderately, or poorly differentiated (grade 1, 2, or 3, respectively, per FIGO criteria).

There are no differences in the clinical features of endometrioid carcinoma containing squamous epithelium and endometrioid carcinoma lacking squamous elements. Thus, there are no differences in the frequency of obesity, hypertension, diabetes, and nulliparity among the large series in which this has been analyzed (Alberhasky et al. 1982; Connelly et al. 1982).

Gross and Microscopic Findings

These tumors have no distinctive gross findings. Low-grade tumors (grade 1) are composed of glandular and squamous elements but generally the glandular component predominates; the nests of squamous epithelium are confined to gland lumens. The squamous epithelium resembles metaplastic squamous cells of the cervical transformation zone. Frequently, nests of cells with a prominent oval to spindle cell appearance,

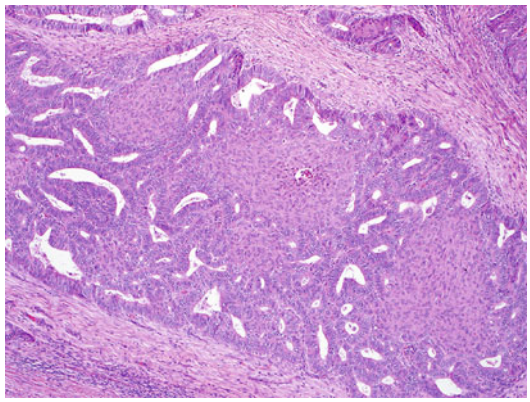

Fig. 23 Endometrioid carcinoma with squamous differentiation, FIGO grade 1. Well-differentiated endometrioid glands are intimately admixed with solid nests of low-grade squamous epithelium. Grading is based on the features of the glandular component alone

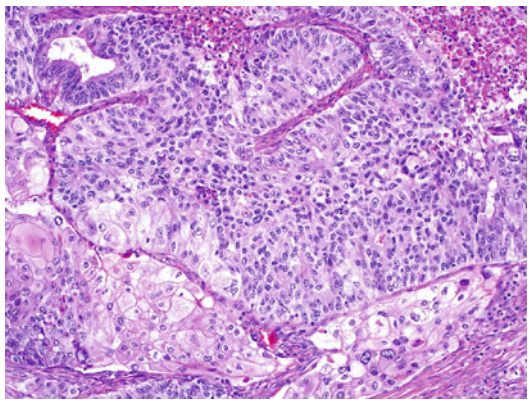

Fig. 24 Endometrioid carcinoma with focal squamous differentiation, FIGO grade 3. Carcinoma has areas of squamous differentiation and is classified as high-grade endometrioid based on the solid non-squamous epithelium (>50%) with focal residual endometrioid glandular differentiation

referred to as morules, are observed (Fig. 23). Intercellular bridges can be identified within the squamous epithelium, and keratin formation is common. The nuclei of the squamous cells are bland, uniform, and lack prominent nucleoli. Mitotic figures are rare. In higher-grade tumors, the squamous element is cytologically more atypical and is not confined to gland lumens but often extends out from the glands (Fig. 24). At times, the squamous cells have a spindle appearance simulating a sarcoma. They may not be in direct continuity with the glandular epithelium, appearing in isolated nests within the myometrium or in vascular spaces. Keratinization and pearl formation occur to varying degrees.

Generally, the glandular component predominates, but masses of epithelial cells that may represent poorly differentiated glandular or squamous cells can lie between glands. This epithelium should be considered glandular unless intercellular bridges are demonstrated or the cells have prominent eosinophilic cytoplasm, well-defined cytoplasmic borders, and a sheet-like proliferation without evidence of gland formation. Both the glandular and squamous components display grade 2 or 3 nuclear atypia, an increased nuclear cytoplasmic ratio, and increased mitotic activity. The glandular architecture usually is poorly differentiated. Tumors of intermediate differentiation are common. These neoplasms contain glandular and solid areas in which the squamous cells display a moderate degree of nuclear atypia, defying separation into a "benign" and "malignant" squamous category.

A rare finding in patients with endometrioid carcinoma with squamous differentiation is the presence of keratin granulomas that may involve a wide variety of sites in the peritoneal cavity including the ovaries, tubes, omentum, and serosa of the uterus and bowel (Chen et al. 1978; Kim and Scully 1990; van der Horst and Evans 2008). Microscopically, these lesions consist of a central mass of keratin and necrotic squamous cells surrounded by a foreign body granulomatous reaction. A proliferation of mesothelial cells also may be present. The granulomas probably result from exfoliation of necrotic cells from the tumor, followed by transtubal spread and implantation on peritoneal surfaces. It is important to distinguish pure keratin granulomas from lesions with both viable-appearing tumor cells and keratin accompanied by a foreign body-type giant cell reaction because the former lesions have not been associated with an unfavorable prognosis. Thus, pure keratin granulomas should not be diagnosed as metastatic endometrioid carcinoma; the latter requires a viable-appearing carcinomatous component.

Differential Diagnosis

The most common problem in the differential diagnosis of the low-grade tumors is with atypical hyperplasia showing squamous metaplasia. To distinguish between the two, the criteria for identifying endometrial stromal invasion should be employed (see ► Chap. 8, "Precursors of Endometrial Carcinoma"). At times, a low-grade tumor may be confused with a high-grade carcinoma because the masses of squamous epithelium are misconstrued as a solid proliferation of neoplastic cells. The nuclear grade is high in poorly differentiated carcinoma, however. Occasionally, squamous morules may be confused with granulomas, but the presence of foreign body giant cells and an inflammatory infiltrate helps identify the latter. For high-grade adenocarcinomas with squamous epithelium, the major problem in differential diagnosis in curettings is distinguishing a primary carcinoma of the endometrium from an adenosquamous carcinoma arising in the endocervix. In the cervix, the squamous component usually predominates, whereas in the endometrium the glandular component predominates. A profusion of cell types, especially mucinous or signet ring cells, is more characteristic of an endocervical neoplasm. (See above section on differential diagnosis).

Behavior and Treatment

As already described, when stratified according to stage, grade, and depth of myometrial invasion, there are few differences in the behavior of carcinomas with squamous epithelium compared with endometrioid carcinomas without squamous epithelium (Abeler and Kjorstad 1992; Zaino and Kurman 1988; Zaino et al. 1991). As occurs with endometrioid carcinomas, the low-grade carcinomas with squamous epithelium tend to be only superficially invasive and seldom invade vascular channels. In contrast, high-grade tumors have a high frequency of deep myometrial invasion, vascular space involvement, and pelvic and paraaortic lymph node metastasis. Metastasis of high-grade tumors occurs widely throughout the pelvis and abdomen, involving bowel, mesentery, liver, kidney, spleen, and lymph nodes. Distant metastasis may involve the lungs, heart, skin, and bones. Nearly two-thirds of metastases contain both glandular and squamous elements, but pure adenocarcinoma or squamous carcinoma is encountered in 20% and 8%, respectively (Ng et al. 1973). Often it is the squamous component that is identified in vascular channels. Accordingly, the treatment for carcinomas with squamous differentiation is the same as that for endometrioid carcinomas without squamous differentiation of comparable stage.

Villoglandular Carcinoma

Villoglandular carcinoma is a variant of endometrioid carcinoma that displays a papillary architecture in which the papillary fronds are composed of a delicate fibrovascular core covered by columnar cells that generally contain bland nuclei (Chen et al. 1985; Hendrickson et al. 1982). The median age is 61 years, similar to that of women with typical endometrioid carcinoma. In all other respects, women with these tumors are similar to patients with low-grade endometrioid carcinoma.

The microscopic appearance of villoglandular carcinoma is characterized by thin, delicate fronds covered by stratified columnar epithelial cells with oval nuclei that generally display mild to moderate (grade 1 or 2) atypia (Figs. 25 and 26). Occasionally, more atypical (grade 3) nuclei may be observed. Mitotic activity is variable, and abnormal mitotic figures are rare (Chen et al. 1985). Myometrial invasion usually is superficial.

Differential Diagnosis

The main consideration in the differential diagnosis is serous carcinoma because both villoglandular and serous carcinomas have a prominent papillary pattern. In contrast to serous carcinomas, villoglandular carcinomas have long delicate papillary fronds and are covered by columnar cells with only mild to moderate nuclear atypia. The cells look distinctly endometrioid with a smooth, luminal border. To have significance as a distinctive entity, the diagnosis is reserved for

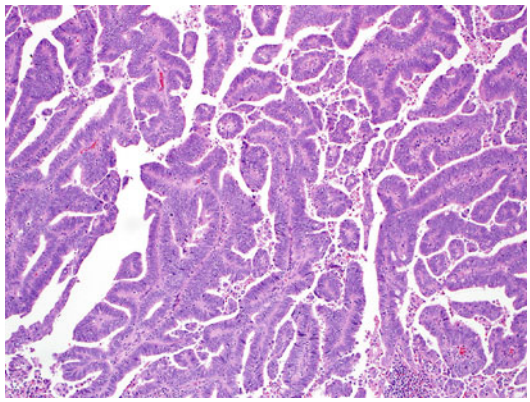

Fig. 25 Endometrioid carcinoma, villoglandular type. Tumor has papillary architecture, which might lead to misclassification as serous carcinoma, but columnar epithelium with low-grade cytologic features (see Fig. 23) is consistent with endometrioid carcinoma

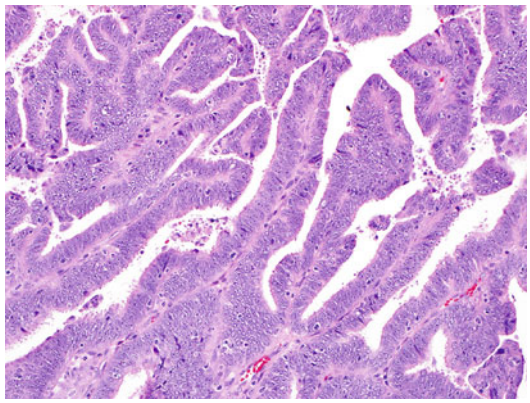

Fig. 26 Endometrioid carcinoma, villoglandular type. Endometrioid differentiation is confirmed by the presence of columnar epithelium and low-grade cytologic features (elongated uniform nuclei)

tumors in which most of the neoplasm has a villoglandular appearance. In contrast to villoglandular carcinomas, serous carcinomas tend to have shorter, thick, densely fibrotic papillary fronds (Bartosch et al. 2011). The most important distinguishing feature is the cytologic appearance. The cells of serous carcinoma tend to be rounder, forming small papillary clusters that are detached from the papillary fronds, a finding that is often referred to as papillary tufts. As a consequence, the luminal border has a scalloped appearance. The nuclei of serous carcinomas are highly pleomorphic and atypical (grade 3). Cherry red macronucleoli typically are present and the cells have a hobnail appearance, often with smudged, hyperchromatic nuclei. It should be noted that considerable nuclear heterogeneity can be observed. If the possibility of serous carcinoma cannot be excluded based on morphologic findings, immunohistochemical analyses for p53, p16, ER, and PR will aid in the distinction. Villoglandular tumors show a wild-type p53 expression pattern, patchy p16 expression and the vast majority will show intense, diffuse expression of ER and PR. Further discussion of this immunohistochemical panel is presented in the serous carcinoma section.

Villoglandular carcinomas are generally better differentiated than typical endometrioid carcinomas but are not significantly different with respect to depth of invasion or frequency of nodal metastases (Zaino et al. 1998). In addition, villoglandular carcinomas are frequently admixed with typical endometrioid carcinoma. In view of the frequent admixture of the two patterns and similar prognosis, villoglandular carcinoma is considered a variant of endometrioid carcinoma. Treatment is the same as for endometrioid carcinoma of comparable stage, grade, and depth of invasion.

Secretory Carcinoma

Secretory carcinoma is a variant of typical endometrial carcinoma in which the majority of cells exhibit subnuclear or supranuclear cytoplasmic vacuoles resembling early secretory endometrium. An unusual pattern, it represents only 1–2% of endometrial carcinomas (Tobon and Watkins 1985). The age range is from 35 to 79 years, with a mean age of 55–58 (Tobon and Watkins 1985; Christopherson et al. 1982a). Most patients are postmenopausal and experience abnormal bleeding. This histologic subtype also may be seen after progestin treatment of an endometrioid carcinoma. In all other respects, including the association of obesity, hypertension, diabetes mellitus, and exogenous estrogen administration,

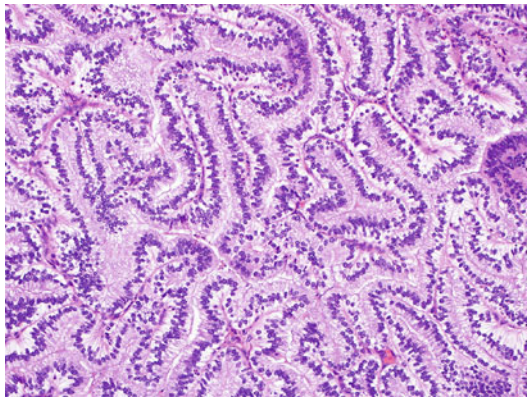

Fig. 27 Endometrioid carcinoma, secretory type, FIGO grade 1. Endometrioid-type epithelium displays prominent sub- and supranuclear vacuolization, reminiscent of day 18 secretory endometrium

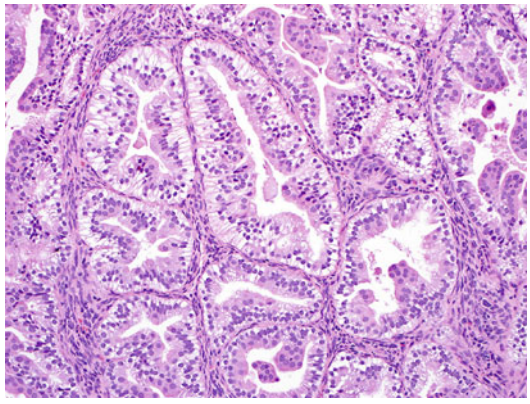

Fig. 28 Endometrioid carcinoma, secretory type, FIGO grade 1. Endometrioid-type glands with secretory differentiation are present within a desmoplastic stroma. Prominent subnuclear vacuolization is reminiscent of day 17 secretory endometrium

patients with secretory carcinoma are similar to women with endometrioid carcinoma.

Microscopically, secretory carcinoma displays a well-differentiated glandular pattern and is composed of columnar cells, often unstratified, with subnuclear or supranuclear vacuolization closely resembling day 17–22 secretory endometrium (Figs. 27, 28, and 29) (Tobon and Watkins 1985). Usually the nuclei are grade 1. The secretory pattern may be focal or diffuse, and it is frequently admixed with typical endometrioid adenocarcinoma. The endometrium adjacent to

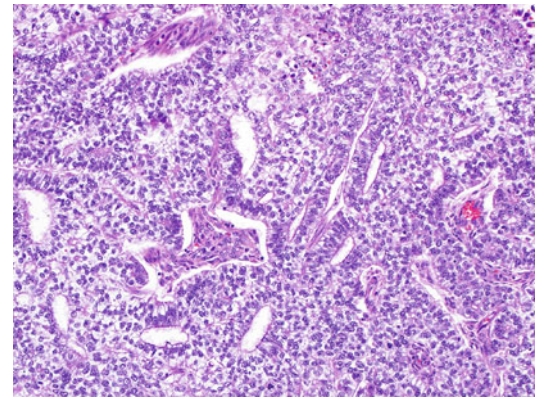

Fig. 29 Endometrioid carcinoma, secretory type, FIGO grade 2. Endometrioid-type glands and solid non-squamous epithelium exhibit diffuse secretory differentiation manifested as clear cytoplasmic change. Tumor has uniform low-grade cytologic features and lacks any of the characteristic architectural patterns of clear cell carcinoma, supporting a diagnosis of secretory type endometrioid carcinoma

secretory carcinoma in young women typically shows a secretory pattern that is more advanced than 17 days, and a corpus luteum is found in most premenopausal patients when a hysterectomy and bilateral salpingo-oophorectomy are performed. Nonetheless, a relationship to progesterone stimulation is not always demonstrable. In fact, secretory carcinoma may occur spontaneously in postmenopausal women without exogenous or abnormal levels of progesterone. The secretory activity in the tumor may be transient because it has been observed in curettings but not in the later hysterectomy specimen (Christopherson et al. 1982a).

Differential Diagnosis

It is important to distinguish secretory carcinoma from clear cell carcinoma in view of the excellent prognosis of the former and unfavorable prognosis of many of the latter. Although both tumors are composed of cells with clear, glycogen-rich cytoplasm, the histologic features are distinctive. At times a secretory carcinoma that has a predominantly glandular pattern can become solid and simulate clear cell carcinoma. The tumors are distinguished by their architectural and cytologic appearance. Secretory carcinoma displays a

glandular architecture like endometrioid carcinoma, is rarely papillary or cystic, and usually is not solid. The cells of secretory carcinoma are columnar, similar to those in endometrioid carcinoma, except that they have supranuclear or subnuclear vacuoles. In contrast, clear cell carcinoma often exhibits tubulocystic and/or papillary architecture but can be glandular. The cells usually have marked nuclear atypia (grade 3), with rounded cells having a variety of characteristic features including hobnail morphology, smudgy hyperchromasia, and prominent nucleoli (Bartosch et al. 2011). Cells with clear cytoplasm also may be seen in the squamous component of an endometrioid adenocarcinoma with squamous differentiation. The clear appearance of these cells is also due to the presence of glycogen. Clear squamous cells tend to be polygonal and usually merge with more typical squamous cells with abundant eosinophilic cytoplasm. The distinction of secretory carcinoma from atypical hyperplasia with secretory effect can be difficult and is based on the presence of stromal invasion in the carcinoma (see ▶ Chap. 8, "Precursors of Endometrial Carcinoma"). Treatment is the same as that for endometrioid carcinoma of the same stage and grade. Secretory carcinoma usually is low grade with a good prognosis (Tobon and Watkins 1985). Death from recurrent disease is rare (Christopherson et al. 1982a).

Ciliated Carcinoma

Ciliated carcinoma is a very rare type of low-grade endometrioid carcinoma (Hendrickson and Kempson 1983). It does not need to be classified separately from endometrioid carcinoma; its only importance is to remind the pathologist that endometrial proliferations with cilia may still be carcinomas. Estrogen induces cilia formation in the normal endometrium. Despite the prevalence of estrogen use, ciliated carcinoma is an extremely rare carcinoma, and most endometrial proliferations in which cilia are observed represent hyperplasias associated with eosinophilic or ciliated change. Patients range in age from 42 to 79 years, are often postmenopausal, and present with bleeding. Ciliated carcinoma has an association with exogenous estrogen treatment. Microscopically, ciliated carcinoma is well differentiated and often displays a cribriform pattern. The gland lumens in the cribriform areas are lined by cells with prominent eosinophilic cytoplasm and cilia. The nuclei of ciliated cells generally have an irregular nuclear membrane and display coarse nuclear chromatin with prominent nucleoli. In most cases, ciliated carcinoma is admixed with nonciliated endometrioid carcinoma and occasionally areas of mucinous carcinoma. Although some ciliated carcinomas are moderately differentiated and invade to the middle third of the myometrium, none of the patients has developed recurrence or died of disease. Thus, the presence of cilia in a bona fide carcinoma identifies a low-grade neoplasm.

Corded and Hyalinized Endometrioid Carcinoma

This is an unusual variant of endometrioid carcinoma that is perhaps most important because its histologic features may suggest a carcinosarcoma. The defining feature of this tumor is the presence of cords of epithelial cells or spindle cells embedded in hyalinized stroma that may mimic a sarcomatous component (Fig. 30). However, unlike carcinosarcomas, this pattern is usually associated with typical low-grade endometrioid carcinoma, often with areas of squamous differentiation. In addition, endometrial hyperplasia is found in approximately half of the cases. On careful examination, the corded epithelial cells and the spindle cells have low-grade cytological atypia in distinction to carcinosarcomas that have high-grade atypia in both the epithelial and sarcomatous components (Murray et al. 2005).

Mucinous Carcinoma

This uncommon type of endometrial carcinoma has an appearance similar to mucinous carcinoma of the endocervix (Czernobilsky et al. 1980; Tiltman 1980). Mucinous carcinoma represents the dominant cellular population in only 1–9%

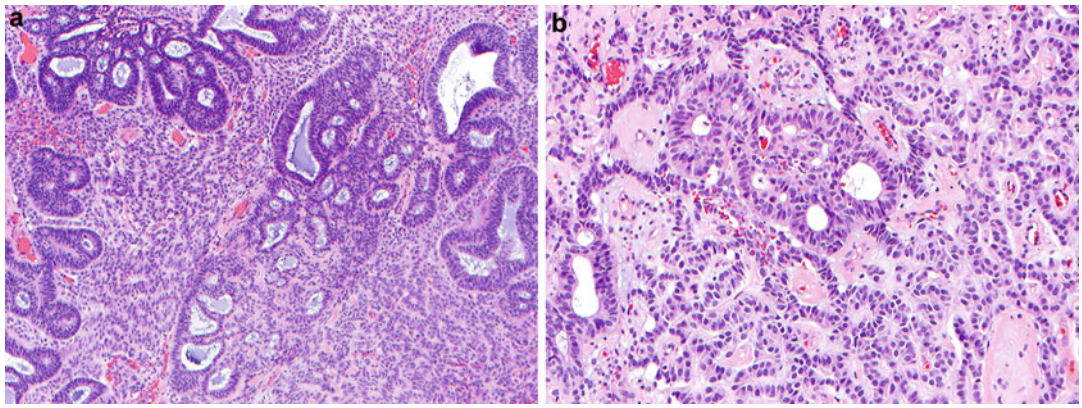

Fig. 30 Endometrioid carcinoma, corded and hyalinized variant. (**a**) Low power magnification demonstrates a typical endometrioid glandular component admixed with a corded epithelioid component, both with low-grade nuclear features. (**b**) Higher magnification demonstrates the hyalinized background with embedded cords of epithelial cells adjacent to well-formed glands

of endometrial carcinomas (Ross et al. 1983; Melhem and Tobon 1987). To qualify as a mucinous carcinoma, more than one-half the cell population of the tumor must contain periodic acid–Schiff- (PAS-) positive, diastase-resistant intracytoplasmic mucin.

Judging from the few published cases, the clinical features of patients with mucinous carcinoma of the endometrium do not differ from those with endometrioid carcinoma. However, one study found that mucinous differentiation is a risk factor for nodal metastases but did not change overall survival (Musa et al. 2012). Patients range in age from 47 to 89 years and typically present with vaginal bleeding. In one study, more than 40% had a history of receiving exogenous estrogens (Melhem and Tobon 1987). Most patients present with stage I disease.

These tumors do not have distinctive gross features. The most frequent architectural pattern is glandular, often in a villoglandular configuration (Figs. 31 and 32). The epithelial cells lining the glands and papillary processes tend to be uniform columnar cells with minimal stratification. Cribriform areas are unusual; cystically dilated glands filled with mucin and papillary fronds surrounded by extracellular lakes of mucin, containing neutrophils, are typical. Curiously, mucinous differentiation sometimes is associated with squamous differentiation. Nuclear atypia is mild to moderate,

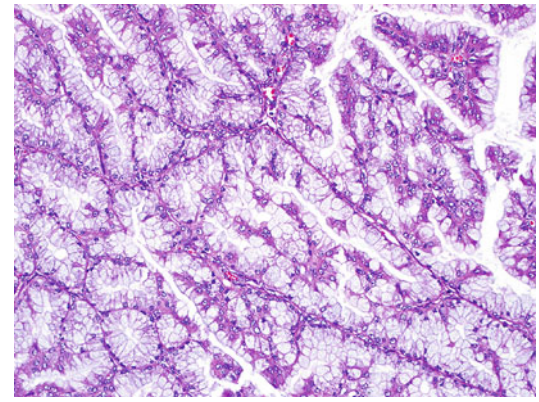

Fig. 31 Mucinous carcinoma, FIGO grade 1. Confluent glands have abundant mucinous cytoplasm and small, basally situated nuclei

and mitotic activity is not prominent. Hyperplasia and mucinous metaplasia sometimes are present in the adjacent endometrium. One study reported that the carcinoma was present in a polyp in 27% of the cases (Melhem and Tobon 1987). The presence of intracytoplasmic mucin can be identified on H&E stains by its distinctive granular, foamy, or bubbly appearance and can be confirmed by PAS, mucicarmine, or alcian blue stains. The intracytoplasmic mucin is variable in both the distribution of mucinous cells in the tumor and in the location of the mucin within individual cells. Mucin may be diffusely present

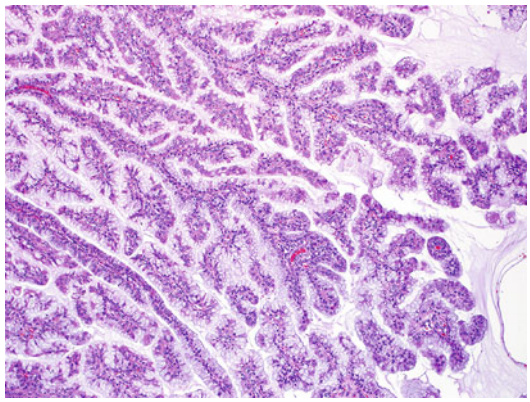

Fig. 32 Mucinous carcinoma, FIGO grade 1. Tumor has extensive mucinous differentiation and confluent glandular and papillary growth; these architectural patterns allow for establishing a diagnosis of carcinoma

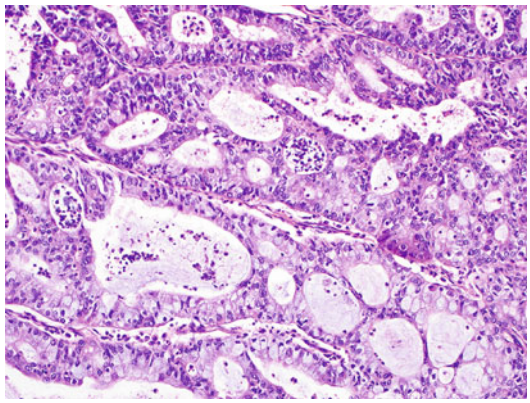

Fig. 33 Endometrioid carcinoma with mucinous differentiation, FIGO grade 1. Tumor exhibits a cribriform growth pattern and is comprised of glands with prominent mucinous cytoplasm as well as ones with a typical endometrioid appearance

in the cytoplasm, confined to the apical area, or show a combination of both patterns. Tumors dominated by typical endometrioid carcinoma with less than 50% of a mucinous component can be designated as endometrioid carcinomas with mucinous differentiation (Fig. 33).

Differential Diagnosis

Endocervical epithelium merges with the endometrium in the lower uterine segment, so it is not surprising that the distinction of primary endocervical from endometrial mucinous carcinoma in curettings can be difficult. There is no histochemical difference in the mucin at either site (Ross et al. 1983). The distinction of endocervical from endometrial adenocarcinomas has been discussed earlier (see differential diagnosis section for Endometrioid Carcinoma).

The distinction of mucinous carcinoma of the endometrium from clear cell or secretory carcinoma is made on the basis of morphology and PAS and mucin stains. The cells in secretory carcinoma are clear (not granular or foamy) because of the presence of glycogen, which is PAS positive and is removed by diastase treatment. Mucin in these tumors is focal at most. Clear cell carcinoma is almost always papillary or solid in contrast to the glandular pattern of mucinous carcinoma. The cells in clear cell carcinoma tend to be polygonal rather than columnar and hobnail cells are almost invariably present, a cytologic feature that is absent in mucinous carcinoma.

Rarely, a mucinous carcinoma or a mixed mucinous and endometrioid carcinoma may contain areas that simulate microglandular hyperplasia of the cervix (Young and Scully 1992; Zaloudek et al. 1997). Such foci are characterized by cells showing mucinous and eosinophilic change with microcystic spaces containing acute inflammatory cells. The patients are in their fifties and sixties, in contrast to women with microglandular hyperplasia, who are young. The complexity of the glandular pattern and the degree of cytologic atypia distinguish this type of carcinoma from microglandular hyperplasia.

Behavior and Treatment

When stratified by stage, grade, and depth of myometrial invasion, mucinous tumors behave like endometrioid carcinomas (Ross et al. 1983). Mucinous carcinomas, however, tend to be low grade and minimally invasive and therefore as a group have an excellent prognosis. Treatment is the same as for endometrioid carcinoma. Because most of the tumors are stage I, low grade, and minimally invasive, total abdominal hysterectomy and bilateral salpingo-oophorectomy usually suffice.

Serous Carcinoma

The existence of papillary patterns within endometrial carcinoma has been recognized since the turn of the century. In the past several decades, reports have described the morphologic similarity of serous carcinomas of the endometrium, which frequently display papillary architecture, to ovarian serous carcinomas and identified them as a highly aggressive type of endometrial carcinoma (Hendrickson et al. 1982; Christopherson et al. 1982b; Lauchlan 1981; Walker and Mills 1982). Although papillary architecture is a common finding in serous carcinoma, most other types of endometrial carcinoma can display papillary architecture but are usually not highly aggressive tumors. In addition, serous carcinomas can be predominantly glandular or solid without evident papillary growth. What distinguishes serous carcinoma from these other types is the uniformly marked cytologic atypia. Thus, the designation "serous carcinoma," rather than "papillary serous carcinoma," is preferred so that cell type rather than architecture is emphasized.

Clinical Features

The prevalence of serous carcinomas reported from referral centers usually is about 10%; however, in a population-based study from Norway it was only 1% (Abeler and Kjorstad 1990). Patients with serous carcinoma range in age from 39 to 93 years but typically are postmenopausal and, in contrast to women with endometrioid carcinoma, are older (reported median and mean ages are in the late sixties). In addition, they are less likely to have received estrogen replacement therapy and are more likely to have abnormal cervical cytology. There are some data to suggest that women with this neoplasm are less likely to be obese and that a higher proportion of women are black (Dunton et al. 1991). In other respects, they appear similar.

Gross Findings

On gross examination, uteri containing these tumors often are small and atrophic. Generally, the tumor is exophytic and has a papillary appearance. Depth of invasion is difficult to assess on macroscopic examination. It is not unusual to find a benign-appearing polyp containing the carcinoma in the hysterectomy specimen after a diagnosis of serous carcinoma or serous endometrial intraepithelial carcinoma (SEIC) has been made on a curetting, because these tumors frequently develop within a polyp (see chapter ▶ "Precursors of Endometrial Carcinoma") (Carcangiu and Chambers 1992; Carcangiu et al. 1997; Sherman et al. 1992; Silva and Jenkins 1990; Soslow et al. 2000b; Wheeler et al. 2000).

Microscopic Findings

As experience with serous carcinoma has increased, it has become apparent that this neoplasm demonstrates considerable diversity in its architectural features (Figs. 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, and 44). Although a papillary pattern typically predominates, glandular and solid patterns also occur (Darvishian et al. 2004; Hendrickson et al. 1982; Sherman et al. 1992; Lee and Belinson 1991). Serous carcinoma originally was described as having thick, short papillae, but subsequent studies have shown that thin papillae may be present in more than half of them. The cytologic features of these tumors also are quite varied. Polygonal cells with eosinophilic and clear cytoplasm often are seen, but hobnail cells are among the most frequently observed cells. Marked nuclear atypia is always present and is required for a tumor to qualify as serous carcinoma (Figs. 35, 37, 39, and 42). Thus, serous

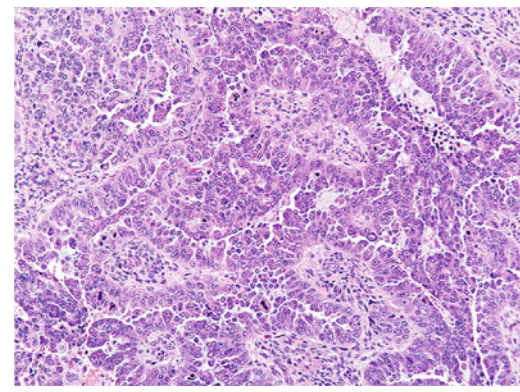

Fig. 34 Serous carcinoma. Papillary tumor is lined by markedly atypical epithelium composed of cells with scalloped luminal borders, including hobnail-type cells

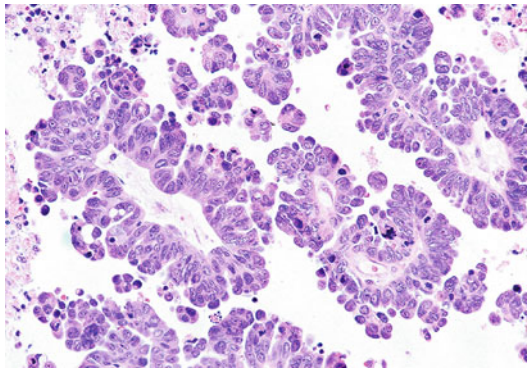

Fig. 35 Serous carcinoma. Papillary structures and detached epithelial clusters have markedly atypical cells, including hobnail-type cells

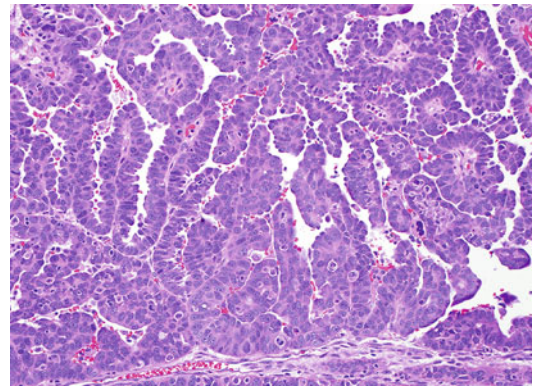

Fig. 38 Serous carcinoma. Tumor is composed of papillae lined by epithelium having prominent scalloped luminal borders

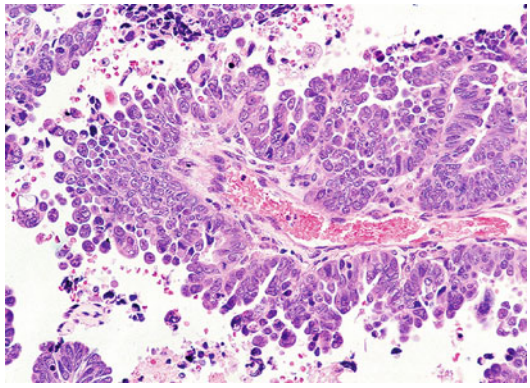

Fig. 36 Serous carcinoma. Papillary structure is lined by markedly atypical hobnail-type cells

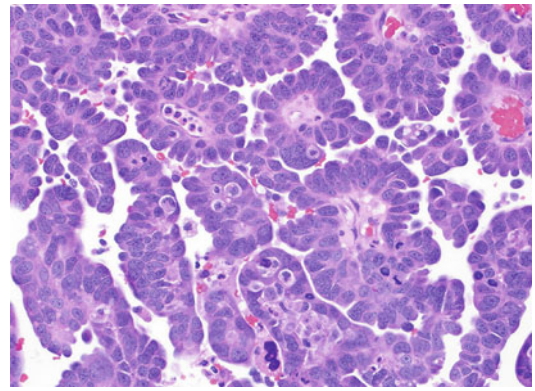

Fig. 39 Serous carcinoma. Papillae are lined by cells with enlarged, vesicular nuclei with evident nucleoli. Several mitotic figures are present

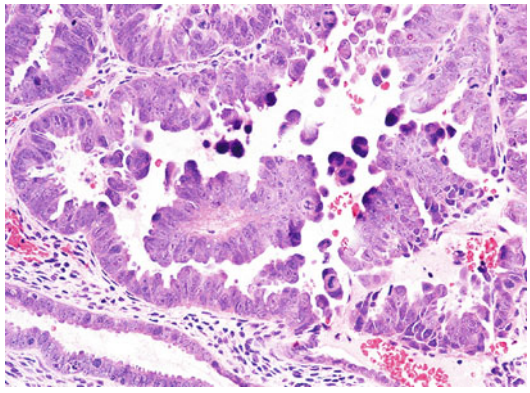

Fig. 37 Serous carcinoma. Most nuclei are vesicular with prominent red nucleoli but some detached atypical cells have smudged hyperchromatic nuclei

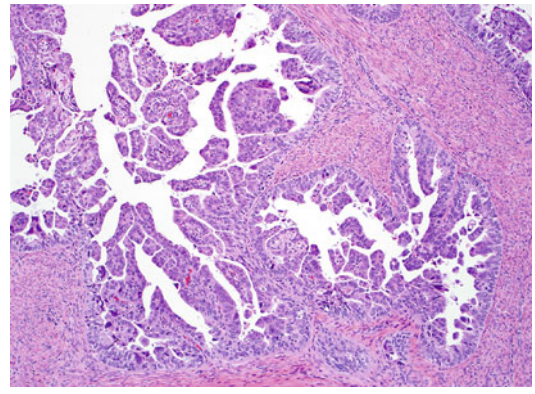

Fig. 40 Serous carcinoma. Glands with prominent intraglandular papillary architecture infiltrate myometrium

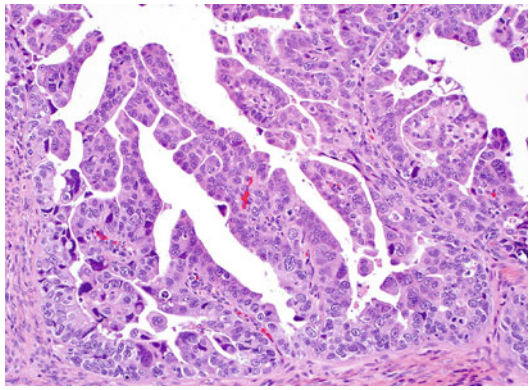

Fig. 41 Serous carcinoma. Papillae are lined by markedly atypical epithelium

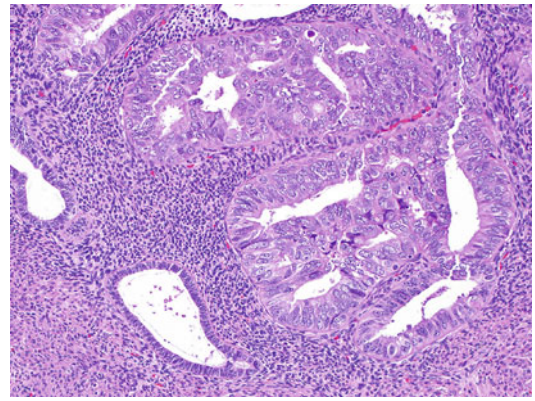

Fig. 43 Serous carcinoma. An area of endometrial intraepithelial carcinoma (serous intraepithelial carcinoma) is present within a background of atrophic endometrium. Markedly atypical epithelium replaces pre-existing endometrial glands

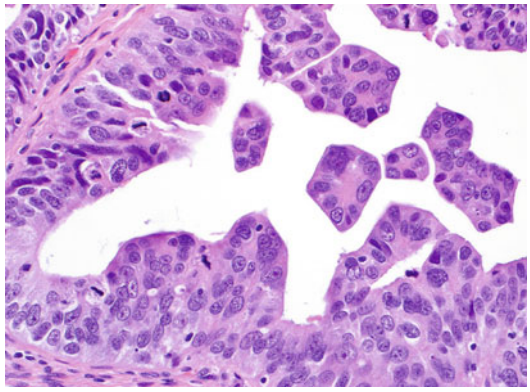

Fig. 42 Serous carcinoma. Some glandular epithelium has smooth luminal borders but papillary epithelial tufts and marked nuclear atypia, with numerous mitotic figures, are characteristic of serous carcinoma

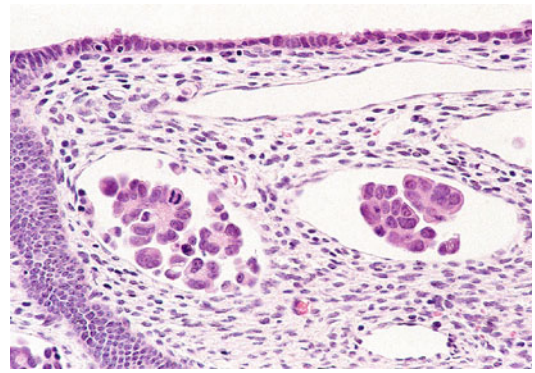

Fig. 44 Serous carcinoma. Detached papillary epithelial cell clusters are present within lymphatic spaces of endometrium

carcinoma is defined by the discordance between its architecture, which appears well differentiated (papillary or glandular pattern), and its nuclear morphology, which is high grade (grade 3 nuclei) (Demopoulos et al. 1996). Areas containing clear cells do not preclude the diagnosis of serous carcinoma.

Microscopically, the exophytic component of a serous carcinoma typically has a complex papillary architecture. The papillary fronds may be either short and densely fibrotic or thin and delicate. The cells covering the papillae and lining the glands form small papillary tufts, many of which are detached and float freely in spaces between the papillae and in gland lumens. The cells are cuboidal or hobnail shaped and contain abundant granular eosinophilic or clear cytoplasm. The cells tend to be loosely cohesive. There may be considerable cytologic variability throughout the tumor, as many cells tend to show marked cytologic atypia manifested by nuclear pleomorphism, hyperchromasia, and macronucleoli whereas others are small and not so ominous in appearance. Multinucleated cells, giant nuclei, and bizarre forms occur in half the tumors. Lobulated nuclei with smudged chromatin also are frequently encountered. Mitotic activity usually is high and abnormal mitotic figures are easily

identified. Psammoma bodies are encountered in a third of cases. The invasive component of the neoplasm can show contiguous downgrowth of papillary processes, or solid masses or glands, the latter often have a gaping appearance. Nests of cells within vascular spaces are commonly found (Fig. 44).

The adjacent endometrium in hysterectomy specimens with serous carcinoma is atrophic in almost all cases. Hyperplasia, generally without atypia, is present in less than 10% of the cases (Carcangiu and Chambers 1992; Sherman et al. 1992; Spiegel 1995). In nearly 90% of the cases, the surface endometrium adjacent to the carcinoma or at other sites away from the neoplasm is replaced by one or several layers of highly atypical cells that overlie atrophic endometrium and extend into normal glands. These cells are identical to those of the invasive carcinoma and at times form micropapillary processes. This lesion, which has been designated SEIC (Fig. 41), is discussed in detail in ▶ Chap. 8, "Precursors of Endometrial Carcinoma" (Spiegel 1995; Ambros et al. 1995). The intraepithelial carcinoma can extensively replace the surface endometrium and underlying glands without stromal invasion. The clinicopathologic features and distinction of extensive SEIC from early invasive serous carcinoma have been reported (Wheeler et al. 2000). It has been proposed that SEIC and serous carcinoma measuring 1 cm or less should be designated minimal uterine serous carcinoma because these lesions are difficult to distinguish and they behave in a similar fashion when confirmed as stage IA by meticulous surgical staging. It is important to recognize that patients whose uteri demonstrate only SEIC, without evidence of invasive serous carcinoma in the completely sampled endometrium, can have metastatic serous carcinoma in the ovary, peritoneum, or omentum, presumably as a result of exfoliation and implantation of the loosely cohesive tumor cells (Soslow et al. 2000b; Wheeler et al. 2000).

Differential Diagnosis

Serous carcinoma must be distinguished from villoglandular carcinoma, which also has papillary architecture. Unlike serous carcinoma, villoglandular carcinoma is characterized by the predominance of long, delicate papillary fronds that do not display papillary tufting. In addition, the cells are columnar, resembling cells in endometrioid carcinoma and lack high-grade nuclear atypia (see "Villoglandular Carcinoma"). A serous carcinoma with a prominent glandular pattern that lacks prominent papillary features may be confused with an endometrioid carcinoma. In this case, it is predominantly the nuclear morphology that aids in the distinction. The glands in an endometrioid carcinoma have a smooth luminal border and are lined by columnar cells with nuclei that are grade 1 or 2. Endometrioid carcinomas with grade 3 nuclei are almost always solid, not glandular. In contrast, the glands in a serous carcinoma are lined by cells with high-grade nuclei, some of which are hobnail shaped, thus imparting a scalloped luminal border to the glands. In addition, in most cases papillary tufts project or lie detached in the gland lumens. Immunohistochemical analysis can aid in the distinction of glandular serous carcinoma from endometrioid carcinoma. Several studies have demonstrated a very high frequency of strong, diffuse positivity for p53, or uncommonly a complete lack of staining, in serous carcinomas, and these patterns of staining are correlated with the presence of mutations in the *TP53* gene (see above "Molecular Genetics of Endometrial Carcinoma") (Tashiro et al. 1997a; Lax et al. 2000b; Sherman et al. 1995; Kovalev et al. 1998; Moll et al. 1996). In addition, most serous carcinomas demonstrate diffuse p16 expression which appears identical to the pattern observed in high-risk HPV-related endocervical adenocarcinoma but is unrelated to high-risk HPV (Yemelyanova et al. 2009a; Ansari-Lari et al. 2004). Serous carcinomas also have a relative lack of expression of ER and PR and very high proliferation indices as measured by immunohistochemical expression of Ki-67 compared to endometrioid carcinoma (Lax et al. 1998a; Carcangiu et al. 1990). In contrast, endometrioid carcinomas (particularly grade 1 and 2 tumors) frequently express hormone receptors and have lower proliferation indices (Lax et al. 1998a, b; Carcangiu et al. 1990). In addition, strong, diffuse

immunohistochemical expression of p53 is confined to a subset of grade 3 endometrioid carcinomas and is rarely encountered in lower-grade endometrioid carcinomas (Lax et al. 1998a, b). p16 expression in endometrioid carcinomas is typically patchy; even tumors with more extensive expression usually have interspersed negative patches or cells (usually <80% of tumor cells positive) and only on occasion is diffuse expression encountered (Alkushi et al. 2010). Hence, glandular carcinomas with high-grade cytology for which the differential diagnosis includes grade 2 endometrioid carcinoma and serous carcinoma can be distinguished by immunohistochemistry for p53, p16, Ki-67, and hormone receptors. The distinction of serous carcinoma from clear cell carcinoma is discussed later (see "Clear Cell Carcinoma").

At times, papillary syncytial eosinophilic change, particularly in a small curettage specimen in an older patient, may be difficult to distinguish from serous carcinoma. The papillary processes in eosinophilic change lack fibrovascular support and the cells that form these processes are small and lack significant nuclear atypia or mitotic activity. Typically, small microcystic spaces containing neutrophils are present in the syncytial masses (see ▶ Chap. 8, "Precursors of Endometrial Carcinoma"). At times it may not be clear if a serous carcinoma involving the endometrium is primary or metastatic from the ovary or fallopian tube. More often than not the uterus is the primary site, even when invasion cannot be demonstrated in the hysterectomy specimen (Warren et al. 1998). In these cases the ovarian involvement is typically bilateral and characterized by small foci of tumor on the ovarian surface or nodules of tumor in the parenchyma with clusters of tumor cells in hilar vascular spaces.

Immunohistochemical Findings

Approximately 90% of endometrial serous carcinoma show p53 overexpression (intense expression in greater than 80% of tumor cell nuclei; Fig. 45) as a result of *TP53* mutation and the consequent accumulation of mutant protein (Tashiro et al. 1997a; Soslow et al. 1998; Lax et al. 2000b; Sherman et al. 1995; Zheng et al. 1998). Some of the remaining tumors, which show absolutely no p53 expression, have *TP53* mutations that result in a truncated p53 protein or a protein with conformational changes that cannot be detected using commercially available antibodies (Tashiro et al. 1997a). The Ki-67 labeling index is extremely high (i.e., greater than 50–75% of tumor cell nuclei)(Lax et al. 1998a). The typical serous carcinoma lacks diffuse ER and PR expression (Soslow et al. 2000a; Lax et al. 1998a; Darvishian et al. 2004; Carcangiu et al. 1990), although many carcinomas with hybrid endometrioid/serous features and admixtures of endometrioid and serous components express considerable amounts of ER, particularly (Alkushi et al. 2007). PR is less frequently expressed, compared to ER. Diffuse/strong p16 is characteristic of serous carcinomas (Fig. 46) (Reid-Nicholson et al. 2006; Chiesa-Vottero et al. 2007) (Yemelyanova et al. 2009a). In contrast to most endocervical carcinomas, this does not imply high-risk HPV infection; rather, it may reflect disturbances in the cell cycle that favor hyperproliferative activity. In contrast to endometrioid adenocarcinomas, nuclear ß-catenin expression and loss of PTEN, MLH1, MSH2, MSH6, and PMS2 are almost never encountered.

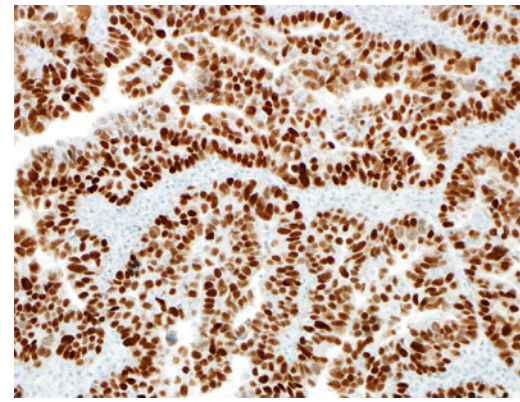

Fig. 45 Serous carcinoma. Tumor exhibits diffuse/strong nuclear expression of p53

Despite important immunophenotypic differences that distinguish between clear-cut examples of serous and endometrioid carcinomas of the endometrium, these tumors share some notable features. Like endometrioid carcinomas,

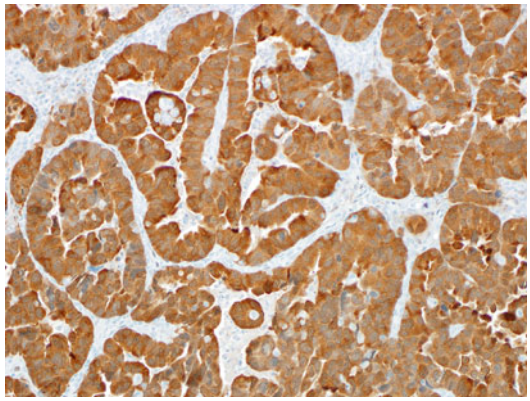

Fig. 46 Serous carcinoma. Tumor exhibits diffuse/strong expression of p16

endometrial serous carcinomas commonly express pan-cytokeratins, EMA, CA125, Ber EP4, B72.3, CK7, and vimentin, while they are usually negative for CK20 and lack diffuse, strong cytoplasmic expression of CEA.

Finally, there are some important differences between the immunophenotype of endometrial and ovarian, tubal, and peritoneal serous carcinomas as a group. The most important is infrequent WT1 expression in endometrial serous carcinomas (reported in 7.5–30% of such cases) and the very common diffuse nuclear expression of WT1 in ovarian, tubal, and primary peritoneal examples (at least 70–80% of such cases) (Acs et al. 2004; Egan et al. 2004; Goldstein and Uzieblo 2002).

Molecular Genetics

The most commonly mutated gene in serous carcinoma is the *TP53* tumor suppressor gene with mutations identified in greater than 90% of cases (Tashiro et al. 1997a; Moll et al. 1996). Prior to next generation sequencing, very few other genes, with the exception of *PIK3CA*, had been described. This is perhaps not surprising, given the characteristic feature of serous carcinoma is the presence of what has been in the past referred to as chromosomal instability and is now called copy number high in The Cancer Genome Atlas (TCGA) molecular categorization. The inverse correlation of high copy number alterations and mutation frequency has been previously described in a number of different tumor types. With the contributions of high throughput DNA analysis, mutations in a number of other genes have been detected with a frequency as follows: *FBXW7 (22%)*, *PPP2R1A (22%)*, *CHD4 (13%)*, *PIK3R1* (13%), *SPOP (5%)*, and *TAF1*(unknown frequency). As was discussed in the molecular genetics section of endometrioid carcinoma, *PIK3CA* (frequency of mutation 37–42%) is the catalytic subunit of PI3K and mutations in this gene lead to constitutive activation of this important pathway with a wide range of effects on cell proliferation, cell growth, and apoptosis. The *FBXW7* and *SPOP* genes encode proteins involved in the ubiquitin-mediated degradation of a number of protein substrates. Specifically, FBXW7 promotes the degradation of cyclin E, cMYC, NOTCH1, and MCL1. Previous studies have shown amplification and overexpression of cyclin E and cMYC in serous carcinoma. In addition, studies have reported increased expression/amplification of HER-2/neu in 35% of serous carcinomas (Buza et al. 2013). However, to date, our understanding of their roles in the development of serous carcinoma remains largely unexplored.

Of note, approximately 75% of SEICs, the putative precursor of serous carcinoma, have mutations in *TP53* (Tashiro et al. 1997a). In this setting, it has been shown that intense, diffuse immunohistochemical staining for p53 correlates well with mutation. These findings suggest that in serous carcinoma, *TP53* mutations occur relatively early and are central to the development of this tumor type; this is in contrast to endometrioid carcinoma, in which *TP53* mutations are relatively uncommon and, when they do occur, they are largely confined to grade 3 tumors. Thus, it is possible that mutation of *TP53* early in the pathogenesis of serous carcinoma is an important factor that accounts for its aggressive behavior. In addition, the fact that *TP53* mutations occur most commonly in grade 3 endometrioid and serous carcinomas most likely explains the finding that it is an indicator of tumors that behave aggressively (Alkushi et al. 2004).

In contrast to endometrioid carcinoma, mutations in *KRAS* and *PTEN* appear to be very

uncommon in serous carcinoma, and MSI is rare in this tumor type (Lax et al. 2000b).

Behavior and Treatment

Serous carcinoma has a propensity for myometrial and lymphatic invasion. The hysterectomy specimen often discloses tumor in lymphatics extensively within the myometrium, cervix, broad ligament, fallopian tube, and ovarian hilus. In addition, intraepithelial carcinoma, similar to that involving the endometrium, has been reported on the surface of the ovaries, peritoneum, and mucosa of the endocervix and fallopian tube, in the absence of gross disease in these sites (Sherman et al. 1992; Wheeler et al. 2000). Involvement of peritoneal surfaces in the pelvis and abdomen, as in ovarian serous carcinoma, occurs early in the course of disease. Not surprisingly, most studies report that uterine serous carcinoma is clinically understaged in approximately 40% of cases (Dunton et al. 1991; Carcangiu and Chambers 1992). In addition to intraperitoneal spread, serous carcinoma can metastasize to the liver, brain, and skin.

The 5- and 10-year actuarial survival rates for all stages were 36% and 18%, respectively, in a study from Norway (Abeler and Kjorstad 1990); surprisingly the 5-year survival in one study for pathologic stage I serous carcinoma was similar (40%) (Carcangiu and Chambers 1992). Another study of stage I and II serous and clear cell carcinomas reported a 5-year survival rate of 57% for patients with carcinomas confined to the endometrium, which was similar to that for patients with stage IA and IB tumors (53%) (Cirisano et al. 2000). A recent retrospective study of stage I serous carcinoma evaluated outcomes in patients treated with different modalities. Patients who received chemotherapy, with our without radiation therapy, experienced more favorable outcomes when compared to patients treated with radiation or observation alone. Only 11% of patients treated with chemotherapy and radiation experienced recurrence, compared to 30% without therapy and 25% when radiation was the sole treatment modality. The only subgroup that did not appear to benefit from chemotherapy included patients with stage IA serous carcinoma; only 2 of 27 such patients experienced recurrence (Fader et al. 2009; Tate et al. 2018). In addition, prognostic factors for shorter survival included age greater than 60 years, vascular invasion, and greater than 50% myometrial invasion. Nearly half the serous carcinomas and 40% of the clear cell carcinomas in this study were thought to be early stage (clinical stage I and II). Interestingly, although the majority of these tumors invaded only the inner third of the myometrium, they were upstaged to surgical stage III or IV (Cirisano et al. 1999). In addition, 13% of the serous carcinomas that were confined to the endometrium had paraaortic lymph node metastases. Patients with mixed endometrial carcinomas containing a component of serous carcinoma that accounted for at least 25% of the tumor have the same survival as patients with pure serous carcinoma, underscoring the importance of identifying areas of serous carcinoma in uterine carcinomas (Sherman et al. 1992).

The current approach to treatment is hysterectomy and bilateral salpingo-oophorectomy along with omentectomy and careful surgical staging, including peritoneal cytology and pelvic and paraaortic lymph node sampling or sentinel lymph node evaluation. In view of their highly aggressive behavior, adjuvant therapy should be considered for all tumors except those that qualify as minimal uterine serous carcinoma (less than 1 cm of carcinoma in the endometrium). In a study of 21 cases with pure SEIC or minimal uterine serous carcinoma, all 14 patients whose tumors lacked myometrial or vascular invasion and who had no evidence of extrauterine disease at staging had an overall survival of 100% after a mean follow-up of 27 months (Wheeler et al. 2000). The majority of these patients received no treatment after hysterectomy. Included among these cases were a few patients with involvement of endocervical glands by SEIC (prior stage IIA disease) who were also alive without evidence of disease at intervals ranging from 12 to 54 months. In contrast, the patients with either SEIC or minimal serous carcinoma and evidence of extrauterine disease (even microscopic disease) all died of disease despite intensive chemotherapy. In another study of stage IA

serous carcinoma, 11 of 13 patients were alive without evidence of disease after a median follow-up of 38 months (Carcangiu et al. 1997). Another study of 16 noninvasive serous carcinomas of the endometrium found that 6 tumors were stage IA and the remaining 10 had metastases identified at staging. Two of the six patients with stage IA disease experienced a recurrence but none died of disease during the follow-up period, which ranged from 2 to 73 months. Three patients with stage IIA disease also were alive without evidence of disease at intervals ranging from 37 to 61 months (Fader et al. 2009). The finding of advanced-stage disease in the absence of myometrial invasion in 10 patients emphasizes the need for complete staging of all patients with serous carcinoma. Another study of eight patients with serous or clear cell carcinoma confined to endometrial curettings without evidence of residual high-grade carcinoma (serous, clear cell, or FIGO grade 3 endometrioid) or vascular invasion in the hysterectomy specimen were without evidence of recurrence after a median follow-up of 3 years (Aquino-Parsons et al. 1998). In a study evaluating cisplatin, doxorubicin (Adriamycin), and cyclophosphamide (PAC) chemotherapy, which has a 70% response rate in previously untreated ovarian serous carcinoma, the response rate for uterine serous carcinoma was only 20%, suggesting that there are inherent differences in uterine and ovarian serous carcinomas (Levenback et al. 1992). This is not entirely surprising as, in our experience, there are significant morphologic differences in high-grade serous carcinoma of the ovary/fallopian tube and uterine serous carcinoma. Another study of platinum-based chemotherapy found that 8 of the 12 treated women were alive without evidence of disease, including 4 patients with advanced-stage disease and mean follow-up of 23 months, suggesting a possible role for chemotherapy (Gitsch et al. 1995b). More recent studies have proposed that systemic platinum base therapies with or without taxane may be effective in the treatment of high stage serous carcinoma of the endometrium (Kelly et al. 2004, 2005). These tumors are unresponsive to hormonal treatment because they typically/often lack hormone receptors.

In summary, it is very important for patients with serous carcinoma to be carefully staged as there may be extrauterine disease even if there is no or minimal myoinvasion. If there is no evidence of extrauterine disease after thorough staging the prognosis is favorable.

Clear Cell Carcinoma

Clinical Features

In the past, clear cell carcinoma was regarded as mesonephric in origin because of its resemblance to renal cell carcinoma, but the occurrence of clear cell carcinoma in the endometrium, a müllerian derivative, is evidence of its müllerian origin (Kurman and Scully 1976). The prevalence of clear cell carcinoma ranges from 1% to 6% in most series. Almost all studies report that women with clear cell carcinoma are older than women with endometrioid carcinoma (mean age in late sixties) (Christopherson et al. 1982a; Abeler and Kjorstad 1991; Kanbour-Shakir and Tobon 1991; Photopulos et al. 1979; Webb and Lagios 1987; Soslow et al. 2007). Some studies have reported a higher likelihood of abnormal cytology, a lower frequency of some of the associated constitutional symptoms, such as obesity and diabetes mellitus, and a lack of association of estrogen replacement therapy compared with endometrioid carcinomas, but this has not been confirmed by other studies. Clear cell carcinoma tends to be high grade, deeply invasive, and although many are advanced stage at presentation, 40–60% are confined to the uterus. Similar to serous carcinoma, clear cell carcinomas are more frequently associated with deep myometrial invasion, high nuclear grade, lymph-vascular space invasion, and pelvic lymph node metastasis compared to low-grade endometrioid carcinomas (Sakuragi et al. 2000). Occasionally they are confined to a polyp (Kanbour-Shakir and Tobon 1991). The survival of patients with clear cell carcinoma differs considerably as reported in various series, ranging from 21% to 75% (Christopherson et al. 1982a; Kurman and Scully 1976; Abeler and Kjorstad 1991; Photopulos et al. 1979; Webb and Lagios 1987). In one series, none

of the patients with tumor beyond stage I survived for 5 years, and even in stage I the 5-year survival was only 44% (Webb and Lagios 1987). Another report of low-stage tumors demonstrated better survival, with an estimated survival rate of 71% (Malpica et al. 1995). In a series of 97 patients, the 5-year crude survival was 42% and the 10-year survival was 31% (Abeler and Kjorstad 1991). In one study, 5- and 10-year actuarial disease-free survival rates of 43% and 39% were reported (Abeler et al. 1996) and in another study, median survival for clear cell carcinoma was 29 months and 5-year survival was 50% (Soslow et al. 2007). The wide range in survival reported suggests that different investigators may be applying different criteria for the diagnosis of clear cell carcinoma and/or that clear cell carcinoma represents a heterogeneous group of tumors. The latter interpretation has been supported by molecular studies (see below). Treatment is variable and in some institutions chemotherapy is used irrespective of stage. The role of adjuvant radiation or chemotherapy is not established at present. In view of the poor prognosis and because these tumors often have high nuclear grade and invade the myometrium deeply, adjuvant therapy often is administered.

Gross and Microscopic Features

These tumors do not have distinctive gross features. Clear cell carcinoma may exhibit solid, papillary, tubular, and cystic patterns (Figs. 47, 48, 49, 50, 51, 52, 53, and 54). The solid pattern is composed of masses of clear cells intermixed with eosinophilic cells, whereas papillary, tubular, and cystic patterns are composed predominantly of hobnail-shaped cells with interspersed clear and eosinophilic cells. Cystic spaces frequently are lined by flattened cells. Psammoma bodies can be found in association with papillary areas within the tumor. The cells typically are large, with clear or lightly stained eosinophilic cytoplasm. The clear cytoplasm results from the presence of glycogen, demonstrated with a PAS stain and diastase digestion. Cells that have discharged their glycogen and lost most of their cytoplasm are characterized by a naked nucleus, the so-called hobnail cell. Nuclear atypia within a given tumor

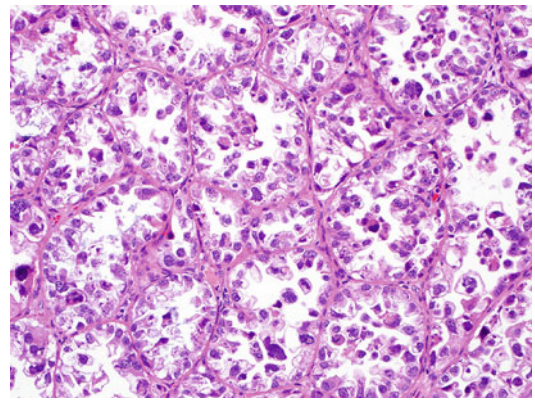

Fig. 47 Clear cell carcinoma. Glands are lined by markedly atypical hobnail-type cells with clear cytoplasm. This appearance is reminiscent of the Arias-Stella reaction in gestational endometrium

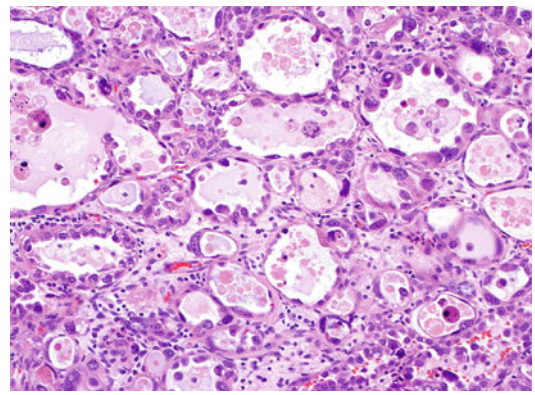

Fig. 48 Clear cell carcinoma. Glands are lined by pleomorphic cells, some attenuated and others with prominent hobnail morphology

can be variable, ranging from mild to marked (Figs. 52 and 53), but areas of marked atypia are almost always found. The atypia is manifested by pleomorphic, often large nuclei with prominent nucleoli. Mitotic activity is high, and abnormal mitoses are readily seen. PAS-positive, diastase-resistant intracellular and extracellular hyaline bodies, similar to those in yolk sac tumors, can be found in nearly two-thirds of clear cell carcinomas.

Differential Diagnosis

The differential diagnosis of clear cell carcinoma includes secretory carcinoma, serous carcinoma,

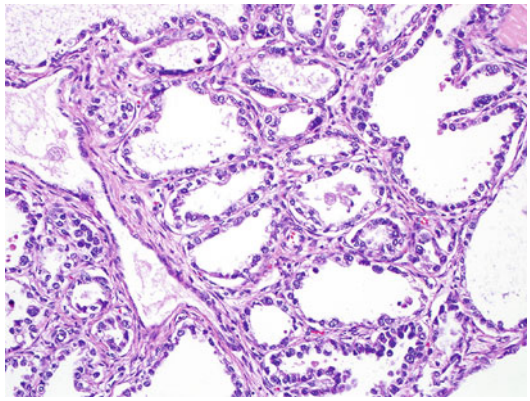

Fig. 49 Clear cell carcinoma. Glands are lined by cells with clear cytoplasm and predominantly a uniform cuboidal appearance with only focal hobnail features

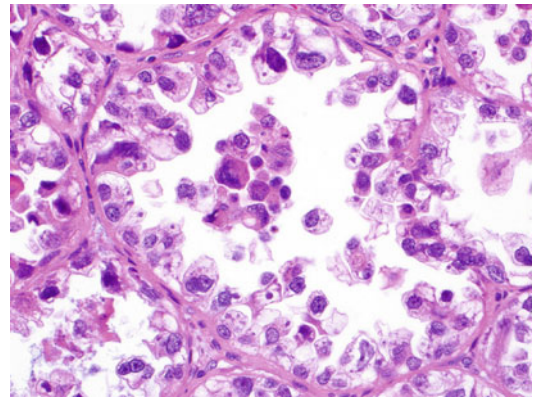

Fig. 52 Clear cell carcinoma. Hobnail-type cells protrude prominently into the gland lumen and are pleomorphic with hyperchromatic nuclei

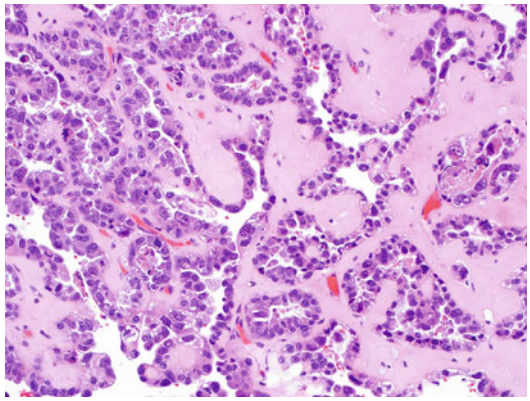

Fig. 50 Clear cell carcinoma. Papillary tumor exhibits characteristic features, including hyalinized stroma and cells with clear to granular eosinophilic cytoplasm and hobnail morphology

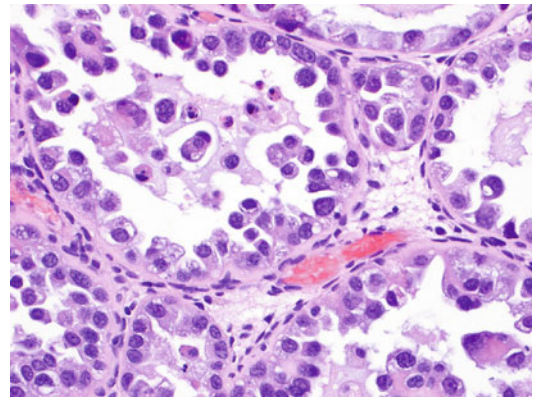

Fig. 53 Clear cell carcinoma. Hobnail-type cells have hyperchromatic nuclei and vacuolated clear cytoplasm

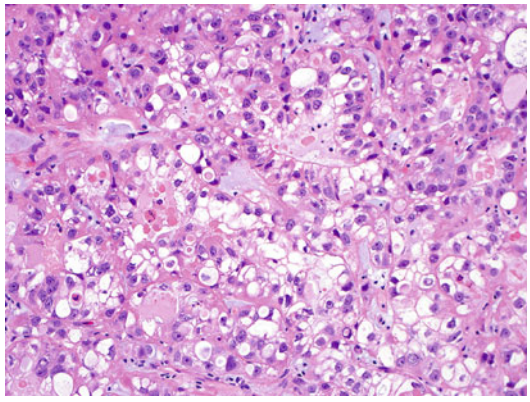

Fig. 51 Clear cell carcinoma. Solid tumor is composed of cells with prominent clear cytoplasm and characteristic nuclei with vesicular chromatin and nucleoli

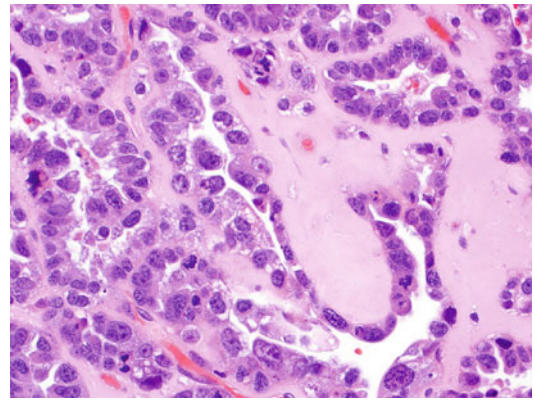

Fig. 54 Clear cell carcinoma. Hyalinized papillae are lined by cells with clear to eosinophilic cytoplasm and pleomorphic nuclei

and yolk sac tumor. The differential diagnosis of secretory carcinoma has been previously discussed (see "Secretory Carcinoma"). Clear cell carcinoma can be distinguished from serous carcinoma by architectural and cytoplasmic rather than nuclear features because both tumors display similar high-grade nuclear features, including vesicular nuclei with prominent nucleoli, hobnail cells, and cells with hyperchromatic, smudged nuclei. Serous carcinomas do not display the tubulocystic growth pattern, clear cytoplasm, and hyalinized stroma that are characteristic of clear cell carcinomas. In some cases, mixtures of both types are found. Yolk sac tumors occur rarely in the endometrium but the patients are young, in contrast to women with clear cell carcinoma, who are almost always postmenopausal. Microscopically, yolk sac tumors often have a microcystic pattern that can resemble the tubulocystic pattern of clear cell carcinoma. Characteristically, the yolk sac tumor contains Schiller–Duval bodies, which are lacking in clear cell carcinoma. Yolk sac tumors are associated with elevated serum alpha-fetoprotein (AFP) levels, and AFP can be identified in the tumor by immunohistochemistry.

Immunohistochemical Findings

Like endometrioid and serous carcinomas, clear cell carcinomas usually express pan-cytokeratins, EMA, CA125, BerEP4, B72.3, CK7, and vimentin, while they are usually negative for CK20 and WT1, and lack diffuse, strong cytoplasmic expression of CEA.

Clear cell carcinomas are typically ER/PR negative and show p16 and Ki-67 expression that are intermediate between endometrioid and serous carcinomas (Reid-Nicholson et al. 2006; Vang et al. 2001; Lax et al. 1998b). Approximately 40% of clear cell carcinomas harbor *TP53* mutations and show abnormal p53 immunohistochemical expression.

Molecular Genetics

Molecular studies have supported heterogeneity within tumors classified as clear cell carcinoma even when expert review has been performed. Early studies on small numbers of cases suggested that some had mutation profiles of endometrioid carcinoma while others had similarities to serous carcinoma. A recent next-generation sequencing study added further support to these earlier findings in the analysis of 32 cases of histopathologically confirmed cases of clear cell carcinoma (DeLair et al. 2017). The most common mutations are found in the following genes: *TP53* (46%), *PIK3CA* (36%), *PPP2R1* (36%), *FBXW7* (25%), *ARID1A* (21%), *PIK3R1* (18%), *SPOP* (18%) with amplifications of *CCNE1* (18%), and *ERBB2* (11%). Interestingly, using a described surrogate model for TCGA molecular classification, all four TCGA subtypes were represented in the 32 cases. Two cases were of the ultramutated/POLE subtype, 4 were hypermutated/MSI positive, 15 copy number low/MSS, and 11 were in the high-copy number/"serous-like" subtype. An additional next-generation sequencing study reported similar findings but minor differences were found in both the frequency of mutations in some genes and the identification of novel genetic alterations (Le Gallo et al. 2017). Thus, clear cell carcinoma, as presently classified, is morphologically and molecularly heterogeneous, which accounts for the different outcomes that have been reported.

Neuroendocrine Tumors

These are uncommon tumors of the endometrium and are classified as low-grade neuroendocrine tumors (carcinoid) or high-grade neuroendocrine tumors (small cell and large cell carcinomas) by 2014 WHO classification. The low-grade tumors are rare with only scattered case reports present in the literature. In a recent study of 25 high-grade neuroendocrine carcinomas, the largest number of cases in a single study, 15 were associated with other histologic types of endometrial carcinoma, most commonly endometrioid, and 10 were pure neuroendocrine tumors. The neuroendocrine component was predominately large cell (15 cases), small cell (4 cases), and an admixture of the two (6 cases). Importantly, in 89% of the cases, the neuroendocrine component had not been recognized by the pathologist who rendered the original diagnosis. All of the tumors stained

with at least one of the neuroendocrine immunohistochemical markers (chromogranin, synaptophysin, or CD56). However, if only CD56 is positive, caution should be taken in making the diagnosis without a strong suspicion based on the morphologic features. Interestingly, 8 of 18 cases had abnormal immunohistochemical staining for DNA MMR proteins indicating the presence of MSI (Pocrnich et al. 2016).

Mixed Cell Adenocarcinoma

An endometrial carcinoma may show combinations of two or more of the pure types. By convention, a mixed carcinoma has at least one other component comprising at least 10% of the tumor. For example, an endometrioid carcinoma containing a clear cell carcinoma that constitutes 10% of the tumor is classified as an endometrioid carcinoma with areas of clear cell carcinoma. Except for a few studies evaluating the significance of foci of serous carcinoma admixed with endometrioid carcinoma, there are no data that can be used as a basis for making valid recommendations concerning what proportion of an additional component justifies being separately classified. Mixed serous and endometrioid carcinomas containing at least 10% of a serous component behave as pure serous carcinomas, excluding those with POLE mutations or MSI (Sherman et al. 1992). Except for serous and possibly clear cell components, it is likely that the combination of other tumor types has little, if any, clinical significance.

Undifferentiated/Dedifferentiated Carcinoma

The 2014 WHO defined undifferentiated endometrial carcinoma as a tumor lacking any evidence of differentiation. The most common entity considered in the differential diagnosis of an undifferentiated tumor is a FIGO grade 3 endometrioid adenocarcinoma, which should only be diagnosed when the tumor is obviously endometrioid in character. Confirmatory endometrioid features in this context include even focal glandular architecture, squamous differentiation, or trabecular and nested growth patterns. Most FIGO grade 3 endometrioid carcinomas either contain focal glandular architecture and/or resemble non-keratinizing, poorly differentiated squamous cell carcinoma. However, this must be distinguished from dedifferentiated carcinoma, which is undifferentiated carcinoma associated with FIGO grade 1 endometrioid carcinoma.

Different types of undifferentiated carcinomas can now be recognized, which means that tumors lacking differentiation on review of H&E stained slides probably represent a very heterogeneous group. Small cell carcinoma of neuroendocrine type is one tumor that should be separately identified, as these tumors demonstrate a unique combination of immunohistochemical, ultrastructural, clinical, and biologic features.

Clinical Features

Patients with undifferentiated and dedifferentiated carcinomas span a wide age range, from the third to eighth decade. Endometrial primaries are more common than ovarian primaries. Some patients have synchronous endometrial and ovarian endometrioid carcinomas, with the presence of the undifferentiated component recognizable in only one site. The most common presentation is vaginal bleeding. In many cases, patients are suspected of having lymphoma because of extensive, systemic lymph node involvement coupled with high serum lactate dehydrogenase (LDH) levels. Approximately one-half of patients have extrauterine disease at surgery. These are described as highly aggressive tumors and are almost always fatal. In some cases, a diagnosis of well-differentiated endometrioid adenocarcinoma may be followed by the emergence of undifferentiated carcinoma in a metastatic site.

Microscopic Findings

Undifferentiated carcinoma (Altrabulsi et al. 2005) is a tumor composed predominately of a monotonous proliferation of small to intermediate-sized, discohesive cells arranged in sheets without an obvious nested or trabecular

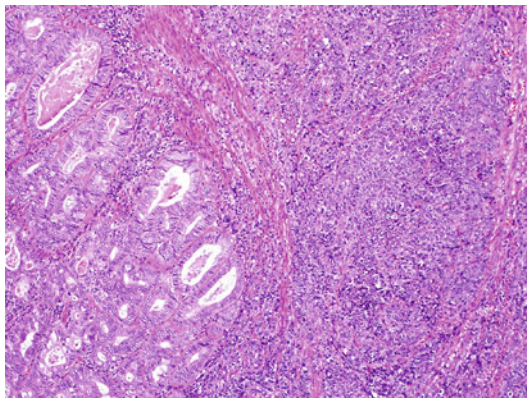

Fig. 55 Undifferentiated carcinoma. Solid tumor lacking any differentiating features is present adjacent to, but not admixed with, FIGO grade 1 endometrioid carcinoma

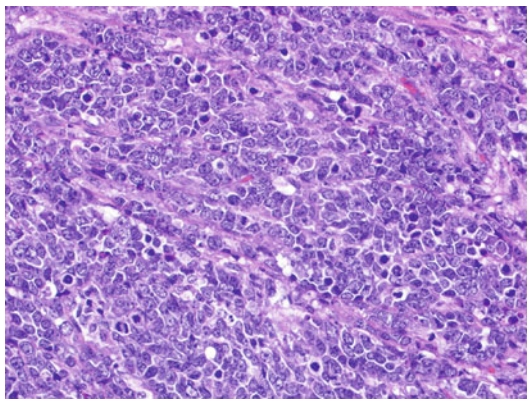

Fig. 56 Undifferentiated carcinoma. Dyscohesive atypical cells lacking any differentiating features suggest a differential diagnosis of undifferentiated carcinoma versus lymphoma

architecture or gland formation (Figs. 55 and 56), although rare foci of abrupt keratinization are allowed. The low power appearance is reminiscent of endometrial stromal sarcoma, although the tongue-like pattern of myometrial infiltration and characteristic vasculature are lacking. The nuclear features, which often include vesicular chromatin with small chromocenters or nucleoli, along with the very high mitotic index, are also incompatible with endometrial stroma sarcoma. In many cases, the cytologic appearance of this type of undifferentiated carcinoma recalls large cell lymphoma when the cytoplasm is scant and plasmacytoma when the cytoplasm is more abundant and rhabdoid. Although the tumor stroma is generally inapparent, some tumors display a myxoid matrix. Many examples also contain numerous tumor-infiltrating lymphocytes. When this feature is prominent, the tumor may resemble a lymphoepithelial-like carcinoma of the cervix or nasopharynx. Small cell carcinoma of neuroendocrine type is also a diagnostic consideration, but undifferentiated carcinoma does not typically demonstrate salt-and-pepper chromatin, nuclear molding, or neuroendocrine marker (chromogranin and synaptophysin) expression in greater than 10% of cells. Many endometrial carcinomas containing undifferentiated components also contain foci of well- or moderately differentiated endometrioid adenocarcinoma (Fig. 55). These tumors have been called "de-differentiated endometrial carcinoma" (Silva et al. 2006). In these tumors, the gland forming, or differentiated, components are superficial, adjacent to the endometrial cavity, whereas the undifferentiated areas are deeper in the endometrium and myometrium and sharply delimited from the differentiated areas. This accounts for the occasional scenario in which the well-differentiated endometrioid component is diagnosed on endometrial curettage, followed by recognition of the presence of a more deeply placed undifferentiated component on hysterectomy.

Immunohistochemical Findings

Immunohistochemically, the undifferentiated cells in general fail to express markers that would support a diagnosis of lymphoma, plasmacytoma, rhabdomyosarcoma, or a neuroendocrine tumor. Exceptions to this rule include CD138 expression in some examples and low-level expression of synaptophysin and chromogranin in others. The undifferentiated component characteristically shows only focal or weak keratin expression, but nearly every case exhibits intense EMA and cytokeratin 18 expression in scattered, rare cells (Altrabulsi et al. 2005). PAX8, ER, and PR staining is negative and there is loss of E-cadherin expression. Perhaps as many as one-half demonstrate abnormal DNA MMR protein expression.

Molecular Genetics

The most recent data suggest that undifferentiated carcinomas demonstrate molecular heterogeneity. The majority of the dedifferentiated carcinomas demonstrate an abnormal DNA MMR gene expression profile that places some of them within the spectrum of tumors encountered among patients with Lynch syndrome. Although the data are limited, the undifferentiated tumors share molecular features of high-copy number and low-copy number TCGA subtypes. These findings have potential prognostic implications and future studies are critical to further define these tumors.

Carcinosarcoma (Malignant Mixed Mullerian Tumor (MMMT))

Although synonymous, the 2014 WHO Classification recommends the term "carcinosarcoma" to "malignant mixed mullerian tumor (MMMT)" that represents less than 5% of malignant neoplasms of the uterine corpus (Silverberg et al. 1990). By definition, they are composed of malignant epithelial and mesenchymal components as recognized by light microscopy. Because of their biphasic appearance, there has been considerable controversy about their histopathogenesis. Recent clinicopathologic, immunohistochemical, and molecular genetic studies have provided substantial evidence that most of them represent carcinomas with a mesenchymal component as a consequence of divergent differentiation and/or tumor progression (McCluggage 2002; Fujii et al. 2000). Some might also arise via progression from an adenosarcoma. This is supported by the recognition that as many as one-third of carcinosarcomas contain zones that closely resemble adenosarcoma (Seidman and Chauhan 2003) and by studies that report metastases from adenosarcomas that resemble carcinosarcoma (Clement and Scully 1990). It is also possible that these tumors arise by a process of bidirectional differentiation from a single multipotent stem cell.

The risk factors for carcinosarcoma have been difficult to determine as robust epidemiologic studies have not been done due to the low prevalence of the disease. One small study suggested that they may share risk factors (body weight, exogenous estrogen use, and nulliparity) with endometrial carcinoma (Zelmanowicz et al. 1998). Tamoxifen therapy has also been noted as a possible contributor to their development (Curtis et al. 2004; Rieck et al. 2005; Swerdlow and Jones 2005). The risk apparently persists and might even increase after cessation of treatment (Ferguson et al. 2006). Carcinosarcomas, along with high-grade endometrial carcinomas, have also been reported to arise in patients previously treated with pelvic irradiation for rectal or cervical carcinomas (Pothuri et al. 2006; Hagiwara et al. 2005).

Endometrial carcinomas and carcinosarcomas share many clinical features. Like carcinomas, carcinosarcomas metastasize to pelvic and paraaortic lymph nodes, pelvic soft tissues, vagina, peritoneal surfaces, and lungs (Chuang et al. 1970a; Fleming et al. 1984; Norris and Taylor 1966a). The histologic appearance of metastases is variable. Three studies on metastatic carcinosarcoma have demonstrated that invasive foci in lymphatic or vascular spaces are essentially always pure carcinoma, and metastatic lesions are most commonly purely carcinoma; occasionally, mixtures of carcinoma and sarcoma are found and only rarely is pure sarcoma encountered (Silverberg et al. 1990; Bitterman et al. 1990; Sreenan and Hart 1995). Studies have also suggested that staging surgery usually performed for carcinomas, with omentectomy, peritoneal biopsies, and lymph node dissection, are better suited to detecting occult metastatic carcinosarcoma than are staging procedures commonly performed for sarcomas (Ferguson et al. 2007a; Yamada et al. 2000). Both carcinomas and carcinosarcomas respond well to cisplatin-based chemotherapy (Sutton et al. 2000; van Rijswijk et al. 1994).

Clinical Features

The mean age of patients with carcinosarcomas is in the seventh decade, but the age range spans from the fourth through tenth decades. The disease tends to present like other endometrial cancers, with vaginal bleeding being common.

Another typical presentation of carcinosarcoma is a polypoid mass that protrudes through the cervical os.

Gross Findings

Carcinosarcomas are frequently polypoid and usually fill the entire endometrial cavity. Many invade the myometrium but some are confined to polyps. The tumors often protrude through the cervical os, simulating a cervical neoplasm or "aborting" uterine leiomyoma. The protruding tip of the mass can be necrotic, making diagnosis based on biopsy of this portion of the tumor difficult. In approximately a quarter of the cases, the uterine tumor extends into the endocervix. The tumors are variably soft to firm and tan with areas of necrosis and hemorrhage.

Microscopic Findings

Carcinosarcomas are composed of an admixture of histologically malignant epithelial and mesenchymal components, but the epithelial component is frequently difficult to subclassify (Figs. 57, 58, 59, 60, 61, 62, and 63). In the most recent clinicopathologic review, the authors reported that serous carcinomas and high-grade carcinomas, not otherwise specified, were the most frequent carcinoma components in carcinosarcoma (Ferguson et al. 2007a). Older studies have reported endometrioid carcinomas to be more common. Clear cell, mucinous, squamous, and mesonephric carcinoma also can be found as the

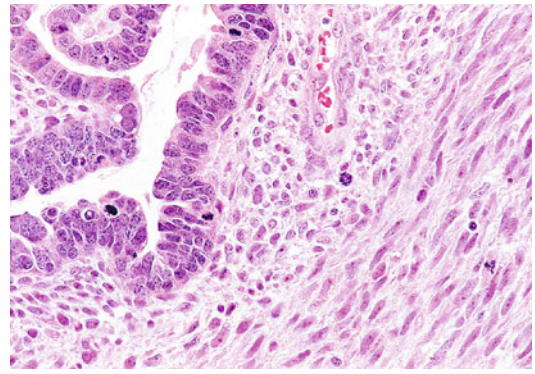

Fig. 58 Carcinosarcoma. Both carcinomatous and sarcomatous components have malignant cytologic features (nuclear pleomorphism and mitotic activity)

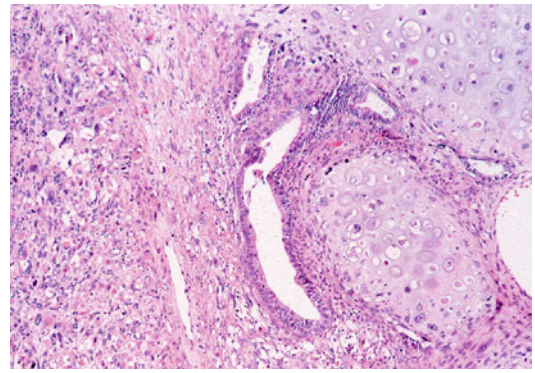

Fig. 59 Carcinosarcoma. Adenocarcinoma is intimately admixed with heterologous elements, including chondrosarcoma and rhabdomyosarcoma

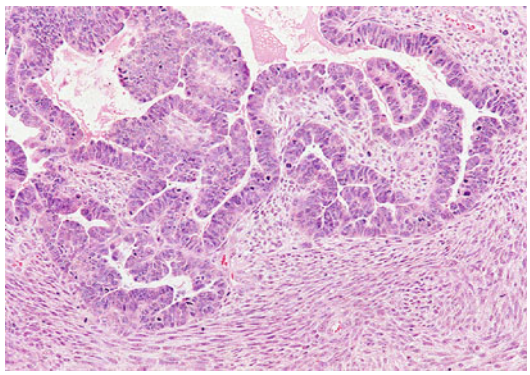

Fig. 57 Carcinosarcoma. High-grade adenocarcinoma with features of serous carcinoma is intimately admixed with a malignant spindle cell component (sarcoma)

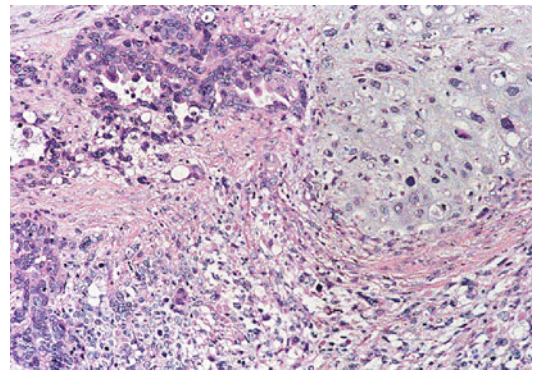

Fig. 60 Carcinosarcoma. Carcinoma is adjacent to spindle cell and chondroid components with malignant cytologic features

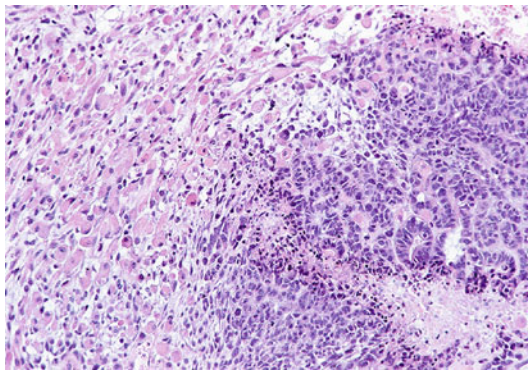

Fig. 61 Carcinosarcoma. Adenocarcinoma merges with rhabdomyosarcoma

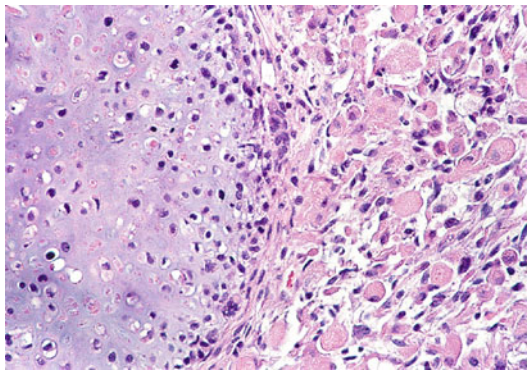

Fig. 62 Carcinosarcoma. Chondrosarcoma and rhabdomyosarcoma represent heterologous sarcomatous elements

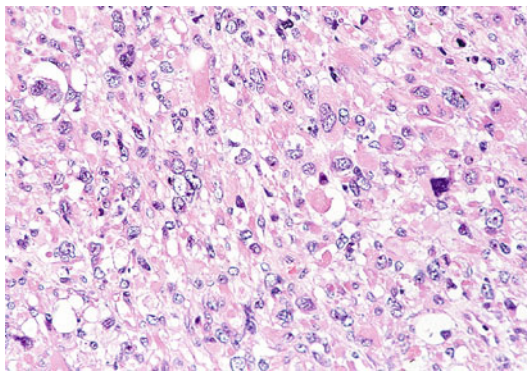

Fig. 63 Carcinosarcoma. Rhabdomyosarcoma is characterized by globoid pleomorphic cells with abundant eosinophilic cytoplasm

epithelial component, but this is less common (Silverberg et al. 1990; Norris and Taylor 1966a; Bitterman et al. 1990; Larson et al. 1990; Norris and Taylor 1966b). Approximately half the cases demonstrate a homologous stromal component, which is high-grade spindle cell (like fibrosarcoma) or pleomorphic (like malignant fibrous histiocytoma) in most cases. The homologous stromal component only rarely resembles leiomyosarcoma or low-grade endometrial stromal sarcoma (Silverberg et al. 1990; Ferguson et al. 2007a). When heterologous elements are present, rhabdomyosarcoma and chondrosarcoma are the most common types encountered (Silverberg et al. 1990; Ferguson et al. 2007b; Barwick and LiVolsi 1979)(Figs. 59, 60, 61, 62, and 63). Heterologous elements can usually be recognized easily by light microscopy. Immunohistochemical stains to establish the presence of such elements are not recommended unless such confirmation is needed after review of hematoxylin and eosin-stained slides. Rhabdomyosarcoma can often be identified by finding round or elongated cells with fibrillar eosinophilic cytoplasm. Striated rhabdomyoblasts are apparent on occasion. Some carcinosarcomas are composed of cells that contain cytoplasmic eosinophilic globules that should not be misinterpreted as evidence of rhabdomyoblastic differentiation. Importantly, carcinosarcomas as a group are enriched for highly aggressive, biphasic, malignant mixed epithelial and mesenchymal neoplasms. Some tumors failing to meet these criteria arguably resemble carcinosarcoma morphologically, but most of them are clinically and biologically distinct from them.

Differential Diagnosis

Monophasic tumors should not be diagnosed as a carcinosarcoma, although it is acknowledged that either the mesenchymal or epithelial components of carcinosarcoma might predominate in small samples such as biopsies and scant curettage specimens. Finding fragments of highly pleomorphic sarcoma, a high-grade carcinoma that is difficult to subclassify or heterologous elements in a small biopsy is usually sufficient to suggest that the biopsy might represent an incompletely

sampled carcinosarcoma, but immunohistochemical results showing coexpression of epithelial and mesenchymal-associated markers are, by themselves, insufficient for a carcinosarcoma diagnosis.

Dedifferentiated endometrial carcinoma is an example of a biphasic tumor containing differentiated and undifferentiated components (Silva et al. 2006). However, unlike carcinosarcomas, the differentiated carcinoma is usually a well-differentiated endometrioid and the undifferentiated component is composed of small, round cells of uniform size instead of spindle shaped or obviously pleomorphic cells (as discussed above with undifferentiated carcinomas). Endometrioid adenocarcinoma of the corded and hyalized variant with spindle cell elements is another biphasic endometrial neoplasm that mimics carcinosarcoma; however, these tumors are composed of histologically low-grade elements and are less aggressive than typical carcinosarcoma and high-grade carcinoma (Murray et al. 2005). In this tumor, the endometrioid component frequently contains squamous elements that fuse imperceptibly with spindle cell elements but are never histologically high grade. In most cases, the endometrioid component is no more than FIGO grade 2 and the spindle cell component is cellular and sometimes mitotically active but not high grade. In contrast, carcinosarcoma contains easily separable, high-grade epithelial and mesenchymal elements, whereas the endometrioid carcinoma with squamous differentiation shows seamless fusion of the two components. If there is confusion between this entity and carcinosarcoma, the tumor grade and the presence or absence of element fusion can be used to inform the decision. Endometrioid carcinomas rarely contain heterologous components such as chondroid and osteoid elements; by themselves these elements in an endometrioid carcinoma are insufficient for a diagnosis of carcinosarcoma. On the other hand, finding rhabdomyosarcoma along with adenocarcinoma almost always signifies carcinosarcoma.

Molecular Genetics

Early molecular studies of carcinosarcoma identified *TP53* as a commonly mutated gene but also showed that the tumors demonstrated heterogeneity with some having a more serous profile, and others harboring mutations in genes commonly mutated in endometrioid tumors (e.g., *PTEN*). These early studies also found that the mutations were shared between the carcinomatous and sarcomatous components supporting the notion, developed from clinicopathological studies, that they represent carcinomas with sarcomatous differentiation. Recent next-generation studies have validated the early studies and extended our understanding of this type of endometrial cancer. The largest studies published to date include 27 and 57 cases analyzed by a targeted approach and whole exome sequencing, respectively (McConechy et al. 2015; Cherniack et al. 2017). The percentage of mutations found in individual genes were similar with *TP53* (80–91%) and *PIK3CA* (35–40%) being the most commonly mutated genes. The other most commonly mutated genes include those that are mutated in serous and endometrioid carcinoma, supporting the endometrioid or serous differentiation noted in previous morphologic descriptions of carcinosarcoma. The genes include: *PTEN* (19–27%), *PIK3R1* (11–17%), *FBXW7* (20–28%), *PPP2R1A* (13–28%), *KRAS* (10–12%), *ARID1A* (10–12%), *CDH4* (18%), and *SPOP* (7%). In addition to next-generation sequencing, one study included a transcriptosome analysis to determine the expression profiles of carcinosarcomas. They found a subset of tumors exhibit a strong EMT gene signature. Interestingly, proteomic studies on the same group of tumors showed that carcinosarcomas were not dichotomous but shared proteomic features of both carcinomas and sarcomas. Although the samples underwent pathology review to ensure the diagnosis, it is not clear that the analyzed samples contained both elements nor that the biphasic elements were analyzed separately (Cherniack et al. 2017). Future studies will undoubtedly continue to address the molecular underpinnings of this aggressive form of endometrial cancer and build on the solid foundation provided by these high-throughput analyses.

Behavior and Treatment

Since carcinosarcomas have been historically regarded as sarcomas, many studies have included patients with only clinical staging or incomplete surgical staging. Many older studies have also likely included histologic mimics of carcinosarcoma, particularly dedifferentiated carcinoma and endometrioid adenocarcinoma with spindle cell elements. Despite this, studies of comprehensively staged patients and others comprised of clinically staged patients agree that the behavior of carcinosarcomas is significantly worse than FIGO grade 3 endometrial carcinomas, serous carcinomas, and clear cell carcinomas (Ferguson et al. 2007a; Vaidya et al. 2006; George et al. 1995; Amant et al. 2005). Surgical stage is likely the most important prognostic factor.

Pathologically determined prognostic features in clinically staged carcinosarcoma patients are generally the same as for patients with suboptimally staged endometrial carcinoma. Extrauterine extension and/or deep myometrial invasion along with lymph-vascular invasion are reported to be independent predictors of survival in numerous analyses (Yamada et al. 2000; Barwick and LiVolsi 1979; Inthasorn et al. 2002; Rovirosa et al. 2002; Bodner-Adler et al. 2001; Nordal et al. 1997; Arrastia et al. 1997; Gagne et al. 1989; Nielsen et al. 1989; Sartori et al. 1997). The presence of serous or clear cell carcinoma also is reported to have a significant tendency to be associated with metastatic disease, but the histologic appearance of the sarcomatous component does not appear to have any prognostic significance in many studies of clinically staged patients (Silverberg et al. 1990; Larson et al. 1990; Nordal et al. 1997; Gagne et al. 1989; Spanos et al. 1984). However, there are recent data to suggest that the amount of the sarcomatous component may correlate with behavior. Advanced age may also be associated with poor outcome (Inthasorn et al. 2002; Nordal et al. 1997). The 5-year survival for patients with advanced-stage disease is only 15–30% (George et al. 1995; Nielsen et al. 1989; Spanos et al. 1984).

One study evaluating the clinical and pathologic features of comprehensively staged patients with FIGO stage I carcinosarcoma confirmed that stage I tumors are more aggressive when compared to a control group of comprehensively staged patients with FIGO stage I, FIGO grade 3 endometrioid, and serous or clear cell carcinoma (Ferguson et al. 2007a). The 3-year disease-free survival was 87% for women with high-grade carcinoma compared with 42% for women with carcinosarcoma. Unlike studies of clinically staged patients, epithelial tumor type, lymph-vascular invasion, depth of myometrial invasion, and predominance of carcinoma relative to sarcoma had no relationship to overall survival. The grade of the epithelial and mesenchymal components had no bearing on overall survival either, but they were almost always high grade. The only clinical or pathologic factor found to have statistical significance with respect to clinical outcome was the presence of heterologous sarcomatous differentiation (principally rhabdomyoblastic), as assessed on review of H&E stained slides that conferred very poor survival (Ferguson et al. 2007a). When outcomes were stratified based on the presence of heterologous sarcomatous elements, the survival of patients with homologous carcinosarcoma was found to be indistinguishable from that of patients with high-grade endometrial carcinoma. The 3-year overall survival for surgical stage I carcinosarcoma was only 45% for heterologous tumors compared with 93% for homologous tumors. This study evaluated the significance of heterologous sarcomatous elements in comprehensively staged FIGO stage I carcinosarcoma patients only, so it remains to be determined whether heterologous elements drive prognosis in patients with high-stage disease. The clinical significance of heterologous elements had been noted previously (Major et al. 1993), but studies of other clinically staged patients failed to support this view (Silverberg et al. 1990; Larson et al. 1990; Gagne et al. 1989; Macasaet et al. 1985; Wheelock et al. 1985).

Carcinosarcomas metastasize to pelvic and paraaortic lymph nodes, pelvic soft tissues, vagina, peritoneal surfaces, and lungs (Fleming et al. 1984; Norris and Taylor 1966a; Chuang et al. 1970b). They are treated by total hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node dissection, pelvic

washings, and tumor debulking, if indicated. Older studies reported a decrease in local recurrences with external beam radiation therapy to the pelvis (Hornback et al. 1986). This was confirmed in a more recent retrospective study, but a convincing effect on overall survival was not appreciated (Callister et al. 2004). In an analysis of recurrence patterns, this study also reported a 38% overall local recurrence rate and a 57% frequency of distant recurrences, most of which were peritoneal (Callister et al. 2004). A GOG study of ifosfamide with or without cisplatin for the treatment of advanced, persistent, or recurrent carcinosarcoma demonstrated that the addition of cisplatin provided a small improvement in progression-free survival but no significant survival benefit (Sutton et al. 2000).

The GOG published results that favored the use of combination chemotherapy (three cycles of cisplatin, ifosfamide, and mesna) over whole abdominal radiotherapy (Wolfson et al. 2007). Although the estimated probability of recurrence in each arm of the study did not differ significantly, the recurrence rate was lower in the chemotherapy arm, when adjusted for stage and age, and the estimated mortality rate was lower in the chemotherapy group. In practice, many patients are offered combination therapy with carboplatin and taxol (Raspollini et al. 2006; Raspollini et al. 2005; Cimbaluk et al. 2007; Livasy et al. 2006; Sawada et al. 2003). Studies that address which, if any, carcinosarcoma patients are good candidates for targeted therapies are ongoing.

Miscellaneous Epithelial Tumors

A number of rare examples of unusual neoplasms arising in the endometrium have been reported, but the data consist largely of case reports precluding a detailed clinicopathologic analysis. Some of these are discussed next.

Squamous Cell Carcinoma

Squamous carcinoma develops in the endometrium, but it is extremely rare. In a population-based study from Norway, the prevalence was 0.1% (Abeler et al. 1992). To qualify as primary squamous carcinoma of the endometrium, three criteria must be met: (1) adenocarcinoma is not present in the endometrium, (2) the squamous carcinoma in the endometrium does not have any connection with the squamous epithelium of the cervix, and (3) squamous carcinoma is not present in the cervix. By these criteria, only 56 cases of primary squamous carcinoma of the endometrium have been reported (Goodman et al. 1996). The mean age of patients is 67 years. There is a strong association with cervical stenosis, pyometra, chronic inflammation, and nulliparity. The tumor may arise from ichthyosis uteri, a condition in which the endometrium is replaced by keratinized squamous epithelium. In the past, this condition was considered a sequela of the use of steam as treatment for endometritis. With the abandonment of this procedure, ichthyosis uteri have become quite rare.

Microscopically, squamous carcinomas of the endometrium resemble those in the cervix; however, at times they can be extremely well differentiated and therefore difficult to diagnose with certainty in curettings. Sometimes the diagnosis is not established until a hysterectomy is performed.

In addition to typical squamous cell carcinoma, verrucous carcinoma may arise as a primary tumor in the endometrium (Fig. 55). The prognosis of squamous cell carcinoma is related to stage at diagnosis. In a review of the reported cases, 80% of stage I patients survived whereas survival for patients with stage III disease was only 20% (Goodman et al. 1996).

Glassy Cell Carcinoma

Glassy cell carcinoma is regarded as a variant of a mixed adenosquamous carcinoma and rarely occurs in the endometrium (Arends et al. 1984; Christopherson et al. 1982c). First described in the cervix, glassy cell carcinoma is a poorly differentiated neoplasm with little or no glandular or squamous differentiation, composed of masses and nests of characteristic polygonal cells separated by a fibrous stroma that often contains an

abundance of inflammatory cells. The cells have well-defined borders and granular eosinophilic or amphophilic cytoplasm, giving a ground glass appearance. The nuclei are enlarged and round, with centrally placed, prominent, eosinophilic nucleoli. Mitotic activity, including the presence of abnormal mitotic figures, is high. The behavior, based on a small series of cases, is highly aggressive.

Yolk Sac Tumor

A recent study (Ravishankar et al. 2017) reported 15 cases of extragonadal yolk sac tumor of which 11 were located in the uterus. The patients ranged in age from 17–87 years. The histologic patterns consisted of: microcystic/reticular, glandular, solid, papillary and hepatoid. In 10 cases mixed histologic patterns were observed and Schiller-Duval bodies were identified in only 3 cases. Eight of the 11 uterine cases had an associated somatic component and 2 had a second germ cell component. Immunohistochemical stains contributed to the diagnosis including SALL4 expression in 12/12 cases, CDX2 in 10/12, AFP in 7/14, glypican-3 in 9/10. Chemotherapy was administered to all patients, and all but one patient underwent surgery. Follow-up ranged from 5–86 months for 13 patients and 5 died of disease, 6 were alive with disease and 2 had no evidence of disease. Although most extragonadal yolk sac tumors arise from germ cells it is possible that uterine yolk sac tumors associated with somatic tumors may represent carcinomas with specialized differentiation and may represent a unique subset of patients.

Giant Cell Carcinoma

Rare primary endometrial carcinomas may contain multinucleated giant cells resembling giant cell carcinomas in other sites such as the lung, thyroid, pancreas, and gallbladder. In a report of six cases, the giant cells accounted for a substantial part of the tumor (Jones et al. 1991). The remainder of the neoplasm contained undifferentiated carcinoma and areas of more differentiated endometrioid carcinoma. Immunohistochemical studies demonstrated positive immunoreactivity for cytokeratin and EMA in the giant cell component. Vimentin, desmin, and smooth muscle actin were negative. Four of the six patients in whom the tumor invaded more than superficially developed recurrent tumor, and three patients died of disease within 3 years. Tumors with cells resembling osteoclast-like giant cells also have been observed in the endometrium.

Choriocarcinoma

Rarely, primary choriocarcinoma of the endometrium may develop in a postmenopausal woman, representing a form of differentiation of a carcinoma derived from somatic cells rather than germ cells or trophoblasts. Six patients ranging in age from 48 to 78 years have been reported (Kalir et al. 1995; Pesce et al. 1991; Savage et al. 1987; Tunc et al. 1998). Most patients had elevated serum human chorionic gonadotropin (hCG) levels and/or hCG detected in the syncytiotrophoblastic element in the tumor. A case of choriocarcinoma associated with a carcinosarcoma (malignant mesodermal mixed tumor) has been reported, and we have observed one such case as well (Khuu et al. 2000). These tumors appear to behave in an aggressive fashion.

Transitional Cell Carcinoma

Ten cases of transitional cell carcinoma of the endometrium have been reported (Lininger et al. 1997; Spiegel et al. 1996). Patients have ranged in age from 41 to 83 years, with a mean of 62. The tumors are typically polypoid and present with uterine bleeding. Transitional cell carcinomas often are papillary and resemble transitional cell carcinomas of other organs. They are invariably admixed with other patterns of endometrial carcinoma, including endometrioid, squamous, and serous components. The overall prognosis does not appear to be worse than expected for the stage

of disease, but the transitional cell component seems to be the more aggressive subtype among the patterns with which it is admixed (Lininger et al. 1997).

Other Rare Variants

Other rare types of carcinomas of the endometrium that have been reported include an oxyphilic variant of endometrioid carcinoma, a primary signet-ring cell carcinoma, and an AFP-secreting hepatoid adenocarcinoma associated with endometrioid carcinoma (Hoshida et al. 1996; Mooney et al. 1997; Pitman et al. 1994). In addition, an endometrioid carcinoma associated with Ewing sarcoma/peripheral primitive neuroectodermal tumor has been reported (Sinkre et al. 2000).

Tumors Metastatic to the Endometrium

Ovarian Carcinoma

Simultaneous cancers involving the endometrium and the ovary may represent (1) metastasis from the endometrium to the ovary, (2) metastasis from the ovary to the endometrium, or (3) independent primary tumors. The distinction may be important because the prognosis and treatment differ. It has been suggested that when the endometrial carcinoma is small and minimally invasive, the two neoplasms should be considered independent. One study found that if the two carcinomas have an endometrioid pattern, the prognosis is good, and therefore the two neoplasms probably are independent (Eifel et al. 1982). When serous or clear cell carcinoma is found, the prognosis is poor and a primary tumor with metastasis is likely. The primary neoplasm is identified by its larger size or more advanced stage.

Another study proposed that tumors be classified as primary in the endometrium with metastasis to the ovaries when there is multinodular ovarian involvement or at least two of the following criteria are met: (1) small (5 cm) ovaries, (2) bilateral ovarian involvement, (3) deep myometrial invasion, (4) vascular invasion, or (5) fallopian tube involvement (Ulbright and Roth 1985). When these criteria are used, there is a significant difference in the frequency of distant metastasis in the group classified as metastatic versus the group classified as an independent primary. Metastasis from the endometrium to the ovary occurs more often than the reverse. About a third of the cases were thought to be independent tumors involving both sites simultaneously, however more recent data suggest that they may be clonally related (see below). Independent tumors display either well-differentiated endometrioid or nonendometrioid patterns, whereas grade 3 endometrioid carcinoma and carcinosarcomas generally are primary in one organ and metastatic to the other when detected.

A recent molecular study using targeted sequence analysis of specific genes commonly altered in endometrial and ovarian cancer found that the majority of synchronous low-grade and low-stage endometrioid carcinomas demonstrated evidence of clonality. These findings support the metastatic nature of the lesions but does not shed light on the directionality of the metastases. Given the good prognosis for patients with such tumors, it is speculated that the tumor cells have restricted dissemination capability with limited ability to spread beyond the female genital tract (Anglesio et al. 2016).

Carcinomas from Extragenital Sites

When an extragenital tumor metastasizes to the uterus, it usually is a manifestation of obvious dissemination. The diagnosis in curettings may, on rare occasion, be the first clue of an occult primary tumor. The mean age of patients is 60 years. Metastatic breast cancer is the most frequent extragenital tumor that metastasizes to the uterus (47%) (Fig. 64), followed by the stomach (29%), cutaneous melanoma (5%), lung (4%), colon (3%), pancreas (3%), and kidney (3%) (228) (Kumar and Hart 1982). Metastatic neoplasms to the endometrium frequently infiltrate the endometrium diffusely, sparing the glands. Most neoplasms metastatic to the endometrium are poorly differentiated and lack squamous

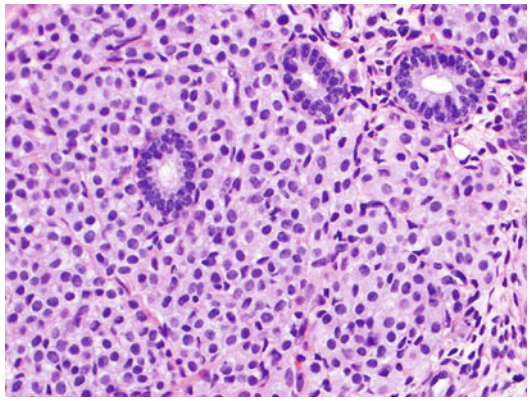

Fig. 64 Metastatic breast carcinoma. Monotonous cells with uniform nuclei and pale eosinophilic cytoplasm replacing the stroma and surrounding residual inactive endometrial glands are consistent with metastatic lobular breast carcinoma

differentiation, unlike primary endometrial carcinoma. The myometrium can contain metastatic nodules as well.

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