

Chapter 2

Classification of Endometrial Carcinoma

Sigurd F. Lax

A Putative Pathogenetic Model for Endometrial Carcinoma

A simplified model has been developed based on clinicopathologic and molecular parameters in order to better understand endometrial tumorigenesis. According to this model, (Table 2.1) there are two types of endometrial carcinoma that are characterized by distinct features and that develop along different pathways (Table 2.2). Type I carcinomas, which account for the great majority of endometrial carcinomas (approximately 80–90%), are characterized by low stage at diagnosis and a favorable clinical course. They typically develop in a normal-sized or a myohyperplastic uterus and are associated with disordered proliferative or hyperplastic endometrium. The latter reflects unopposed estrogenic stimulation, which may be caused by persistent follicles due to anovulatory cycles, an estrogen producing tumor such as adult granulosa cell tumor, endogenous estrogen production by the aromatase of adipose tissue in the setting of high body mass index, or hormone replacement therapy by pure estrogens. Thus, the typical age of a patient with type I carcinoma is in the peri- and postmenopausal period. The patients also have elevated levels of free estrogen in the serum [5]. Histologically, type I carcinomas are endometrioid adenocarcinoma, including its variants and mucinous carcinoma, and are mostly low histological grade (good or moderate histopathologic differentiation). Atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia (EIN) is considered the precursor lesion. The fact that these carcinomas usually highly express estrogen (ER) and progesterone receptors (PR) further underlines their relationship to an estrogenic pathway.

S.F. Lax (✉)

Department of Pathology, Hospital Graz Sued-West,
Academic Teaching Hospital of the Medical University,
LKH Graz Süd-West, Standort West,
Göstingerstrasse 22, 8020 Graz, Austria
e-mail: sigurd.lax@kages.at

Table 2.1 Histopathologic classification of endometrial carcinoma (WHO 2014) [1]

Histological type	ICD-O
Endometrioid adenocarcinoma	8380/3
Endometrioid adenocarcinoma-variants	
With squamous differentiation	
Secretory variant	8570/3
Villoglandular variant	8263/3
Ciliated cell variant	8382/3
Mucinous adenocarcinoma	8480/3
Serous endometrial intraepithelial carcinoma (SEIC)	8441/2
Serous adenocarcinoma	8441/3
Clear cell adenocarcinoma	8310/3
Mixed cell adenocarcinoma	8323/3
Undifferentiated carcinoma	8020/3
Monomorphic type	
Dedifferentiated type (dedifferentiated carcinoma)	
Neuroendocrine tumors	
Well differentiated neuroendocrine tumor (carcinoid tumor)	8240/3
Poorly differentiated small cell neuroendocrine carcinoma	80412/3
Poorly differentiated large cell neuroendocrine carcinoma	8013/3

Table 2.2 An expanded dualistic model for endometrial carcinoma

Features	Type I carcinoma	Type II carcinoma
Estrogen-related	Yes	No
Endometrial histology	Usually hyperplastic or disordered proliferative	Usually atrophic
Estrogen- and progesterone receptors	Usually positive	Usually negative or weakly positive
Age (median)	55–65 years	65–75 years
Stage	Mostly stage I	Mostly stages II–IV
Prognosis	Favorable	Unfavorable
Histological type	Endometrioid + variants; Mucinous	Serous, clear cell
Molecular alterations	PTEN inactivation Microsatellite instability β-catenin mutations K-ras mutations	P53 mutations E-cadherin inactivation
Molecular type according to TCGA	Hypermutated, copy number low (endometrioid-like)	Copy number high (serous like)

In contrast, type II carcinomas are diagnosed at high stage and are aggressive tumors with a poor outcome. The histologic prototype is serous carcinoma, but clear cell and undifferentiated carcinomas are also considered type II carcinomas. These tumors are usually not related to estrogenic stimulation, as reflected by the following features: they usually occur in an atrophic uterus and are associated with atrophic or inactive endometrium; they may occur in atrophic polyps; serum estrogen is low in these patients; in addition, ER and PR immunoreactivity is weak or negative. Serous endometrial intraepithelial carcinoma (SEIC) had been considered the precursor of serous carcinoma. Recently, our concept of SEIC has transitioned to a non-invasive carcinoma, since it is frequently associated with extensive extrauterine disease. In this setting, SEIC may be part of pelvic serous carcinoma without a clear site of origin. For other type II carcinomas putative precursors are unknown, although EIC has been found in a subset of clear cell carcinomas. In addition to SEIC, a less atypical lesion has been characterized and described as dysplasia [6–9].

Type I and type II carcinomas are also distinct on the molecular level [3]. Most type I carcinomas are characterized by minor changes in the genome as evidenced by a low number of somatic copy number alterations, whereas most type II carcinomas are characterized by major changes in the genome, such as a high number of somatic copy number alterations and aneuploidy. Frequent mutations of *PTEN* (>50%), *K-RAS* (20–30%), *ARID1A* (40% of low grade endometrioid carcinomas), *CTNNB1* (β -catenin) (30%) and *PIK3R1* (20–45%) are typical for type I carcinomas, whereas mutations of *TP53* (80–90%), *FBXW7* (20–30%) and *PPP2R1A* (20–30%) are more frequently found in type II carcinomas [10–16]. In addition, a mutator phenotype leading to microsatellite instability (MSI) is found in 25–40% of type I carcinomas, but is very rare in type II carcinomas (<5%). Microsatellite instability leads to frameshift mutations in repetitive sequences, which may be located in crucial genes such as Bax, an apoptosis related gene [17]. On the other hand, mutations of *PIK3CA* are almost equally found in type I and type II carcinomas [18–20], and *TP53* mutations can be found in a subset of type I carcinomas, grade 3 endometrioid adenocarcinoma (30%) [13].

The studies of The Cancer Genome Atlas (TCGA) project revealed four prognostic groups of endometrial carcinoma, of which tumors with “serous-like” genomic changes, particularly high copy number changes, had the worst prognosis. Tumors with mutations in the polymerase E gene (*POLE*) had an excellent prognosis; the prognosis of tumors with low copy number changes and of hypermutated tumors was in between [21]. Recent studies reported *POLE* mutations in endometrial carcinomas with serous and high grade endometrioid phenotypes that had an excellent prognosis [22]. Subsequently, a novel molecular based classification system for endometrial carcinoma has been proposed, including immuno-histochemistry for p53 and mismatch repair proteins, as well as mutational analysis for *POLE* [23].

Although clear cell carcinoma is considered biologically and clinically a type II carcinoma, it shares some molecular alterations with type I carcinoma, in particular *PTEN* mutations (30–40%) and loss of *ARID1A* expression, but without mutations

(25%) [24, 25]. A recent study found a serous-like mutation profile of clear cell carcinoma with concurrent mutations in *TP53* and *PPP2R1A*, but wild type *ARID1A*, *PTEN*, *CTNNB1* and *POLE* [26].

In summary, type I carcinoma seems to follow an adenoma-carcinoma sequence, developing from atypical hyperplasia/EIN and progressing from low grade to high grade carcinoma. Some of the molecular changes, such as mutations in *PTEN*, *K-RAS* and *ARID1A*, seem to occur early, particularly in atypical hyperplasia and grade 1 endometrioid adenocarcinoma; others, such as *TP53* mutations, seem to represent late events since they occur in high grade endometrioid adenocarcinoma [13, 14, 27]. In contrast, serous carcinoma seems to develop de novo from atrophic endometrium through SEIC [28]. Mutations of *TP53*, *PIK3CA*, *FBXW7* and *PPP2R1A* as well as overexpression of *cyclin E1* are considered early events in the development of serous carcinoma since they are present in SEIC [16, 29, 30]. Some of these genetic alterations seem to be strong drivers of tumorigenesis. In particular, mutated *TP53* seems to be a strong driver for growth in serous carcinoma that leads to a strong selective advantage. The diffuse strong or flat negative immunoreactivity, briefly called “all or null pattern”, is characteristic for *TP53* mutations and seems to reflect an early clonal expansion that involves the whole tumor.

Histopathologic Classification

Endometrioid Adenocarcinoma

Endometrioid adenocarcinoma is by the far most frequent histologic type of endometrial carcinoma [1, 31, 32]. It typically displays glandular, papillary or solid patterns (Fig. 2.1). The glandular structures are typically well formed and show regular luminal borders resembling the glands of non-neoplastic endometrium. The nuclei are elongated and pseudostratified or round. Villous and papillary structures are commonly found and need to be distinguished from the papillae of serous carcinoma.

Endometrioid adenocarcinoma may be associated with various types of cellular differentiation that do not have clinical significance. Nevertheless, it is important to be aware of these histologic features, and they should be included in the pathology report since they may help in recognition of a local recurrence or metastasis. **Squamous differentiation** occurs in about 10–25% of endometrioid adenocarcinomas and may present as focal morular structures within glandular lumens (Figs. 2.1 and 2.2) or as confluent sheets [33]. Squamous differentiation may be characterized by polygonal or spindle cells resembling squamous differentiation in the uterine cervix. Other characteristics include intercellular bridges and the formation of squamous pearls. The squamous areas often have bland or slightly polymorphic nuclei, but the degree of atypia usually concurs with the histopathologic grade of the tumor [34]. Extensive immature squamous differentiation may

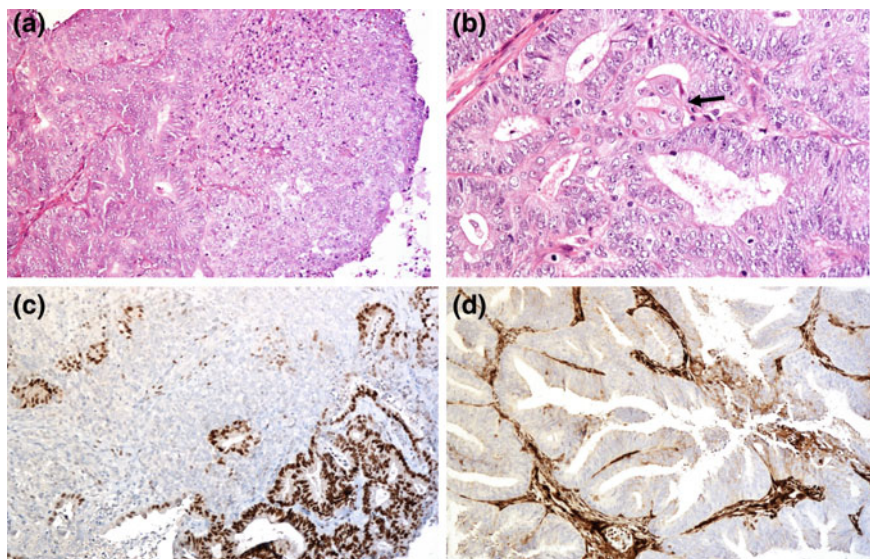


Fig. 2.1 FIGO grade 2 endometrioid adenocarcinoma with glandular and solid patterns (a). The glands are well formed and have regular luminal borders (b). A small focus of squamous differentiation is present (arrow). Estrogen receptor immunoreactivity is strong in the glandular area and weak in the solid area (c), PTEN immunoreactivity is lost in the tumor, but present in the stromal cells (d)

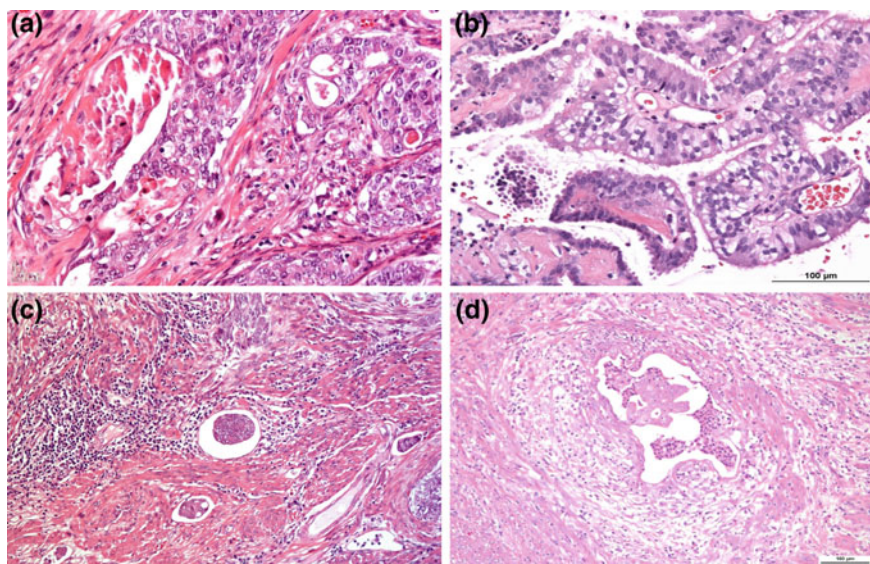


Fig. 2.2 Endometrioid adenocarcinoma with squamous differentiation (a). Secretory variant of endometrioid adenocarcinoma with cytoplasmic vacuoles resembling early secretory phase (b). Lymphovascular space involvement (LVSI) (c) and a microcystic elongated and fragmented glandular pattern (d) as poor prognostic factors in histologically low grade endometrioid adenocarcinomas

significantly influence the histopathologic grade of a carcinoma if it is not recognized and is misinterpreted as solid non-squamous growth [35]. For the differentiation of these two, it is helpful to take into account the nuclear atypia of the solid area. Ki-67 can be used as an adjunct since its labeling index is low in low grade “metaplastic” squamous areas, but high in solid non-squamous structures. Poorly differentiated endometrioid adenocarcinoma with squamous differentiation (the former “adenosquamous carcinoma”) may infiltrate as small nests of atypical squamous cells or grow in sheets of atypical spindle cells resembling a sarcomatoid carcinoma [33]. Extensive keratinization is rare, but can be associated with keratin granulomas at various sites outside the uterus [36]. Mucinous differentiation associated with squamous differentiation in endometrioid adenocarcinoma is not unusual.

The **villoglandular variant** is usually low grade and composed of glands and delicate papillae, covered by columnar epithelium with mild to moderate nuclear atypia [37]. It often presents with low stage and superficial myometrial invasion. The prognosis of the villoglandular variant with myoinvasion is controversial and has been under debate [37, 38]. Differentiating it from serous carcinoma is crucial and may be challenging in some cases; criteria are detailed in the serous carcinoma section.

The **secretory variant** or **variant with secretory differentiation** resembles early secretory phase endometrium with glands containing sub- and/or supranuclear vacuoles (Fig. 2.2). The secretory changes may be focal or diffuse, and they may be associated with the secretory phase or with exogenous progestins, and thus represent a transient change. If the changes occur in premenopausal women, the adjacent endometrium may show similar changes. The secretory variant is usually low grade and predominantly glandular, but if it contains solid areas it must not be misinterpreted as clear cell carcinoma. In contrast to clear cell carcinoma, the secretory variant of endometrioid adenocarcinoma lacks significant nuclear atypia and other characteristic features of clear cell carcinoma [39, 40].

The **ciliated variant** is rare, although cells with apical cilia are not unusual in typical endometrioid adenocarcinoma. These are usually low grade and low stage tumors, and there is some evidence of association with estrogens [41].

Endometrioid adenocarcinoma may also have variant growth patterns. An unusual pattern of invasion contains microcystic, elongated and fragmented glands (MELF) (Fig. 2.2) and seems to be frequently associated with LVSI [42]. Extensive lymph vascular space involvement (LVSI) is a prognostic factor for increased risk of recurrence (Fig. 2.2). Myometrial invasion may be clearly recognizable, particularly when it contains haphazardly distributed glands or diffusely arranged cords and clusters of cells or individual cells. The infiltrated myometrium frequently has a desmoplastic reaction, or less often an inflammatory response. In other cases of endometrial carcinoma, myometrial invasion may have a smooth, pushing border and lack desmoplasia, akin to adenoma malignum of the cervix [43]. A similar pattern can be found when endometrial carcinoma extends into adenomyosis. The distinction from true myometrial invasion is important, since prognosis is not adversely influenced by involvement of adenomyosis. The presence of clearly

recognizable adenomyosis on H&E sections is required for the diagnosis of carcinoma involving adenomyosis. This may be difficult, particularly when the glands in adenomyosis are sparse and the stroma is atrophic or fibrotic. Similarly, the diagnosis of superficial myometrial invasion can be problematic because of irregularity of the endomyometrial junction [44]. For the diagnosis of myometrial invasion, clear evidence of irregularly distributed tumor nests within the myometrium, without proximity to residual non-neoplastic glands or endometrial stroma, is needed.

The proportion of the solid, non-squamous component of the tumor determines the FIGO histologic grade of endometrioid adenocarcinoma (Table 2.3) (Fig. 2.1). In FIGO grade 1 carcinomas, solid areas account for less than 5%, in FIGO grade 2 carcinomas 6–50% and FIGO grade 3 carcinomas have more than 50% of non-squamous solid areas. Solid areas of squamous differentiation are not considered for grading purposes. There are several problems with FIGO grading, such as the recognition of small areas with solid growth, the distinction between solid squamous and non-squamous areas and the interobserver reproducibility of bizarre nuclear atypia. Finally, the reproducibility of a three-tier system may have its weaknesses. Alternative grading systems using only two tiers and considering patterns of growth have been proposed and subsequently validated, but have not been generally accepted [45–48].

The differential diagnosis of endometrioid adenocarcinoma includes atypical hyperplasia and atypical polypoid adenomyoma (APAM). Distinction from atypical hyperplasia may be particularly difficult in biopsies and curettage specimens. The best proof of carcinoma is evidence of invasion into adjacent stroma or myometrium. A confluent glandular or cribriform pattern resulting in a complex labyrinth- or maze-like appearance is considered invasive as it reflects loss of stroma [49]. Other criteria for invasion are a desmoplastic stromal response, and extensive papillary architecture [50]. APAM consists of crowded glands, often with squamous morules, surrounded by spindle cell stroma [51]. If the arrangement of the glands is complex, the differential diagnosis may be difficult, particularly since the stromal cells are of myofibroblastic origin and may suggest a desmoplastic reaction. Immunohistochemistry may not be helpful for the differential diagnosis between APAM and myoinvasive endometrioid adenocarcinoma [52]. In contrast to endometrioid adenocarcinoma, APAM has an organoid pattern with a mixture of the glandular and mesenchymal components, and a lobulated appearance of the glandular component. Rarely, endometrioid adenocarcinoma may arise in APAM and is characterized by a confluent glandular growth pattern.

Table 2.3 FIGO grading of endometrioid carcinoma of the endometrium

FIGO grade	Amount of solid non-squamous, non-morular growth (%)
FIGO grade 1 ^a	≤ 5
FIGO grade 2 ^a	6–50
FIGO grade 3	>50

^aThe presence of bizarre nuclear atypia raises the grade by 1
Serous and clear cell carcinoma are by definition high grade (grade 3) and not further graded. According to UICC carcinosarcoma (MMMT) is also by definition grade 3

Table 2.4 Immunohistochemical typing of endometrial carcinoma

Histologic type	Typical immunohistochemical findings
Endometrioid G1/2 incl. variants	ER++/+++ , PR++/+++ , p53 wild type ^a , Ki67+/+++ , PTEN-/- , p16 heterogeneous
Endometrioid G3 incl. variants	ER++/+, PR+/+++ , p53 heterogeneous, Ki67++/+++ , PTEN-/-+
Mucinous	ER++/+++ , PR++/+++ , p53 wild type, Ki67+/+++ , PTEN-/- , p16 ++ (diffuse)
Serous	ER+ , PR+ , p53 mutant ^a , Ki67+++ , PTEN++ , p16+++
Clear cell	ER-/- , PR-/- , p53 heterogeneous, PTEN+/- , p16+/- , HNF1B ++ , Napsin A++ , Rcmase++ , ARID1A -/+

^aP53 immunoreactivity: A diffuse positive or flat negative (all or null) pattern is associated with p53 mutation and therefore considered mutant. A heterogeneous pattern with at least a third strong positive nuclei is also associated with p53 mutations. A weak to moderate staining pattern is considered “wild type” [13]

Immunohistochemical staining for ER and PR is usually intense in low grade endometrioid adenocarcinoma, but may be absent in areas of squamous differentiation (Table 2.4). β-catenin often shows aberrant (nuclear) staining, and PTEN and PAX-2 staining is reduced or lost (Fig. 2.1) [53, 54]. Ki-67 staining is variable. p53 immunoreactivity shows heterogenous, mostly weak to moderate nuclear staining with interspersed intense or negative nuclei, which is considered a “wild type pattern” [13]. P16 immunoreactivity is negative or patchy with focal staining [55]. High-grade endometrioid adenocarcinomas may partially show intense nuclear immunoreactivity for p53, suggestive of mutated TP53 [13]. ER and PR immunoreactivity is weak to moderate, or may be negative; the Ki-67 labeling index is usually 30–50% [56, 57].

Mucinous Carcinoma

Pure mucinous carcinoma of the endometrium is rare. By definition, more than 50% of cells contain PAS positive diastase resistant intracytoplasmic mucin [1]. More commonly, focal mucinous differentiation is found in endometrioid adenocarcinoma, often in combination with squamous differentiation. Cribriform or microglandular areas may resemble microglandular hyperplasia of the uterine endocervix, which should be considered in the differential diagnosis in biopsy specimens. The histological grade (assessed according to FIGO) and stage are usually low. Its association with exogenous estrogen has been reported [58]. Immunohistochemical staining shows diffuse positivity for ER and PR, and positivity for vimentin, which can be helpful in its differentiation from endocervical adenocarcinoma [59]. The Ki-67 labeling index is low (Table 2.4). An potential pitfall to note is the frequently high and diffuse immunoreactivity for p16, which is unrelated to HPV [60].

Serous Carcinoma

Serous carcinoma is considered a distinctive tumor, both histologically and at the molecular level [28, 61]. The diagnostic hallmark of serous carcinoma is the combination of low grade, often papillary architecture, and high nuclear grade [1]. However, the histologic pattern may vary by containing both short thick, and thin elongated papillae, but also glandular and solid structures (Fig. 2.3). Therefore, the term serous “papillary” carcinoma is misleading and should be avoided. Serous carcinomas are by definition high grade (grade 3). The tumor cells are usually polygonal and characterized by highly atypical nuclei, often with prominent nucleoli and frequent mitoses. Furthermore, the tumor cells are irregularly arranged and form buds and tufts, and are detached in small groups. The luminal borders of the glands and the surface of the papillae are scalloped. Serous carcinoma often occurs in a small uterus with atrophic endometrium and may be found within endometrial polyps. It may be associated with extensive LVSI.

The typical patient’s median age is around 65–70 years. About one half of the patients are diagnosed at an advanced stage (stage >I). Serous carcinoma requires full surgical staging, since stage I uterine serous carcinoma can be associated with an excellent outcome [62, 63].

The differential diagnosis of serous carcinoma includes the papillary variant of endometrioid adenocarcinoma and clear cell carcinoma (detailed in Table 2.5). The

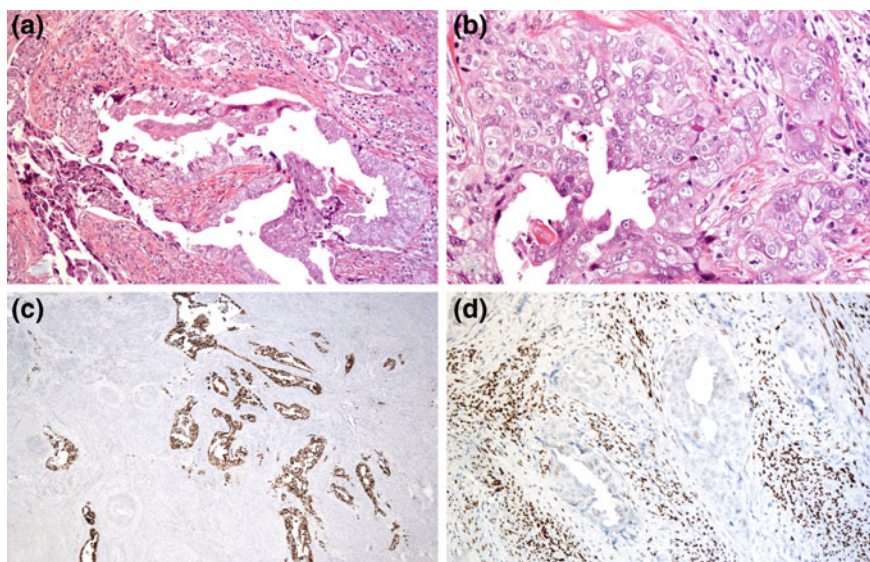


Fig. 2.3 Serous carcinoma with papillary, glandular, and solid growth patterns (a, b). Diffuse and strong p53 immunoreactivity (c) and weak ER immunoreactivity (d) are typical

Table 2.5 Differential diagnosis between serous, clear cell and endometrioid adenocarcinoma (papillary variant)

	Serous carcinoma	Papillary variant	Clear cell carcinoma
Papillae	Variable: short, thick, densely fibrotic or thin	Uniform, thin and delicate or broad	Short, thick with hyaline bodies
Cells	Columnar/polygonal; proliferation with tufting and budding; detached cell clusters	Columnar, pseudostratified; cohesive	Polygonal or hobnail shaped; slightly detached
Luminal borders	Scalloped	Regular, smooth (“straight”)	Irregular
Nuclear features	Marked pleomorphism, frequent mitoses	Mild pleomorphism, infrequent mitoses	At least focal marked pleomorphism, frequent mitoses
Immuno-histochemistry	P53 diffusely positive or flat negative ER and PR negative/focal positive Ki-67 high	P53 negative/focally positive ER diffusely or heterogenously positive Ki-67 low/moderate	P53 focally positive ER and PR negative or mildly positive Ki-67 moderate to high

papillary variant of endometrioid adenocarcinoma usually has thin papillae and lacks marked nuclear atypia. Clear cell carcinoma usually contains at least focally cells with clear cytoplasm, hyalinized bodies, and eosinophilic globules.

Serous endometrial intraepithelial carcinoma (SEIC) consists of highly atypical cells replacing the endometrial surface and glands that do not invade the myometrium. SEIC has been considered an immediate precursor of serous carcinoma [64]. Biologically, SEIC is now considered a non-myoinvasive carcinoma since it may be associated with extensive extrauterine disease involving the peritoneum (e.g. omentum), the ovaries, and the fallopian tube [65]. (Endometrial glandular dysplasia was not adopted by the recent WHO classification.) In the setting of extensive pelvic serous carcinoma, it may be difficult to determine a site of origin. WT-1 immunohistochemistry may be helpful in the distinction between uterine and extra-uterine origin, since it is negative in about 90% of uterine serous carcinomas and positive in 70–100% of serous carcinomas originating from the ovary, fallopian tube, and peritoneum [66–68].

Immunohistochemistry shows a typical “all or null” or “mutant” immunoreactive pattern for p53 that correlates well with TP53 mutations (Table 2.4) (Fig. 2.3). Flat negative immunostaining is associated with frameshift mutations or a stop codon leading to a truncated protein that is not detectable with the usual p53 antibodies

[29]. ER immunoreactivity is usually weak or negative, and PR is often negative [56]. In cases with extensive extrauterine disease and a putative ovarian/tubal origin, ER and PR immunoreactivity may be moderate to strong.

Clear Cell Carcinoma

Clear cell carcinoma is composed of polygonal or hob-nail shaped cells with clear or eosinophilic cytoplasm and high grade nuclear features [69]. The architectural pattern may be tubulo-cystic, papillary, or solid (Fig. 2.4). The papillae are short and branching with hyalinized stroma. Other typical features are densely eosinophilic extracellular globules and hyaline bodies. Like serous carcinoma, clear cell carcinoma can occur in atrophic endometrium, within endometrial polyps, and is by definition high grade (grade 3) [1].

Immunohistochemical staining (Table 2.4) shows negativity or mild positivity for ER and PR, a Ki-67 proliferation index of at least 25–30%, and frequent positivity for HNF-1 β , Napsin A and racemase (AMACR) [57, 70–72]. Focal strong positivity for p53 is found in about one third of the cases and correlates with TP53 mutations on the genomic level (Fig. 2.4) [25]. About 30% of the cases show loss of PTEN [25]. Approximately 50% of the patients are diagnosed at stages II–IV and have a poor outcome, with a 5-year survival rate of less than 50% [69, 73, 74]. In contrast, an excellent prognosis is reported for stage I, particularly IA tumors [75].

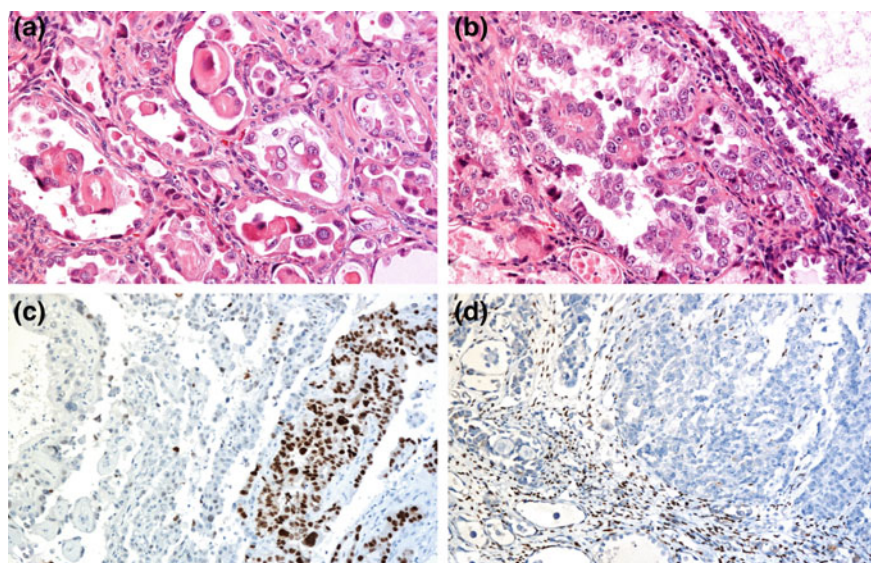


Fig. 2.4 Clear cell carcinoma with glandular (a) and papillary architecture (b). The cells are hob-nail shaped and the glands contain eosinophilic material. The typical immunoprofile is heterogeneous for p53 (c) and negative for ER (d)

Mixed Carcinoma

The recent WHO consensus defined mixed carcinoma as a composition of two or more different histologic types of endometrial carcinoma, of which at least one is of the type II category, particularly serous and clear cell carcinoma [1]. These different tumor types should be clearly visible on H&E stained sections and the minimum percentage of the minor component has been arbitrarily set at 5%. The most frequent combinations are endometrioid and serous carcinoma, and endometrioid and clear cell carcinoma. Immunohistochemistry can help support the diagnosis [76]. The high grade carcinoma determines the prognosis, even if it is present as a minor component (i.e. 5%) [77]. It was suggested that progression from endometrioid to serous carcinoma could lead to a mixed serous and endometrioid carcinoma [11, 78].

Undifferentiated Carcinoma

Undifferentiated carcinoma is a rare tumor that is defined by its lack of specific differentiation. The recent WHO classification distinguishes between monomorphic and dedifferentiated undifferentiated carcinoma [1]. The **monomorphic type** is composed of small to intermediate sized, relatively uniform cells usually arranged in sheets. The nuclei are hyperchromatic with frequent mitoses and may exhibit focal pleomorphism. The stroma may contain myxoid matrix resembling a carcinosarcoma, but in contrast to the latter a biphasic histological pattern is absent. The differential diagnosis includes other high grade neoplasms, such as high grade sarcomas, lymphoma and neuroendocrine carcinoma [79].

The **dedifferentiated type** is characterized by a sharply demarcated second component that consists of a low grade (FIGO grade 1 or 2) endometrioid adenocarcinoma [80]. Typically, the undifferentiated component infiltrates the myometrium, whereas the low grade component lines the endometrial cavity (Fig. 2.5). The undifferentiated component may have a sarcomatous appearance and lack immunoreactivity or have focal staining for cytokeratin and EMA, whereas vimentin is usually diffusely positive (Fig. 2.5). ER and PR are negative. Focal positivity for synaptophysin and chromogranin may be found and should not by itself lead to a diagnosis of neuroendocrine carcinoma [81]. The median patient age is about 55 years, which may reflect the fact that a subset of undifferentiated carcinomas occurs in patients with Lynch syndrome. The prognosis is poor with more than 50% of cases having a fatal outcome.

The differential diagnosis includes any high grade neoplasm of the endometrium, including carcinosarcoma (mixed malignant Mullerian tumor/MMMT). Carcinosarcoma has been considered an epithelial neoplasm with a special kind of epithelial-mesenchymal transition during its pathogenesis [82]. The pattern of metastatic spread resembles that seen in carcinoma, and the metastases of carcinosarcoma often contain predominantly or purely the carcinomatous component

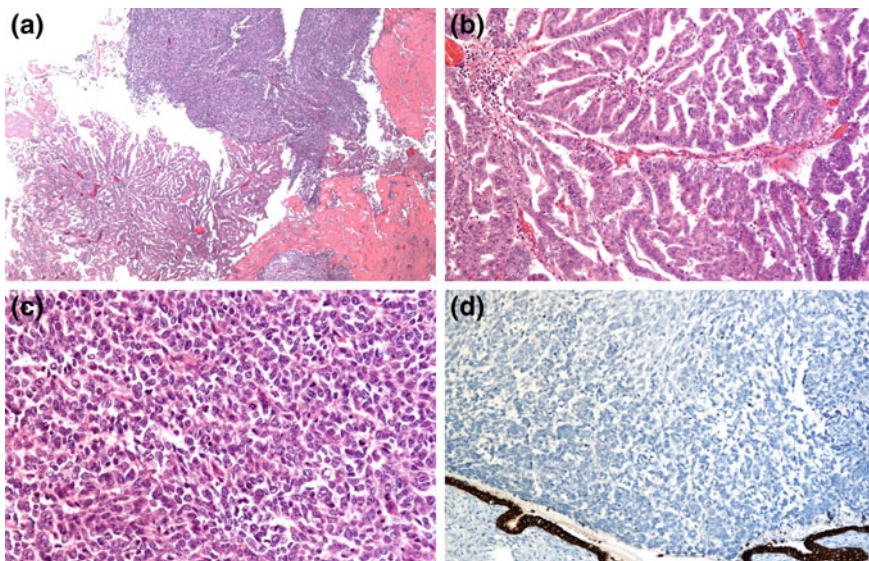


Fig. 2.5 Dedifferentiated type of undifferentiated carcinoma containing well differentiated endometrioid (a, b) and undifferentiated components (a, c). The latter consists of small, loosely cohesive cells (c) that are not immunoreactive with antibodies against cytokeratins (AE1/AE3) (d). The undifferentiated component was strongly immunoreactive for vimentin (not shown)

[83]. Carcinosarcoma is by definition a grade 3 tumor and is treated as an endometrial carcinoma for FIGO staging. However, in the WHO classification carcinosarcoma is categorized among the mixed tumors [1]. Histologically, carcinosarcoma is characterized by a biphasic pattern containing a variety of homologous or heterologous malignant mesenchymal tissues that are mixed with the malignant epithelial component [84]. The tumor components are often, but not necessarily, high grade [85]. The outcome is poor, comparable to high grade endometrioid adenocarcinoma, and seems to be influenced by the presence of heterologous elements. This biphasic intermixed histologic pattern differs from that seen in dedifferentiated carcinoma, which resembles collision tumors with large areas of demarcation between the two components. In addition, the components of dedifferentiated carcinoma are less heterogeneous as compared to those in carcinosarcoma.

Neuroendocrine Tumors

Neuroendocrine tumors were newly defined in the recent WHO classification (Table 2.1) [81]. They are very rare and occur at a median age of between 60 and 65 years. So far, only a few cases of low grade neuroendocrine tumor (carcinoid

tumor) have been reported [86–88]. **Small cell neuroendocrine carcinoma (SCNEC)** resembles its counterparts at other sites (e.g. lung, gastrointestinal tract) [89, 90], grows diffusely or in nests, and may have trabecular and rosette-like structures. **Large cell neuroendocrine carcinoma (LCNEC)** consists of highly atypical cells with frequent mitoses that grow in well-demarcated nests, trabeculae and cords with palisading at the periphery. Extensive tumor cell necrosis is typical. A neuroendocrine growth pattern is generally present in at least a part of the tumor [91]. Immunohistochemistry with positivity for at least synaptophysin or chromogranin A is necessary to confirm the diagnosis of low grade neuroendocrine tumors. In poorly differentiated neuroendocrine carcinomas, chromogranin A is usually negative; CD56 (NCAM) may be positive, but is considered less specific. SCNEC shows a dot-like staining pattern for cytokeratins. The differential diagnosis includes other high grade neoplasms, in particular undifferentiated carcinoma. The prognosis for SCNEC and LCNEC is poor.

Staging of Endometrial Carcinoma

Endometrial carcinoma is surgically staged and, therefore, final staging is arrived at postoperatively. The current staging system as proposed by both FIGO and UICC in 2009 is detailed in Table 2.6. Several changes were made from the prior system, particularly for stages I and II. Stage IA now includes both carcinomas without invasion and those with invasion of the inner half of the myometrium, which helps in cases with difficult assessment of myometrial invasion. Stage II is now confined to tumors with invasion of cervical stroma; tumors that involve endocervical glands only are now grouped under stage I. This revised staging system provides a simplified approach, but has been challenged [92–97].

Prognostic Factors

The strongest prognostic factor for endometrial carcinoma is stage. Carcinomas that are confined to the uterine corpus (stage I) generally have a favorable prognosis [98]. Histologic type and grade, depth of myometrial invasion, and the presence of (lymph) vascular invasion stratify this group for prognosis [99, 100]. Although peritoneal cytology has been excluded from staging, positivity for tumor cells has been demonstrated as an adverse prognostic factor in multivariate analysis [101]. Three different risk groups for recurrence and distant metastases of endometrial carcinomas confined to the uterus have been developed by radiation oncologists [99, 102, 103]. The TCGA project resulted in a molecular based stratification with three major prognostic groups, of which the serous-like had the worst prognosis [21].

Table 2.6 2009 FIGO/UICC staging of endometrial carcinoma (including carcinosarcoma/MMMT)

Stage	pTNM	Definition
I		Tumor confined to the uterine corpus
IA	pT1a	No or less than one half myometrial invasion
IB	pT1b	Invasion equal to or more than one half of the myometrium
II	pT2	Tumor invades cervical stroma but does not extend beyond uterus
III		Local and/or regional spread of the tumor
IIIA	pT3a	Tumor invades the serosa of the uterus and/or adnexa
IIIB	pT3b	Vaginal and/or parametrial involvement
IIIC		Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	pN1	Positive pelvic nodes
IIIC2	pN2	Positive para-aortic nodes with or without positive pelvic nodes
IV		Tumor invades bladder and/or bowel mucosa; distant metastases
IVA	pT4	Tumor invasion bladder and/or bowel mucosa
IVB	pM1	Distant metastases including intra-abdominal metastases and/or inguinal nodes

Hereditary Endometrial Carcinoma

Hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome and Cowden syndrome are heritable syndromes associated with increased risk for endometrial carcinoma [104, 105]. Lynch syndrome is characterized by germline mutations in the mismatch repair proteins MLH1, MSH2, MSH6 or PMS2 and is associated with carcinomas of the colon and rectum, and the endometrium. Additionally, transitional cell carcinoma of the urogenital tract and ovarian carcinoma (particularly the clear cell type) may occur. Approximately 2% of all endometrial carcinomas are associated with Lynch syndrome, most of which are endometrioid histotype [106]. Recently, other histologic types have been described in patients with Lynch syndrome, particularly the dedifferentiated variant of undifferentiated carcinoma. There is evidence that a subset of these tumors arises from the lower uterine segment. In patients with Lynch syndrome there is a 20–60% lifetime risk of developing atypical hyperplasia and endometrial carcinoma [105, 106]. Endometrial carcinoma may be the sentinel event or follow colorectal carcinoma in these individuals. Late onset of either endometrial or colorectal carcinoma is not unusual for Lynch syndrome, since the median age for both cancers is slightly above 60 years. Secondary to the late onset of disease and recent smaller family sizes, the selection criteria for Lynch mutation carriers such as Amsterdam II and Bethesda II are considered increasingly less reliable. Therefore, screening of all newly detected endometrial carcinomas by immunohistochemistry has been proposed [107].

Cowden syndrome is much less frequent than Lynch syndrome. Patients with Cowden syndrome harbor germline mutations for PTEN and may be affected by carcinomas of various organs such as the uterus (endometrium), the thyroid, and the breast.

References

1. Kurman RJ, Carcangiu ML, Herrington S, Young RH (eds) (2014) Tumours of the female reproductive organs. WHO classification of tumours. IARC Press, Lyon.
2. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol.* 1983;15(1):10–7.
3. Lax SF. Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypical to a molecular-based classification. *Virchows Arch.* 2004;444(3):213–23.
4. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. *Mod Pathol.* 2000;13(3):295–308. doi:[10.1038/modpathol.3880051](https://doi.org/10.1038/modpathol.3880051).
5. Sherman ME, Sturgeon S, Brinton LA, Potischman N, Kurman RJ, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD. Risk factors and hormone levels in patients with serous and endometrioid uterine carcinomas. *Mod Pathol.* 1997;10(10):963–8.
6. Jia L, Liu Y, Yi X, Miron A, Crum CP, Kong B, Zheng W. Endometrial glandular dysplasia with frequent p53 gene mutation: a genetic evidence supporting its precancer nature for endometrial serous carcinoma. *Clin Cancer Res.* 2008;14(8):2263–9. doi:[10.1158/1078-0432.CCR-07-4837](https://doi.org/10.1158/1078-0432.CCR-07-4837).
7. Liang SX, Chambers SK, Cheng L, Zhang S, Zhou Y, Zheng W. Endometrial glandular dysplasia: a putative precursor lesion of uterine papillary serous carcinoma. Part II: molecular features. *Int J Surg Pathol.* 2004;12(4):319–31.
8. Zheng W, Liang SX, Yi X, Ulukus EC, Davis JR, Chambers SK. Occurrence of endometrial glandular dysplasia precedes uterine papillary serous carcinoma. *Int J Gynecol Pathol.* 2007;26(1):38–52. doi:[10.1097/01.pgp.0000228138.56222.4e](https://doi.org/10.1097/01.pgp.0000228138.56222.4e).
9. Zheng W, Liang SX, Yu H, Rutherford T, Chambers SK, Schwartz PE. Endometrial glandular dysplasia: a newly defined precursor lesion of uterine papillary serous carcinoma. Part I: morphologic features. *Int J Surg Pathol.* 2004;12(3):207–23.
10. Yeramian A, Moreno-Bueno G, Dolcet X, Catusas L, Abal M, Colas E, Reventos J, Palacios J, Prat J, Matias-Guiu X. Endometrial carcinoma: molecular alterations involved in tumor development and progression. *Oncogene.* 2013;32(4):403–13. doi:[10.1038/onc.2012.76](https://doi.org/10.1038/onc.2012.76).
11. Matias-Guiu X, Prat J. Molecular pathology of endometrial carcinoma. *Histopathology.* 2013;62(1):111–23. doi:[10.1111/his.12053](https://doi.org/10.1111/his.12053).
12. Djordjevic B, Barkoh BA, Luthra R, Broaddus RR. Relationship between PTEN, DNA mismatch repair, and tumor histotype in endometrial carcinoma: retained positive expression of PTEN preferentially identifies sporadic non-endometrioid carcinomas. *Mod Pathol.* 2013;26(10):1401–12. doi:[10.1038/modpathol.2013.67](https://doi.org/10.1038/modpathol.2013.67).
13. Lax SF, Kendall B, Tashiro H, Slebos RJ, Hedrick L. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. *Cancer.* 2000;88(4):814–24.
14. Tashiro H, Blazes MS, Wu R, Cho KR, Bose S, Wang SI, Li J, Parsons R, Ellenson LH. Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecological malignancies. *Cancer Res.* 1997;57(18):3935–40.
15. Guan B, Mao TL, Panuganti PK, Kuhn E, Kurman RJ, Maeda D, Chen E, Jeng YM, Wang TL, Shih Ie M. Mutation and loss of expression of ARID1A in uterine low-grade endometrioid carcinoma. *Am J Surg Pathol.* 2011;35(5):625–32. doi:[10.1097/PAS.0b013e318212782a](https://doi.org/10.1097/PAS.0b013e318212782a).

16. Kuhn E, Wu RC, Guan B, Wu G, Zhang J, Wang Y, Song L, Yuan X, Wei L, Roden RB, Kuo KT, Nakayama K, Clarke B, Shaw P, Olvera N, Kurman RJ, Levine DA, Wang TL, Shih Ie M. Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses. *J Natl Cancer Inst.* 2012;104(19):1503–13. doi:[10.1093/jnci/djs345](https://doi.org/10.1093/jnci/djs345).
17. Catusas L, Matias-Guiu X, Machin P, Munoz J, Prat J. BAX somatic frameshift mutations in endometrioid adenocarcinomas of the endometrium: evidence for a tumor progression role in endometrial carcinomas with microsatellite instability. *Lab Invest.* 1998;78(11):1439–44.
18. Oda K, Stokoe D, Taketani Y, McCormick F. High frequency of coexistent mutations of PIK3CA and PTEN genes in endometrial carcinoma. *Cancer Res.* 2005;65(23):10669–73. doi:[10.1158/0008-5472.CAN-05-2620](https://doi.org/10.1158/0008-5472.CAN-05-2620).
19. Bashir S, Jiang G, Joshi A, Miller C Jr, Matrai C, Yemelyanova A, Caputo TA, Holcomb KM, Ellenson LH, Gupta D. Molecular alterations of PIK3CA in uterine carcinosarcoma, clear cell, and serous tumors. *Int J Gynecol Cancer.* 2014;24(7):1262–7. doi:[10.1097/IGC.0000000000000183](https://doi.org/10.1097/IGC.0000000000000183).
20. Rudd ML, Price JC, Fogoros S, Godwin AK, Sgroi DC, Merino MJ, Bell DW. A unique spectrum of somatic PIK3CA (p110alpha) mutations within primary endometrial carcinomas. *Clin Cancer Res.* 2011;17(6):1331–40. doi:[10.1158/1078-0432.CCR-10-0540](https://doi.org/10.1158/1078-0432.CCR-10-0540).
21. Cancer Genome Atlas Research N, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C, Laird PW, Ding L, Zhang W, Mills GB, Kuchlerlapati R, Mardis ER, Levine DA. Integrated genomic characterization of endometrial carcinoma. *Nature.* 2013;497(7447):67–73. doi:[10.1038/nature12113](https://doi.org/10.1038/nature12113).
22. Hussein YR, Weigelt B, Levine DA, Schoolmeester JK, Dao LN, Balzer BL, Liles G, Karlan B, Kobel M, Lee CH, Soslow RA. Clinicopathological analysis of endometrial carcinomas harboring somatic POLE exonuclease domain mutations. *Mod Pathol.* 2015;28(4):505–14. doi:[10.1038/modpathol.2014.143](https://doi.org/10.1038/modpathol.2014.143).
23. Talhouk A, McConechy MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, Yang W, Senz J, Boyd N, Karnezis AN, Huntsman DG, Gilks CB, McAlpine JN. A clinically applicable molecular-based classification for endometrial cancers. *Br J Cancer.* 2015;113(2):299–310. doi:[10.1038/bjc.2015.190](https://doi.org/10.1038/bjc.2015.190).
24. Wiegand KC, Lee AF, Al-Agha OM, Chow C, Kalloger SE, Scott DW, Steidl C, Wiseman SM, Gascoyne RD, Gilks B, Huntsman DG. Loss of BAF250a (ARID1A) is frequent in high-grade endometrial carcinomas. *J Pathol.* 2011;224(3):328–33. doi:[10.1002/path.2911](https://doi.org/10.1002/path.2911).
25. An HJ, Logani S, Isacson C, Ellenson LH. Molecular characterization of uterine clear cell carcinoma. *Mod Pathol.* 2004;17(5):530–7. doi:[10.1038/modpathol.3800057](https://doi.org/10.1038/modpathol.3800057).
26. Hoang LN, McConechy MK, Meng B, McIntyre JB, Ewanowich C, Gilks CB, Huntsman DG, Kobel M, Lee CH. Targeted mutation analysis of endometrial clear cell carcinoma. *Histopathology.* 2015;66(5):664–74. doi:[10.1111/his.12581](https://doi.org/10.1111/his.12581).
27. Guan B, Wang TL, Shih Ie M. ARID1A, a factor that promotes formation of SWI/SNF-mediated chromatin remodeling, is a tumor suppressor in gynecologic cancers. *Cancer Res.* 2011;71(21):6718–27. doi:[10.1158/0008-5472.CAN-11-1562](https://doi.org/10.1158/0008-5472.CAN-11-1562).
28. Sherman ME, Bitterman P, Rosenshein NB, Delgado G, Kurman RJ. Uterine serous carcinoma. A morphologically diverse neoplasm with unifying clinicopathologic features. *Am J Surg Pathol.* 1992;16(6):600–10.
29. Tashiro H, Isacson C, Levine R, Kurman RJ, Cho KR, Hedrick L. p53 gene mutations are common in uterine serous carcinoma and occur early in their pathogenesis. *Am J Pathol.* 1997;150(1):177–85.
30. Kuhn E, Bahadiri-Talbot A, Shih Ie M. Frequent CCNE1 amplification in endometrial intraepithelial carcinoma and uterine serous carcinoma. *Mod Pathol.* 2014;27(7):1014–9. doi:[10.1038/modpathol.2013.209](https://doi.org/10.1038/modpathol.2013.209).
31. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127(12):2893–917. doi:[10.1002/ijc.25516](https://doi.org/10.1002/ijc.25516).

32. Abeler VM, Kjorstad KE. Endometrial adenocarcinoma in Norway. A study of a total population. *Cancer*. 1991;67(12):3093–103.
33. Zaino RJ, Kurman R, Herbold D, Gliedman J, Bundy BN, Voet R, Advani H. The significance of squamous differentiation in endometrial carcinoma. Data from a Gynecologic Oncology Group study. *Cancer*. 1991;68(10):2293–302.
34. Abeler VM, Kjorstad KE. Endometrial adenocarcinoma with squamous cell differentiation. *Cancer*. 1992;69(2):488–95.
35. Zaino RJ, Kurman RJ. Squamous differentiation in carcinoma of the endometrium: a critical appraisal of adenoacanthoma and adenosquamous carcinoma. *Semin Diagn Pathol*. 1988;5(2):154–71.
36. Kim KR, Scully RE. Peritoneal keratin granulomas with carcinomas of endometrium and ovary and atypical polypoid adenomyoma of endometrium. A clinicopathological analysis of 22 cases. *Am J Surg Pathol*. 1990;14(10):925–32.
37. Zaino RJ, Kurman RJ, Brunetto VL, Morrow CP, Bentley RC, Cappellari JO, Bitterman P. Villoglandular adenocarcinoma of the endometrium: a clinicopathologic study of 61 cases: a gynecologic oncology group study. *Am J Surg Pathol*. 1998;22(11):1379–85.
38. Malpica A. How to approach the many faces of endometrioid carcinoma. *Mod Pathol*. 2016;29(Suppl 1):S29–44. doi:[10.1038/modpathol.2015.142](https://doi.org/10.1038/modpathol.2015.142).
39. Christopherson WM, Alberhasky RC, Connelly PJ. Carcinoma of the endometrium: I. A clinicopathologic study of clear-cell carcinoma and secretory carcinoma. *Cancer*. 1982;49(8):1511–23.
40. Tobon H, Watkins GJ. Secretory adenocarcinoma of the endometrium. *Int J Gynecol Pathol*. 1985;4(4):328–35.
41. Hendrickson MR, Kempson RL. Ciliated carcinoma—a variant of endometrial adenocarcinoma: a report of 10 cases. *Int J Gynecol Pathol*. 1983;2(1):1–12.
42. Han G, Lim D, Leitao MM Jr, Abu-Rustum NR, Soslow RA. Histological features associated with occult lymph node metastasis in FIGO clinical stage I, grade I endometrioid carcinoma. *Histopathology*. 2014;64(3):389–98. doi:[10.1111/his.12254](https://doi.org/10.1111/his.12254).
43. Mai KT, Perkins DG, Yazdi HM, Thomas J. Endometrioid carcinoma of the endometrium with an invasive component of minimal deviation carcinoma. *Hum Pathol*. 2002;33(8):856–8.
44. Ali A, Black D, Soslow RA. Difficulties in assessing the depth of myometrial invasion in endometrial carcinoma. *Int J Gynecol Pathol*. 2007;26(2):115–23. doi:[10.1097/01.pgp.0000233165.56385.0b](https://doi.org/10.1097/01.pgp.0000233165.56385.0b).
45. Sagae S, Saito T, Satoh M, Ikeda T, Kimura S, Mori M, Sato N, Kudo R. The reproducibility of a binary tumor grading system for uterine endometrial endometrioid carcinoma, compared with FIGO system and nuclear grading. *Oncology*. 2004;67(5–6):344–50. doi:[10.1159/000082917](https://doi.org/10.1159/000082917).
46. Lax SF, Kurman RJ, Pizer ES, Wu L, Ronnett BM. A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. *Am J Surg Pathol*. 2000;24(9):1201–8.
47. Guan H, Semaan A, Bandyopadhyay S, Arabi H, Feng J, Fathallah L, Pansare V, Qazi A, Abdul-Karim F, Morris RT, Munkarah AR, Ali-Fehmi R. Prognosis and reproducibility of new and existing binary grading systems for endometrial carcinoma compared to FIGO grading in hysterectomy specimens. *Int J Gynecol Cancer*. 2011;21(4):654–60. doi:[10.1097/IGC.0b013e31821454f1](https://doi.org/10.1097/IGC.0b013e31821454f1).
48. Alkushi A, Abdul-Rahman ZH, Lim P, Schulzer M, Coldman A, Kalloger SE, Miller D, Gilks CB. Description of a novel system for grading of endometrial carcinoma and comparison with existing grading systems. *Am J Surg Pathol*. 2005;29(3):295–304.
49. Longacre TA, Chung MH, Jensen DN, Hendrickson MR. Proposed criteria for the diagnosis of well-differentiated endometrial carcinoma. A diagnostic test for myoinvasion. *Am J Surg Pathol*. 1995;19(4):371–406.

50. Kurman RJ, Norris HJ. Evaluation of criteria for distinguishing atypical endometrial hyperplasia from well-differentiated carcinoma. *Cancer*. 1982;49(12):2547–59.
51. Heatley MK. Atypical polypoid adenomyoma: a systematic review of the English literature. *Histopathology*. 2006;48(5):609–10. doi:[10.1111/j.1365-2559.2005.02315.x](https://doi.org/10.1111/j.1365-2559.2005.02315.x).
52. Soslow RA, Chung MH, Rouse RV, Hendrickson MR, Longacre TA. Atypical polypoid adenomyofibroma (APA) versus well-differentiated endometrial carcinoma with prominent stromal matrix: an immunohistochemical study. *Int J Gynecol Pathol*. 1996;15(3):209–16.
53. Monte NM, Webster KA, Neuberg D, Dressler GR, Mutter GL. Joint loss of PAX2 and PTEN expression in endometrial precancers and cancer. *Cancer Res*. 2010;70(15):6225–32. doi:[10.1158/0008-5472.CAN-10-0149](https://doi.org/10.1158/0008-5472.CAN-10-0149).
54. Moreno-Bueno G, Hardisson D, Sarrio D, Sanchez C, Cassia R, Prat J, Herman JG, Esteller M, Matias-Guiu X, Palacios J. Abnormalities of E- and P-cadherin and catenin (beta-, gamma-catenin, and p120ctn) expression in endometrial cancer and endometrial atypical hyperplasia. *J Pathol*. 2003;199(4):471–8. doi:[10.1002/path.1310](https://doi.org/10.1002/path.1310).
55. Ansari-Lari MA, Staebler A, Zaino RJ, Shah KV, Ronnett BM. Distinction of endocervical and endometrial adenocarcinomas: immunohistochemical p16 expression correlated with human papillomavirus (HPV) DNA detection. *Am J Surg Pathol*. 2004;28(2):160–7.
56. Lax SF, Pizer ES, Ronnett BM, Kurman RJ. Clear cell carcinoma of the endometrium is characterized by a distinctive profile of p53, Ki-67, estrogen, and progesterone receptor expression. *Hum Pathol*. 1998;29(6):551–8.
57. Lax SF, Pizer ES, Ronnett BM, Kurman RJ. Comparison of estrogen and progesterone receptor, Ki-67, and p53 immunoreactivity in uterine endometrioid carcinoma and endometrioid carcinoma with squamous, mucinous, secretory, and ciliated cell differentiation. *Hum Pathol*. 1998;29(9):924–31.
58. Ross JC, Eifel PJ, Cox RS, Kempson RL, Hendrickson MR. Primary mucinous adenocarcinoma of the endometrium. A clinicopathologic and histochemical study. *Am J Surg Pathol*. 1983;7(8):715–29.
59. Staebler A, Sherman ME, Zaino RJ, Ronnett BM. Hormone receptor immunohistochemistry and human papillomavirus in situ hybridization are useful for distinguishing endocervical and endometrial adenocarcinomas. *Am J Surg Pathol*. 2002;26(8):998–1006.
60. Chekmareva M, Ellenson LH, Pirog EC. Immunohistochemical differences between mucinous and microglandular adenocarcinomas of the endometrium and benign endocervical epithelium. *Int J Gynecol Pathol*. 2008;27(4):547–54. doi:[10.1097/PGP.0b013e318177eadc](https://doi.org/10.1097/PGP.0b013e318177eadc).
61. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. *Am J Surg Pathol*. 1982;6(2):93–108.
62. Giuntoli RL 2nd, Gerardi MA, Yemelyanova AV, Ueda SM, Fleury AC, Diaz-Montes TP, Bristow RE. Stage I noninvasive and minimally invasive uterine serous carcinoma: comprehensive staging associated with improved survival. *Int J Gynecol Cancer*. 2012;22(2):273–9. doi:[10.1097/IGC.0b013e318238df4d](https://doi.org/10.1097/IGC.0b013e318238df4d).
63. Seward S, Ali-Fehmi R, Munkarah AR, Semaan A, Al-Wahab ZR, Elshaikh MA, Cote ML, Morris RT, Bandyopadhyay S. Outcomes of patients with uterine serous carcinoma using the revised FIGO staging system. *Int J Gynecol Cancer*. 2012;22(3):452–6. doi:[10.1097/IGC.0b013e31823de6dd](https://doi.org/10.1097/IGC.0b013e31823de6dd).
64. Ambros RA, Sherman ME, Zahn CM, Bitterman P, Kurman RJ. Endometrial intraepithelial carcinoma: a distinctive lesion specifically associated with tumors displaying serous differentiation. *Hum Pathol*. 1995;26(11):1260–7.
65. Wheeler DT, Bell KA, Kurman RJ, Sherman ME. Minimal uterine serous carcinoma: diagnosis and clinicopathologic correlation. *Am J Surg Pathol*. 2000;24(6):797–806.
66. Al-Hussaini M, Stockman A, Foster H, McCluggage WG. WT-1 assists in distinguishing ovarian from uterine serous carcinoma and in distinguishing between serous and endometrioid ovarian carcinoma. *Histopathology*. 2004;44(2):109–15.

67. Goldstein NS, Uzieblo A. WT1 immunoreactivity in uterine papillary serous carcinomas is different from ovarian serous carcinomas. *Am J Clin Pathol.* 2002;117(4):541–5. doi:[10.1309/K84K-005F-TCB8-FV4B](https://doi.org/10.1309/K84K-005F-TCB8-FV4B).
68. Hirschowitz L, Ganesan R, McCluggage WG. WT1, p53 and hormone receptor expression in uterine serous carcinoma. *Histopathology.* 2009;55(4):478–82. doi:[10.1111/j.1365-2559.2009.03390.x](https://doi.org/10.1111/j.1365-2559.2009.03390.x).
69. Kurman RJ, Scully RE. Clear cell carcinoma of the endometrium: an analysis of 21 cases. *Cancer.* 1976;37(2):872–82.
70. Fadare O, Desouki MM, Gwin K, Hanley KZ, Jarboe EA, Liang SX, Quick CM, Zheng W, Parkash V, Hecht JL. Frequent expression of napsin A in clear cell carcinoma of the endometrium: potential diagnostic utility. *Am J Surg Pathol.* 2014;38(2):189–96. doi:[10.1097/PAS.000000000000085](https://doi.org/10.1097/PAS.000000000000085).
71. Fadare O, Parkash V, Gwin K, Hanley KZ, Jarboe EA, Liang SX, Quick CM, Zheng W, Rawish KR, Hecht JL, Desouki MM. Utility of alpha-methylacyl-coenzyme-A racemase (p504s) immunohistochemistry in distinguishing endometrial clear cell carcinomas from serous and endometrioid carcinomas. *Hum Pathol.* 2013;44(12):2814–21. doi:[10.1016/j.humpath.2013.07.033](https://doi.org/10.1016/j.humpath.2013.07.033).
72. Hoang LN, Han G, McConechy M, Lau S, Chow C, Gilks CB, Huntsman DG, Kobel M, Lee CH. Immunohistochemical characterization of prototypical endometrial clear cell carcinoma—diagnostic utility of HNF-1beta and oestrogen receptor. *Histopathology.* 2014;64(4):585–96. doi:[10.1111/his.12286](https://doi.org/10.1111/his.12286).
73. Abeler VM, Kjorstad KE. Clear cell carcinoma of the endometrium: a histopathological and clinical study of 97 cases. *Gynecol Oncol.* 1991;40(3):207–17.
74. Webb GA, Lagios MD. Clear cell carcinoma of the endometrium. *Am J Obstet Gynecol.* 1987;156(6):1486–91.
75. Carcangiu ML, Chambers JT. Early pathologic stage clear cell carcinoma and uterine papillary serous carcinoma of the endometrium: comparison of clinicopathologic features and survival. *Int J Gynecol Pathol.* 1995;14(1):30–8.
76. Alkushi A, Kobel M, Kalloger SE, Gilks CB. High-grade endometrial carcinoma: serous and grade 3 endometrioid carcinomas have different immunophenotypes and outcomes. *Int J Gynecol Pathol.* 2010;29(4):343–50. doi:[10.1097/PGP.0b013e3181cd6552](https://doi.org/10.1097/PGP.0b013e3181cd6552).
77. Qaddus MR, Sung CJ, Zhang C, Lawrence WD. Minor serous and clear cell components adversely affect prognosis in “mixed-type” endometrial carcinomas: a clinicopathologic study of 36 stage-I cases. *Reprod Sci.* 2010;17(7):673–8. doi:[10.1177/1933719110368433](https://doi.org/10.1177/1933719110368433).
78. McConechy MK, Ding J, Cheang MC, Wiegand KC, Senz J, Tone AA, Yang W, Prentice LM, Tse K, Zeng T, McDonald H, Schmidt AP, Mutch DG, McAlpine JN, Hirst M, Shah SP, Lee CH, Goodfellow PJ, Gilks CB, Huntsman DG. Use of mutation profiles to refine the classification of endometrial carcinomas. *J Pathol.* 2012;228(1):20–30. doi:[10.1002/path.4056](https://doi.org/10.1002/path.4056).
79. Tafe LJ, Garg K, Chew I, Tornos C, Soslow RA. Endometrial and ovarian carcinomas with undifferentiated components: clinically aggressive and frequently underrecognized neoplasms. *Mod Pathol.* 2010;23(6):781–9. doi:[10.1038/modpathol.2010.41](https://doi.org/10.1038/modpathol.2010.41).
80. Silva EG, Deavers MT, Bodurka DC, Malpica A. Association of low-grade endometrioid carcinoma of the uterus and ovary with undifferentiated carcinoma: a new type of dedifferentiated carcinoma? *Int J Gynecol Pathol.* 2006;25(1):52–8.
81. Altrabulsi B, Malpica A, Deavers MT, Bodurka DC, Broaddus R, Silva EG. Undifferentiated carcinoma of the endometrium. *Am J Surg Pathol.* 2005;29(10):1316–21.
82. Seidman JD, Chauhan S. Evaluation of the relationship between adenosarcoma and carcinosarcoma and a hypothesis of the histogenesis of uterine sarcomas. *Int J Gynecol Pathol.* 2003;22(1):75–82.
83. Nordal RR, Kristensen GB, Stenwig AE, Nesland JM, Pettersen EO, Trope CG. An evaluation of prognostic factors in uterine carcinosarcoma. *Gynecol Oncol.* 1997;67(3):316–21. doi:[10.1006/gyno.1997.4875](https://doi.org/10.1006/gyno.1997.4875).

84. de Brito PA, Silverberg SG, Orenstein JM. Carcinosarcoma (malignant mixed mullerian (mesodermal) tumor) of the female genital tract: immunohistochemical and ultrastructural analysis of 28 cases. *Hum Pathol.* 1993;24(2):132–42.
85. Silverberg SG, Major FJ, Blessing JA, Fetter B, Askin FB, Liao SY, Miller A. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. *Int J Gynecol Pathol.* 1990;9(1):1–19.
86. Gonzalez-Bosquet E, Gonzalez-Bosquet J, Garcia Jimenez A, Gil A, Xercavins J. Carcinoid tumor of the uterine corpus. A case report. *J Reprod Med.* 1998;43(9):844–6.
87. Chetty R, Clark SP, Bhathal PS. Carcinoid tumour of the uterine corpus. *Virchows Arch A Pathol Anat Histopathol.* 1993;422(1):93–5.
88. Starzynski S, Kubicka-Pertkiewicz M. Carcinoid of the uterine corpus. *Patol Pol.* 1978;29(2):237–40.
89. Huntsman DG, Clement PB, Gilks CB, Scully RE. Small-cell carcinoma of the endometrium. A clinicopathological study of sixteen cases. *Am J Surg Pathol.* 1994;18(4):364–75.
90. van Hoesen KH, Hudock JA, Woodruff JM, Suhrlund MJ. Small cell neuroendocrine carcinoma of the endometrium. *Int J Gynecol Pathol.* 1995;14(1):21–9.
91. Deodhar KK, Kerkar RA, Suryawanshi P, Menon H, Menon S. Large cell neuroendocrine carcinoma of the endometrium: an extremely uncommon diagnosis, but worth the efforts. *J Cancer Res Ther.* 2011;7(2):211–3. doi:[10.4103/0973-1482.82942](https://doi.org/10.4103/0973-1482.82942).
92. Zaino RJ. FIGO staging of endometrial adenocarcinoma: a critical review and proposal. *Int J Gynecol Pathol.* 2009;28(1):1–9. doi:[10.1097/PGP.0b013e3181846c6d](https://doi.org/10.1097/PGP.0b013e3181846c6d).
93. Abu-Rustum NR, Zhou Q, Iasonos A, Alektiar KM, Leitao MM Jr, Chi DS, Sonoda Y, Soslow R, Hensley M, Barakat RR. The revised 2009 FIGO staging system for endometrial cancer: should the 1988 FIGO stages IA and IB be altered? *Int J Gynecol Cancer.* 2011;21(3):511–6. doi:[10.1097/IGC.0b013e31820cc305](https://doi.org/10.1097/IGC.0b013e31820cc305).
94. Haltia UM, Butzow R, Leminen A, Loukovaara M. FIGO 1988 versus 2009 staging for endometrial carcinoma: a comparative study on prediction of survival and stage distribution according to histologic subtype. *J Gynecol Oncol.* 2014;25(1):30–5. doi:[10.3802/jgo.2014.25.1.30](https://doi.org/10.3802/jgo.2014.25.1.30).
95. Kim HS, Kim HY, Park CY, Lee JM, Lee JK, Cho CH, Kim SM, Kim JW. Lymphadenectomy increases the prognostic value of the revised 2009 FIGO staging system for endometrial cancer: a multi-center study. *Eur J Surg Oncol.* 2012;38(3):230–7. doi:[10.1016/j.ejso.2011.12.023](https://doi.org/10.1016/j.ejso.2011.12.023).
96. Werner HM, Trovik J, Marcickiewicz J, Tingulstad S, Staff AC, Amant F, Salvesen HB, MoMa TECsg. Revision of FIGO surgical staging in 2009 for endometrial cancer validates to improve risk stratification. *Gynecol Oncol.* 2012;125(1):103–8. doi:[10.1016/j.ygyno.2011.11.008](https://doi.org/10.1016/j.ygyno.2011.11.008).
97. Korczynski J, Jesionek-Kupnicka D, Gottwald L, Piekarski J. Comparison of FIGO 1989 and 2009 recommendations on staging of endometrial carcinoma: pathologic analysis and cervical status in 123 consecutive cases. *Int J Gynecol Pathol.* 2011;30(4):328–34. doi:[10.1097/PGP.0b013e3182069c30](https://doi.org/10.1097/PGP.0b013e3182069c30).
98. Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, Graham JE. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1991;40(1):55–65.
99. Bosse T, Peters EE, Creutzberg CL, Jurgenliemk-Schulz IM, Jobsen JJ, Mens JW, Lutgens LC, van der Steen-Banasik EM, Smit VT, Nout RA. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer—a pooled analysis of PORTEC 1 and 2 trials. *Eur J Cancer.* 2015;51(13):1742–50. doi:[10.1016/j.ejca.2015.05.015](https://doi.org/10.1016/j.ejca.2015.05.015).
100. Hachisuga T, Kaku T, Fukuda K, Eguchi F, Emoto M, Kamura T, Iwasaka T, Kawarabayashi T, Sugimori H, Mori M. The grading of lymphovascular space invasion in endometrial carcinoma. *Cancer.* 1999;86(10):2090–7.

101. Han KH, Park NH, Kim HS, Chung HH, Kim JW, Song YS. Peritoneal cytology: a risk factor of recurrence for non-endometrioid endometrial cancer. *Gynecol Oncol.* 2014;134(2):293–6. doi:[10.1016/j.ygyno.2014.05.010](https://doi.org/10.1016/j.ygyno.2014.05.010).
102. Group AES, Blake P, Swart AM, Orton J, Kitchener H, Whelan T, Lukka H, Eisenhauer E, Bacon M, Tu D, Parmar MK, Amos C, Murray C, Qian W. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. *Lancet.* 2009;373(9658):137–46. doi:[10.1016/S0140-6736\(08\)61767-5](https://doi.org/10.1016/S0140-6736(08)61767-5).
103. Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, van den Bergh AC, de Winter KA, Koper PC, Lybeert ML, Slot A, Lutgens LC, Stenfert Kroese MC, Beerman H, van Lent M. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the postoperative radiation therapy in endometrial carcinoma trial. *J Clin Oncol.* 2004;22(7):1234–41. doi:[10.1200/JCO.2004.08.159](https://doi.org/10.1200/JCO.2004.08.159).
104. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res.* 2012;18(2):400–7. doi:[10.1158/1078-0432.CCR-11-2283](https://doi.org/10.1158/1078-0432.CCR-11-2283).
105. Bonadona V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M, Guimbaud R, Buecher B, Bignon YJ, Caron O, Colas C, Nogues C, Lejeune-Dumoulin S, Olivier-Faivre L, Polycarpe-Osaer F, Nguyen TD, Desseigne F, Saurin JC, Berthet P, Leroux D, Duffour J, Manouvrier S, Frebourg T, Sobol H, Lasset C, Bonaiti-Pellie C, French Cancer Genetics N. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA.* 2011;305(22):2304–10. doi:[10.1001/jama.2011.743](https://doi.org/10.1001/jama.2011.743).
106. Hampel H, Frankel W, Panescu J, Lockman J, Sotamaa K, Fix D, Comeras I, La Jeunesse J, Nakagawa H, Westman JA, Prior TW, Clendenning M, Penzone P, Lombardi J, Dunn P, Cohn DE, Copeland L, Eaton L, Fowler J, Lewandowski G, Vaccarello L, Bell J, Reid G, de la Chapelle A. Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. *Cancer Res.* 2006;66(15):7810–7. doi:[10.1158/0008-5472.CAN-06-1114](https://doi.org/10.1158/0008-5472.CAN-06-1114).
107. Mills AM, Liou S, Ford JM, Berek JS, Pai RK, Longacre TA. Lynch syndrome screening should be considered for all patients with newly diagnosed endometrial cancer. *Am J Surg Pathol.* 2014;38(11):1501–9. doi:[10.1097/PAS.0000000000000321](https://doi.org/10.1097/PAS.0000000000000321).

Precision Molecular Pathology of Uterine Cancer

Deavers, M.T.; Coffey, D.M. (Eds.)

2017, IX, 286 p. 48 illus., 47 illus. in color., Hardcover

ISBN: 978-3-319-57983-2