The uterine corpus represents the second most common site for malignancy of the female genital system. These neoplasms are divided into epithelial, mesenchymal, mixed epithelial and mesenchymal tumours and trophoblastic tumours.

Endometrial carcinoma occurs predominantly in developed countries and is frequently associated with obesity. Two major types are distinguished. Type I is estrogen-dependent and develops through the hyperplasia-carcinoma sequence. Type II is not estrogen-dependent and develops independently of endometrial hyperplasia. It occurs in older women and is more aggressive.

Carcinosarcoma is still classified morphologically as a mixed epithelial and mesenchymal tumour, although it is considered monoclonal, with immunohistochemical and molecular studies strongly supporting its inclusion in the epithelial group. Its prognosis is worse than that of other members of the epithelial category.

Gestational trophoblastic disease is approximately 10-fold more common in the developing than in developed countries. Risk factors include a history of prior gestational trophoblastic disease, a diet low in vitamin A and blood group A women married to group 0 men.
### WHO histological classification of tumours of the uterine corpus

<table>
<thead>
<tr>
<th>Epithelial tumours and related lesions</th>
<th>Dissecting leiomyoma</th>
<th>Intravenous leiomyomatosis</th>
<th>Metastasizing leiomyoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>8380/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant with squamous differentiation</td>
<td>8570/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villoglandular variant</td>
<td>8262/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretory variant</td>
<td>8382/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciliated cell variant</td>
<td>8393/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>8480/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous adenocarcinoma</td>
<td>8441/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell adenocarcinoma</td>
<td>8310/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed cell adenocarcinoma</td>
<td>8323/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
<td></td>
<td></td>
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<tr>
<td>Transitional cell carcinoma</td>
<td>8120/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>8041/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>8020/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
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<td></td>
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<tr>
<td>Nonatypical hyperplasia</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex (adenomatous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial polyp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen-related lesions</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Others</td>
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<td></td>
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<tr>
<td>Mesenchymal tumours</td>
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<td></td>
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<tr>
<td>Endometrial stromal and related tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial stromal sarcoma, low grade</td>
<td>8901/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial stromal nodule</td>
<td>8920/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated endometrial sarcoma</td>
<td>8920/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth muscle tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>8890/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid variant</td>
<td>8891/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myxoid variant</td>
<td>8896/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth muscle tumour of uncertain malignant potential</td>
<td>8897/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomyoma, not otherwise specified</td>
<td>8899/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histological variants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotically active variant</td>
<td>8892/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular variant</td>
<td>8892/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic cellular variant</td>
<td>8892/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid variant</td>
<td>8891/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myxoid variant</td>
<td>8896/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical variant</td>
<td>8893/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipoleiomyoma variant</td>
<td>8892/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth pattern variants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse leiomyomatosis</td>
<td>8890/1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Miscellaneous mesenchymal tumours       |                      |                           |                        |
| Mixed epithelial and mesenchymal tumours|                      |                           |                        |
| Carcinosarcoma (malignant müllerian mixed tumour; metaplastic carcinoma) | 8980/3 |                           |                        |
| Adenosarcoma                            | 8933/3               |                           |                        |
| Carcinofibroma                          | 8934/3               |                           |                        |
| Adenofibroma                            | 9013/0               |                           |                        |
| Adenomyoma                              | 8932/0               |                           |                        |
| Atypical polypoid variant               | 8932/0               |                           |                        |

### Gestational trophoblastic disease

| Trophoblastic neoplasms                  |                      |                           |                        |
| Choriocarcinoma                          | 9100/3               |                           |                        |
| Placental site trophoblastic tumour       | 9104/1               |                           |                        |
| Epithelioid trophoblastic tumour          | 9105/3               |                           |                        |

| Molar pregnancies                        |                      |                           |                        |
| Hydatidiform mole                        | 9100/0               |                           |                        |
| Complete                                 | 9100/0               |                           |                        |
| Partial                                  | 9103/0               |                           |                        |
| Invasive                                 | 9100/1               |                           |                        |
| Metastatic                               | 9100/1               |                           |                        |

| Non-neoplastic, non-molar trophoblastic lesions |                      |                           |                        |
| Placental site nodule and plaque           |                      |                           |                        |
| Exaggerated placental site                 |                      |                           |                        |

| Miscellaneous tumours                     |                      |                           |                        |
| Sex cord-like tumours                     |                      |                           |                        |
| Neuroectodermal tumours                   |                      |                           |                        |
| Melanotic paraganglioma                   |                      |                           |                        |
| Tumours of germ cell type                 |                      |                           |                        |
| Others                                    |                      |                           |                        |

| Lymphoid and haematopoetic tumours        |                      |                           |                        |
| Malignant lymphoma (specify type)         |                      |                           |                        |
| Leukaemia (specify type)                  |                      |                           |                        |

| Secondary tumours                         |                      |                           |                        |

---

1 Morphology code of the International Classification of Diseases for Oncology (ICD-O) (921) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
TNM and FIGO classification of non-trophoblastic tumours of the uterine corpus

<table>
<thead>
<tr>
<th>TNM and FIGO classification</th>
<th>Categories</th>
<th>Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>T – Primary Tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (preinvasive carcinoma)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumour confined to corpus uteri</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour limited to endometrium</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour invades less than one half of myometrium</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour invades one half or more of myometrium</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades cervix but does not extend beyond uterus</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>Endocervical glandular involvement only</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>Cervical stromal invasion</td>
<td></td>
</tr>
<tr>
<td>T3 and/or N1</td>
<td>Local and/or regional spread as specified in T3a, b, N1, and FIGO IIIA, II, C below</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>Tumour involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>Vaginal involvement (direct extension or metastasis)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades bladder mucosa and/or bowel mucosa</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis (excluding metastasis to vagina, pelvic serosa, or adnexa)</td>
<td></td>
</tr>
</tbody>
</table>

Note: FIGO recommends that Stage I patients given primary radiation therapy can be clinically classified as follows:
- Stage I: Tumour confined to corpus uteri
- Stage IA: Length of uterus cavity 8cm or less
- Stage IB: Length of uterus cavity more than 8cm

N – Regional Lymph Nodes
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

M – Distant Metastasis
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

Stage Grouping
- Stage 0: Tis, N0, M0
- Stage IA: T1a, N0, M0
- Stage IB: T1b, N0, M0
- Stage IC: T1c, N0, M0
- Stage IIA: T2a, N0, M0
- Stage IIB: T2b, N0, M0
- Stage IIIA: T3a, N0, M0
- Stage IIIB: T3b, N0, M0
- Stage IIIC: T1, T2, T3, N1, M0
- Stage IVA: T4, Any N, M0
- Stage IVB: Any T, Any N, M1

1 (51,297).  
2 A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.  
3 The classification applies to carcinomas and malignant mixed mesodermal tumours.  
4 The regional lymph nodes are the pelvic (hypogastric [obturator, internal iliac], common and external iliac, parametrial, and sacral) and the para-aortic nodes.
TNM and FIGO classification of gestational trophoblastic tumours

<table>
<thead>
<tr>
<th>TNM and FIGO classification</th>
<th>Stage grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T–Primary Tumour</strong></td>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour confined to uterus</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour extends to other genital structures: vagina, ovary, broad ligament, fallopian tube by metastasis or direct extension</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis to lung(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Other distant metastasis</td>
</tr>
<tr>
<td>M2</td>
<td>Metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis to lung(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Other distant metastasis</td>
</tr>
</tbody>
</table>

Note: *Stages I to IV are subdivided into A and B according to the prognostic score

Any involvement of non-genital structures, whether by direct invasion or metastasis is described using the M classification.

<table>
<thead>
<tr>
<th>Prognostic score</th>
<th>Prognostic Factor</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&lt;40</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Antecedent pregnancy</strong></td>
<td>Hydatidiform mole</td>
<td>Abortion</td>
<td>Term pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Months from index pregnancy</strong></td>
<td>&lt;4</td>
<td>4&lt;7</td>
<td>7-12</td>
<td>&gt;12</td>
<td></td>
</tr>
<tr>
<td><strong>Pretreatment serum β-hCG (IU/ml)</strong></td>
<td>&lt;10⁰</td>
<td>10⁰&lt;10⁰</td>
<td>10⁰&lt;10⁰</td>
<td>&gt;10⁰</td>
<td></td>
</tr>
<tr>
<td><strong>Largest tumour size, including uterus</strong></td>
<td>&lt;3 cm</td>
<td>3&lt;5 cm</td>
<td>≥5 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Site of metastasis</strong></td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>Gastrointestinal tract</td>
<td>Liver, brain</td>
<td></td>
</tr>
<tr>
<td><strong>Number of metastases</strong></td>
<td>1-4</td>
<td>5-8</td>
<td>&gt;8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Previous failed chemotherapy</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Risk Categories**: Total prognostic score 7 or less = low risk; Total score 8 or more = high risk

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1. (51.2976)
2. A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org
3. The classification applies to choriocarcinoma (9100/3), invasive hydatidiform mole (9100/1), and placental site trophoblastic tumour (9104/1).
**Endometrial carcinoma**

**Definition**
A primary malignant epithelial tumour, usually with glandular differentiation, arising in the endometrium that has the potential to invade into the myometrium and to spread to distant sites.

**ICD-O codes**
- Endometrioid adenocarcinoma: 8380/3
- Variant with squamous differentiation: 8570/3
- Villoglandular variant: 8262/3
- Ciliated cell variant: 8383/3
- Mucinous adenocarcinoma: 8480/3
- Serous adenocarcinoma: 8441/3
- Clear cell adenocarcinoma: 8310/3
- Mixed adenocarcinoma: 8323/3
- Squamous cell carcinoma: 8070/3
- Transitional cell carcinoma: 8120/3
- Small cell carcinoma: 8041/3
- Undifferentiated carcinoma: 8020/3

**Epidemology**
Endometrial carcinoma is the most common malignant tumour of the female genital system in developed countries, where estrogen-dependent neoplasms account for 80-85% of cases and the non-estrogen dependent tumours make up the remaining 10-15% of cases. The estrogen-dependent tumours are low grade, i.e. well or moderately differentiated and predominantly of endometrioid type. Patients with this form of endometrial cancer frequently are obese, diabetic, nulliparous, hypertensive or have a late menopause. Obesity is an independent risk factor (388), and in Western Europe, is associated with up to 40% of endometrial cancer (241a). On the other hand, patients with a large number of births, old age at first birth, a long birth period and a short premenopausal delivery-free period have a reduced risk of postmenopausal endometrial cancer, emphasizing the protective role of progesterone in the hormonal background of this disease (1212).

In contrast, the non-estrogen dependent type occurs in older postmenopausal women; the tumours are high grade and consist predominantly of histological subtypes such as serous or clear cell as well as other carcinomas that have high grade nuclear features. They lack an association with exogenous or endogenous hyperoestrinism or with endometrial hyperplasia and have an aggressive behaviour (497,2005,2646).

**Pathogenesis**
Endometrial cancer is made up of a biologically and histologically diverse group of neoplasms that are characterized by a different pathogenesis. Estrogen-dependent tumours (type I) are low grade and frequently associated with endometrial hyperplasias, in particular atypical hyperplasia. Unopposed estrogenic stimulation is the driving force behind this group of tumours. It may be the result of anovulatory cycles that occur in young women with the polycystic ovary syndrome or due to normally occurring anovulatory cycles at the time of menopause. The iatrogenic use of unopposed estrogens as hormone replacement therapy in older women also is a predisposing factor for the development of endometrial cancer. The second type (type II) of endometrial cancer appears less related to sustained estrogen stimulation.

**Clinical features**

**Signs and symptoms**
Although endometrial carcinoma and related lesions can be incidental findings in specimens submitted to the pathologist for other reasons (for example, endometrial biopsy for infertility or hysterectomy for uterine prolapse), in the great majority of cases they present clinically with abnormal uterine bleeding. Since most of these lesions are seen in postmenopausal women, the most common presentation is postmenopausal bleeding, but earlier in life the usual clinical finding is menometrorrhagia (1104). The most common type of endometrial carcinoma, endometrioid adenocarcinoma, may be manifested by such clinical findings as obesity, infertility and late menopause, since it is often related either to exogenous estrogen
administration or to endogenous hyperoestrinism [2276,2648,2805]. Endometrial hyperplasia and atypical hyperplasia have similar clinical associations.

**Imaging**

Transvaginal ultrasound (US) is the imaging technique of choice for the assessment of the endometrium in symptomatic patients, e.g. in cases of postmenopausal bleeding [133]. In postmenopausal women without hormonal replacement an endometrial thickness of 5 mm is regarded as the upper normal limit [133,2650]. The presence of endometrial thickening on ultrasound or cross sectional imaging is, however, a nonspecific finding. It may be due to endometrial hyperplasia, polyps or carcinoma. The final diagnosis usually needs to be determined by endometrial sampling [133]. Whereas currently magnetic resonance imaging (MRI) has no established role in screening for endometrial pathology, it is regarded as the best imaging technique for preoperative staging of endometrial carcinoma proven by endometrial sampling. MRI was shown to be superior to screening for endometrial pathology, it is regarded as the best imaging technique for preoperative staging of endometrial carcinoma proven by endometrial sampling. MRI was shown to be superior to ultrasound or cross sectional imaging (MRI) has no established role in screening for endometrial pathology, it is regarded as the best imaging technique for preoperative staging of endometrial carcinoma proven by endometrial sampling. MRI was shown to be superior to ultrasound or cross sectional imaging. MRI was shown to be superior to ultrasound or cross sectional imaging.

**Macroscopy**

Endometrial carcinoma usually arises in the uterine corpus, but some cases originate in the lower uterine segment, and recent studies suggest that the latter may have different clinical and histological features [123,3067]. Regardless of the histological type, the macroscopic appearance of endometrial carcinoma is generally that of a single dominant mass, usually occurring in an enlarged uterus, although occasionally the uterus is small or the tumour presents as a diffuse thickening of most of the endometrial surface, particularly in the serous type. Endometrial carcinoma is seen more frequently on the posterior than on the anterior wall [2691]. The typical carcinoma is exophytic and has a shaggy, frequently ulcerated surface beneath which a soft or firm white tumour presents as a diffuse thickening of the underlying myometrium. In advanced cases the tumour may penetrate the serosa or extend into the cervix. An estimate of the extent of tumour may be requested preoperatively or operative-ly in order to determine the extent of the surgical procedure to be performed [594]. In occasional cases no tumour may be visible macroscopically, with carcinoma identified only at histological examination.

**Tumour spread and staging**

The staging of uterine tumours is by the TNM/FIGO classification [51,2976].

**Endometrioid adenocarcinoma**

**Definition**

A primary endometrial adenocarcinoma containing glands resembling those of the normal endometrium.

**Histopathology**

All but a few rare endometrial carcinomas are adenocarcinomas, and the most common of these is the endometrioid type [2691]. Endometrioid adenocarcinoma represents a spectrum of histological differentiation from a very well differentiated carcinoma difficult to distinguish from atypical complex hyperplasia to minimally differentiated tumours that can be confused not only with undifferentiated carcinoma but with various sarcomas as well. A highly characteristic feature of endometrioid adenocarcinoma is the presence of at least some glandular or villoglandular structures lined by simple to pseudostratified columnar cells that have their long axes arranged perpendicularly to the basement membrane with at least somewhat elongated nuclei that are also polarized in the same direction. As the glandular differentiation decreases and is replaced by solid nests and sheets of cells, the tumour is classified as less well differentiated (higher grade). Deep myometrial invasion and lymph node metastases are both more frequent in higher grade carcinomas, and survival rates are correspondingly lower [574,1359]. It should be noted that:

1. Only those cells which are considered to be of glandular type are considered in the grading schema, so that solid nests of cells showing squamous or morular differentiation do not increase the tumour grade.

2. Bizarre nuclear atypia should raise the grade by one, e.g. from 1 to 2 or 2 to 3.

3. It should be emphasized that the presence of bizarre nuclei occurring in even a predominantly glandular tumour may indicate serous or clear cell rather than endometrioid differentiation [2691].

The distinction of very well differentiated

![Fig. 4.02 Well differentiated endometrioid adenocarcinoma. A Invasion is indicated by back to back glands, complex folds and stromal disappearance. B The neoplastic glands are lined by columnar cells with relatively uniform nuclei; note the altered stroma in the top of the field.](image-url)
endometrioid adenocarcinoma from atypical complex hyperplasia is best provided by stromal disappearance between adjacent glands, i.e. confluent, cribriform or villoglandular patterns [1433,1689,2688,2691]. Other features that may be helpful include a stromal desmoplastic response and/or tumour necrosis. Stromal foam cells may be associated with adenocarcinoma or its precursors.

**Variants of endometrioid adenocarcinoma**

Endometrial proliferations may exhibit a variety of differentiated epithelial types including squamous/morules, mucinous, ciliated, cleared or eosinophilic cells, and architectural variations including papillary formations. These cell types are often called metaplasias and may be encountered in benign, premalignant and malignant epithelia. When prominent in a carcinoma the neoplasm is termed a "special variant" carcinoma.

**Variant with squamous differentiation**

From 20-50% or more of endometrioid adenocarcinomas contain varying amounts of neoplastic epithelium showing squamous differentiation. Although the distinction between endometrioid adenocarcinoma with and without squamous differentiation is not clinically important, the recognition of squamous differentiation is nevertheless essential because the squamous or morular elements should not be considered a part of the solid component that increases the grade of an endometrioid carcinoma. The criteria for squamous differentiation [2691] are as follows:

1. Keratinization demonstrated with standard staining techniques.
2. Intercellular bridges and/or
3. Three or more of the following four criteria:
   a. Sheet-like growth without gland formation or palisading.
   b. Sharp cell margins.
   c. Eosinophilic and thick or glassy cytoplasm.
   d. A decreased nuclear to cytoplasmic ratio as compared with foci elsewhere in the same tumour.

**Villoglandular variant**

This type is the next most commonly encountered endometrioid adenocarcinoma variant and is usually seen involving part of a low grade endometrioid carcinoma but not the entire tumour. In this pattern numerous villous fronds are seen, but their central cores are delicate, and cells with the usual cytological features (including stratification perpendicular to the basement membrane) line the villi. These features are in contrast to the more complex papillary architecture and high grade nuclear features that are typical of serous and clear cell adenocarcinomas growing in a papillary pattern.

**Secretory variant**

Occasional endometrioid adenocarcinomas are composed of glands lined by epithelium with voluminous, usually subnuclear, glycogen vacuoles reminiscent of early secretory endometrium. These tumours have minimal nuclear atypia and are diagnosable as carcinoma only by virtue of a confluent, cribriform or villoglandular pattern. As with the other variants, this pattern may be seen as the only one in an endometrioid adenocarci-
noma or may coexist with the usual endometrioid pattern within a single tumour.

Ciliated cell variant
Although occasional ciliated cells may be seen in many endometrioid adenocarcinomas, the diagnosis of the ciliated cell variant is made only when ciliated cells line the majority of the malignant glands. Defined in this manner, this is a rare variant, and the glands often have a strong resemblance to tubal epithelium.

Mucinous adenocarcinoma

Definition
A primary adenocarcinoma of the endometrium in which most of the tumour cells contain prominent intracytoplasmic mucin.

Epidemiology
Mucinous adenocarcinoma comprises up to 9% of all cases of surgical stage I endometrial carcinoma [2454]. However, in most published series it is a relatively rare type of endometrial carcinoma [1842].

Histopathology
Both endometrioid and clear cell adenocarcinomas may have large amounts of intraluminal mucin, but only mucinous adenocarcinoma contains the mucin within the cytoplasm. The mucin is usually easily visible with hematoxylin and eosin staining but may also be demonstrated with a mucicarmine or other mucin stain.

Variants
Some mucinous adenocarcinomas have a microglandular pattern and may be difficult to distinguish from microglandular hyperplasia of the endocervix in a biopsy specimen [2066]. These neoplasms have been reported as microglandular carcinomas [3224,3241]. Rare mucinous adenocarcinomas of the endometrium may show intestinal differentiation, containing numerous goblet cells.

Differential diagnosis
The main differential diagnosis of the usual endometrial mucinous adenocarcinoma is with a primary mucinous adenocarcinoma of the endocervix. The distinction may be particularly difficult in a biopsy or curettage specimen but is crucial for therapy and may have to be resolved by clinical and imaging studies. Some studies have claimed that immunohistochemistry is useful in determining the site of origin of an adenocarcinoma in such a specimen, with endometrial carcinomas being vimentin and estrogen receptor-positive and carcinoembryonic antigen-negative and the opposite findings for endocervical adenocarcinomas [3180]. Others have found, however, that this distinction is based more on differentiation (endometrioid vs. mucinous) than on site of origin [1393].

Grading
Mucinous adenocarcinomas are theoretically graded in the same way as endometrioid adenocarcinomas, but in practice almost all of them are grade 1.

Prognosis and predictive factors
The prognosis appears to be similar to that of other low grade endometrial adenocarcinomas and thus is generally favourable.

Serous adenocarcinoma

Definition and historical annotation
A primary adenocarcinoma of the endometrium characterized by a complex pattern of papillae with cellular budding and not infrequently containing psammoma bodies.

Clinical features
Serous carcinoma typifies the so-called type II endometrial carcinoma, which dif-
fers from the prototypical type I endometrioid adenocarcinoma by its lack of association with exogenous or endogenous hyperoestrinism, its lack of association with endometrial hyperplasia and its aggressive behaviour (497, 2005, 2646).

**Histopathology**
Serous adenocarcinoma is usually, but not always, characterized by a papillary architecture with the papillae having broad fibrovascular cores, secondary and even tertiary papillary processes and prominent sloughing of the cells. The cells and nuclei are generally rounded rather than columnar and lack a perpendicular orientation to the basement membrane. The nuclei are typically poorly differentiated, are often apically rather than basally situated and usually have large, brightly eosinophilic macronucleoli. Mitoses, often atypical and bizarre, and multinucleated cells are commonly present, as are solid cell nests and foci of necrosis. Psammoma bodies are found in about 30% of cases and may be numerous. When the tumour grows in a glandular pattern, the glands are generally complex and "labyrinthine." Serous carcinoma is considered a high grade carcinoma by definition and is not graded.

**Precursor lesions**
A putative precursor of serous adenocarcinoma is serous endometrial intraepithelial carcinoma, which has also been called endometrial carcinoma in situ and surface serous carcinoma (79, 975, 2764, 3256). This lesion is characterized by a noninvasive replacement of benign (most commonly atrophic) endometrial surface and glandular epithelium by highly malignant cells that resemble those of invasive serous carcinoma. Serous endometrial intraepithelial carcinoma has been proposed as the precursor or in situ phase of serous carcinoma, and in most reported studies it has co-existed with invasive serous and, occasionally, clear cell adenocarcinoma. Clinically, serous endometrial intraepithelial carcinoma has a significance very similar to that of invasive serous adenocarcinoma since it can also be associated with disseminated disease outside the uterus (usually in the peritoneal cavity) even in the absence of invasive adenocarcinoma in the endometrium (79, 160, 975, 2764, 3105, 3256).

**Prognosis and predictive factors**
This tumour has a tendency to develop deep myometrial invasion and extensive lymphatic invasion, and patients commonly present with extrauterine spread at the time of diagnosis. However, even in the absence of a large or deeply invasive tumour extrauterine spread is common, as are recurrence and a fatal outcome (160, 1370, 3105).

**Clear cell adenocarcinoma**

**Definition**
An adenocarcinoma composed mainly of clear or hobnail cells arranged in solid, tubulocystic or papillary patterns or a combination of these patterns.

**Epidemiology**
The other major type II carcinoma of the endometrium is clear cell adenocarcinoma. It is less common than serous carcinoma (1-5%, as opposed to 5-10% of all endometrial carcinomas) but occurs in the same, predominantly older, patient population.

**Tumour spread and staging**
Similar to serous adenocarcinoma, patients with clear cell adenocarcinoma are frequently diagnosed in advanced clinical stages.

**Histopathology**
Histologically, clear, glycogen-filled cells and hobnail cells that project individually into lumens and papillary spaces characterize the typical clear cell adenocarcinoma. Unlike similarly glycogen-rich secretory endometrioid adenocarcinomas, clear cell adenocarcinoma contains large, highly pleomorphic nuclei, often with bizarre and multinucleated forms. The architectural growth pattern may be tubular, papillary, tubulocystic or solid and most frequently consists of a mixture of two or more of these patterns. Although psammoma bodies are present in approximately one-third of serous adenocarcinomas, they are rarely seen in clear cell adenocarcinomas. Occasionally, the tumour cells have granular...
eosinophilic (oncocytic) cytoplasm rather than the more characteristic clear cytoplasm [2258,2678]. This cell type may comprise the entire tumour and make it difficult to recognize as a clear cell adenocarcinoma. Endometrial clear cell adenocarcinomas are not graded.

Serous endometrial intraepithelial carcinoma may also be seen in association with clear cell adenocarcinoma, and the associated benign endometrium is generally atrophic rather than hyperplastic.

Prognosis and predictive factors
Patients with clear cell adenocarcinoma are frequently diagnosed in advanced clinical stages, and, thus, have a poor prognosis [24,400,1595,3003]. On the other hand, clear cell adenocarcinoma limited to the uterine corpus has a considerably better prognosis than serous adenocarcinoma of the same stage.

Mixed adenocarcinoma
Definition
Mixed adenocarcinoma is a tumour composed of an admixture of a type I (endometrioid carcinoma, including its variants, or mucinous carcinoma) and a type II carcinoma (serous or clear cell) in which the minor type must comprise at least 10% of the total volume of the tumour. The percentage of the minor component should be stated in the pathology report. It is generally accepted that 25% or more of a type II tumour implies a poor prognosis, although the significance of lesser proportions is not well understood [2648,2691].

Squamous cell carcinoma
Definition
A primary carcinoma of the endometrium composed of squamous cells of varying degrees of differentiation.

Epidemiology
Squamous cell carcinoma of the endometrium is uncommon; only about seventy cases have been reported [2397].

Clinical features
The main complaint at presentation is uterine bleeding.

Macroscopy
The tumours are often polypoid or papillary with a mean size of 3.5 cm. Infiltration of the myometrium is apparent in some cases.

Histopathology
Squamous cell carcinoma of the endometrium usually occurs in postmenopausal women and is often associated with cervical stenosis and pyometra. The transitional cell component is often grade 2 or 3 and assumes a papillary configuration. It is always admixed with another type of carcinoma, most often endometrioid, but it may be clear cell or serous. HPV-associated koilocytic changes occur rarely. Only the transitional cell component invades the myometrum deeply [1669]. All endometrial transitional cell carcinomas are negative for cytokeratin 20 (CK20), but half are positive for cytokeratin 7 (CK7) [1554,1669].

Differential diagnosis
The differential diagnosis includes metastatic transitional cell carcinoma from
the ovary and bladder. Unlike primary endometrial tumours, those metastatic to the endometrium are pure transitional cell tumours. The CK7 positive, CK20 negative immunoprofile also supports müllerian rather than urothelial differentiation.

**Somatic genetics**

Human papillomavirus (HPV) type 16 has been detected in 22% of cases studied; however, the results were negative for types 6, 11, 18, 31 and 33 in all cases assessed (1554,1672). These findings suggest that HPV may play an aetologic role in at least some cases.

**Prognostic and predictive factors**

Although information on prognostic factors is limited on these rare tumours, several women who have survived have had low stage (stage I) disease. At least two cases with extraterine extension of the disease to either the adnexa or ovarian hilus have survived over 5 years following radiation therapy suggesting that these tumours may have a more favourable response to radiation therapy than other stage II endometrial carcinomas.

**Small cell carcinoma**

**Definition**

An endometrial carcinoma resembling small cell carcinoma of the lung.

**Epidemiology**

Small cell carcinoma of neuroendocrine type is an uncommon tumour of the endometrium that comprises less than 1% of all carcinomas.

**Histopathology**

The histological appearance is similar to that of small cell carcinoma in other organs. Small cell carcinomas are positive for cytokeratin and mostly positive for neuroendocrine markers, whereas one-half are positive for vimentin.

**Prognosis and predictive factors**

In contrast to small cell carcinoma elsewhere in the female genital tract, the prognosis is far better in stage I disease with a 5-year survival of about 60% (23, 1271).

**Undifferentiated carcinoma**

Undifferentiated carcinomas are those lacking any evidence of differentiation.
**Rare types of endometrial carcinoma**

Almost every type of carcinoma reported elsewhere has been described in at least a single case report as primary in the endometrium.

**Histopathology**

These tumours are histologically (and usually clinically, if enough cases are available for analysis) identical to their more common counterparts in other organs. They include adenoid cystic carcinoma (985), glassy cell carcinoma (1103) and mesonephric carcinoma (2110). Oncocytic/oxyphilic carcinoma is thought by some to be a variant of clear cell carcinoma, whereas others consider it to be a separate tumour.

**Endometrial hyperplasia**

**Definition**

A spectrum of morphologic alterations ranging from benign changes, caused by an abnormal hormonal environment, to premalignant disease.

**Criteria for histological typing**

The endometrial hyperplasias are classified by their degree of architectural complexity as simple or complex (adenomatous) and by their cytological (nuclear) features as hyperplasia or atypical hyperplasia. The endometrium is uniquely endowed throughout the female reproductive lifespan with a complex regular cycle of periodic proliferation, differentiation, breakdown and regeneration. This high cellular turnover, conditioned by ovarian hormones and growth factors, has many opportunities for losing its regulatory controls. Endometrial hyperplasia encompasses conditions that range from benign estrogen-dependent proliferations of glands and stroma to monoclonal outgrowths of genetically altered glands.

The high degree of morphological variability of endometrial proliferations even within the same sample is responsible for the difficulty in defining consistent and clinically meaningful diagnostic criteria (240,3135). A further complication is fragmentation and scantiness of many aspiration biopsies. Nevertheless, histological interpretation remains the most accessible, albeit somewhat subjective, method of evaluating endometrial hyperplasias.

**WHO classification**

Many classifications had been proposed prior to 1994 when the World Health Organization (WHO) adopted its current

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**Table 4.02 World Health Organization classification of endometrial hyperplasia (2002).**

<table>
<thead>
<tr>
<th>Hyperplasias (typical)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple hyperplasia without atypia</td>
<td></td>
</tr>
<tr>
<td>Complex hyperplasia without atypia</td>
<td></td>
</tr>
<tr>
<td>(adenomatous without atypia)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atypical hyperplasias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple atypical hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Complex atypical hyperplasia</td>
<td></td>
</tr>
<tr>
<td>(adenomatous with atypia)</td>
<td></td>
</tr>
</tbody>
</table>
Although this classification has been widely applied, its reproducibility is somewhat disappointing (240,1433), and molecular data with direct implications for histological diagnosis were unavailable at the time of the 1994 classification (1956). Nevertheless, it remains the best available classification and has been adopted in this new edition.

Endometrial hyperplasias are assumed to evolve as a progressive spectrum of endometrial glandular alterations divided into four separate categories by architecture and cytology. The vast majority of endometrial hyperplasias mimic proliferative endometria, but rare examples demonstrate secretory features. The entire spectrum of metaplastic changes may be observed in hyperplastic endometria.

Hyperplasias without atypia
Hyperplasias without atypia represent the exaggerated proliferative response to an unopposed estrogenic stimulus; the endometrium responds in a diffuse manner with a balanced increase of both glands and stroma. In simple hyperplasia the glands are tubular although frequently cystic or angular, and some even show minor epithelial budding. The lining is pseudostratified with cells displaying regular, elongated nuclei lacking atypia. In complex (adenomatous) hyperplasia the glands display extensive complicated architectural changes represented by irregular epithelial budding into both lumina and stroma and a typical cytology with pseudostratified but uniform, elongated and polarized glandular nuclei; squamous epithelial morules can be present. There is most often a shift in the gland to stroma ratio in favour of the glands.

Atypical hyperplasias
The main feature which differentiates this category from the previous one is the atypical cytology of the glandular lining as represented by loss of axial polarity, unusual nuclear shapes that are often rounded, irregularity in the nuclear membranes, prominent nucleolus and cleared or dense chromatin. Atypia occurs nearly always focally.

Simple atypical hyperplasia features atypical glandular cytology superimposed on the architecture of simple hyperplasia. This pattern is extremely unusual. The frequently found complex atypical (adenomatous with atypia) hyperplasia is a lesion characterized by an increased glandular complexity with irregular outgrowths and cytological atypia. There may be associated foci of non-endometrioid differentiation such as squamous morules. Due to the expansion and crowding of glands, the interglandular stroma is diminished but remains present. Characteristic features of adenocarcinoma are absent.

The assessment of cytological atypia is the key problem in assigning individual cases to one of the four different WHO categories. Definitions of cytological atypia are difficult to apply in the endometrium because nuclear cytological changes occur frequently in hormonal imbalance, benign regeneration and metaplasia (1619,2033). Paradoxically, atypical hyperplasia may exhibit more atypical features than adenocarcinoma (2688), and some grade 1 invasive endometrioid carcinomas have an extremely bland cytology. Perhaps, it would be more appropriate to consider cytological changes in the context of overall glandular architecture. Indeed, architectural focality of the lesion is so closely linked with atypia that they are inseparable. In this way, atypia is best observed by comparison with adjoining normal glands.

Caveat: sampling problems
The focal nature of atypical endometrial hyperplasias may allow young women to maintain fertility, but has the disadvantage of possible underdiagnosis due to incomplete sampling. The problem is greatest in scanty fragmented specimens, something commonly encountered in routine office biopsies. Clearly, this situation is responsible for the false negative biopsies during follow up. Hysteroscopic direction may assist in targeting a macroscopically apparent localized lesion but is not a common practice in most settings.

Contemporary approach to endometrial hyperplasia
Poor reproducibility of the 1994 WHO hyperplasia schema (240,1433) has led to a proposal to reduce the number of diagnostic classes (240). New concepts of pathogenesis have been incorporated into an integrated genetic, histomorphometric and clinical outcome model of
premalignant disease [1956,1958] (see section on genetics of endometrial carcinoma and precursor lesions). The clinical relevance of the model, however, has yet to be established.

**Endometrial polyp**

**Definition**
A benign nodular protrusion above the endometrial surface consisting of endometrial glands and stroma that is typically at least focally fibrous and contains thick-walled blood vessels.

**Histopathology**
Histologically, they are pedunculated or sessile lesions with a fibrous stroma in which characteristic thick-walled, tortuous, dilated blood vessels are found. The glandular component is patchily distributed and shows dilated, occasionally crowded glands lined with an atrophic epithelium, although rarely cyclic activity may be observed. Rare cases of atypical stromal cells have been documented in endometrial polyps [2834], similar to those seen in polyps of the lower female genital system. Polyps can be differentiated from polypoid hyperplasias due to the distinctive stromal and vascular features of the former. Atypical hyperplasias and malignant tumours including endometrioid carcinomas of endometrioid and other types such as serous, as well as sarcomas and mixed tumours [2675] can be found arising in polyps.

**Somatic genetics**
Endometrial polyps constitute benign monoclonal proliferations of mesenchyme [891] and frequently show karyotypic abnormalities of chromosomal regions 6p21 and 12q15 (2854), sites in which the *HMGIC* and *HMGY* genes are located.

**Prognosis and predictive factors**
Polyp resection or polypectomy are the treatments of choice with few recurrences reported [2928].

**Tamoxifen-related lesions**

**Definition**
Lesions that develop in the endometrium in patients undergoing long term tamoxifen therapy.

**Epidemiology**
Patients undergoing long term tamoxifen treatment often have enlarged uteri and frequently show endometrial cysts; up to 25% have endometrial polyps [531].

**Macroscopy**
Tamoxifen-related polyps differ from non-iatrogenic endometrial polyps in that they are larger, sessile with a wide implantation base in the fundus and frequently show a honeycomb appearance.

**Histopathology**
Histologically, the differential features with normal endometrial polyps include the bizarre stellate shape of glands and the frequent epithelial (mucinous, ciliated, eosinophilic, microglandular) and stromal (smooth muscle) metaplasias [665,1437,2558]. There is often a periglandular stromal condensation (cambium layer). Malignant transformation occurs in up to 5% of cases, and endometrioid adenocarcinoma is the most frequent type. However, other types of malignant neoplasm such as serous carcinoma and carcinosarcoma may develop in this setting.

**Somatic genetics**
Despite these histological differences, the cytogenetic profile of tamoxifen-related ed polyps is identical to non-iatrogenic polyps [609].

**Genetics of endometrial carcinoma and precancer**

**Genotype and histotype**
Endometrial adenocarcinoma is characterized by the abrogation of PTEN or TP53 tumour suppressor pathways, respectively, for the endometrioid (type I) and non-endometrioid (type II, including serous and clear cell types) clinicopathological subgroups [2647]. Deletion and/or mutation of the PTEN and TP53 genes themselves are early events with widespread distribution in advanced tumours and a presence in the earliest stages of disease. For PTEN, deletions have been most frequent in the tumour suppressor gene itself, while mutations are more frequent in late stages of disease. For TP53, point mutations have been most frequent in the tumour suppressor gene itself, while deletions are more frequent in late stages of disease.

**Fig. 4.21** Uterine tamoxifen-related lesion. Thickened myometrium in a 69 year old patient with subendometrial cysts and a polyp (arrow).
detectable premalignant (type I) [1959] or non-invasive malignant (type II) phases of tumourigenesis [2647,2863]. A comprehensive model of sequential genetic damage has not been formulated for endometrial cancer despite a growing number of candidate genes. PTEN checks cell division and enables apoptosis through an Akt-dependent mechanism. Functional consequences of PTEN mutation may be modulated in part by the hormonal environment, as PTEN is expressed only during the estrogen-driven proliferative phase of the endometrium [1957]. The use of PTEN immunohistochemistry as a tool for diagnosis of clinically relevant neoplastic endometrial disease is limited by the fact that one-third to one-half of type I cancers continue to express PTEN protein, and loss of PTEN function occurs as an early event that may precede cytological and architectural changes [1959].

**Molecular delineation of premalignant disease**

Type I cancers begin as monoclonal outgrowths of genetically altered premalignant cells, and many bear genetic stigmata of microsatellite instability, KRAS mutation and loss of PTEN function that are conserved in subsequent cancer [1642,1956]. The earliest molecular changes, including PTEN, are detectable at a stage before glands have undergone any change in morphology [1959]. The accumulation of genetic damage is thought to cause emergence of histologically evident monoclonal lesions. Further elaboration of the histopathology of endometrial precancers has been accomplished through correlative histomorphometric analysis of genetically ascertained premalignant lesions [1958]. Because these lesions were initially defined by molecular methods, their diagnostic criteria differ from those of atypical endometrial hyperplasia. They have been designated endometrial intraepithelial neoplasia (‘EIN’) [1955].

**Table 4.03**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Type I</th>
<th>Type II</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>Immunoreactivity (mutant)</td>
<td>5-10%</td>
<td>80-90%</td>
<td>(228,2647)</td>
</tr>
<tr>
<td>PTEN</td>
<td>No immunoreactivity</td>
<td>55%</td>
<td>11%</td>
<td>(1957)</td>
</tr>
<tr>
<td>KRAS</td>
<td>Activation by mutation</td>
<td>13-26</td>
<td>0-10%</td>
<td>(228,1512,1594,1787)</td>
</tr>
<tr>
<td>Beta-catenin</td>
<td>Immunoreactivity (mutant)</td>
<td>25-38%</td>
<td>rare</td>
<td>(1787)</td>
</tr>
<tr>
<td>MLH1</td>
<td>Microsatellite instability / epigenetic silencing</td>
<td>17%</td>
<td>5%</td>
<td>(799,826,1594)</td>
</tr>
<tr>
<td>P27</td>
<td>Low immunoreactivity</td>
<td>68-81%</td>
<td>76%</td>
<td>(2562)</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>High immunoreactivity</td>
<td>41-56%</td>
<td>19%</td>
<td>(2562)</td>
</tr>
<tr>
<td>PI6</td>
<td>Low immunoreactivity</td>
<td>20-34%</td>
<td>10%</td>
<td>(2562)</td>
</tr>
<tr>
<td>Rb</td>
<td>Low immunoreactivity</td>
<td>3-4%</td>
<td>10%</td>
<td>(2562)</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Low immunoreactivity</td>
<td>65%</td>
<td>67%</td>
<td>(1512)</td>
</tr>
<tr>
<td>Bax</td>
<td>Low immunoreactivity</td>
<td>48%</td>
<td>43%</td>
<td>(1512)</td>
</tr>
</tbody>
</table>

**Receptors**

| ER and PR | Positive immunoreactivity | 70-73% | 19-24% | (1512) |

ER = Estrogen receptor
PR = Progesterone receptor

**Table 4.04**

<table>
<thead>
<tr>
<th>EIN Criterion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Architecture</td>
<td>Gland area exceeds that of stroma, usually in a localized region.</td>
</tr>
<tr>
<td>2. Cytological alterations</td>
<td>Cytology differs between architecturally crowded focus and background.</td>
</tr>
<tr>
<td>3. Size &gt;1 mm</td>
<td>Maximum linear dimension should exceed 1 mm. Smaller lesions have unknown natural history.</td>
</tr>
<tr>
<td>4. Exclude benign mimics and cancer</td>
<td></td>
</tr>
</tbody>
</table>
Endometrial intraepithelial neoplasia (EIN)

This lesion is defined as the histopathological presentation of premalignant endometrial disease as identified by integrated molecular genetic, histomorphometric and clinical outcome data. Tissue morphometry (D-Score [153]) predictive of cancer outcome and genetic studies are cross validating in that these methodologically independent techniques provide concordant identification of EIN lesions when applied to a common pool of study material [1958]. The EIN scheme partitions endometrial proliferations into different therapeutic groups. Distinctive diagnostic categories include:

1. Benign architectural changes of unopposed estrogens (endometrial hyperplasia).
2. EIN.
3. Well differentiated adenocarcinoma.

The histological changes produced by unopposed estrogens (non-atypical hyperplasias) are quite unlike localizing EIN lesions. The latter originate focally through monoclonal outgrowth of a mutant epithelial clone with altered cytology and architecture. Computerized morphometric analysis, which quantifies specific architectural patterns associated with increased clinical cancer risk [154], objectively defined the morphological characteristics of monoclonal EIN lesions. Because of differing diagnostic criteria, only 79% of atypical endometrial hyperplasias translate to EIN, and approximately a third of all EIN diagnoses are garnered from non-atypical hyperplasia categories.

Genetic susceptibility

The overwhelming majority of endometrial cancers are sporadic, but they may rarely present as a manifestation of multicancer familial syndromes. Examples include hereditary nonpolyposis colon cancer ([HNPC]), caused by mutation of DNA mismatch repair genes that produce constitutive microsatellite instability [799] and Cowden syndrome in patients with germline PTEN inactivation [1957].

Prognosis and predictive factors

In addition to tumour type and, for type I adenocarcinomas, tumour grade, other histological and non-histological determinations influence the prognosis of endometrial carcinoma. The most important of these is the surgical stage, which in 1988 replaced the clinical staging system that had been in use for many years [2642]. The extent of surgical staging performed is based in part on the medical condition of the patient and in part on the preoperative or intraoperative assessment of tumour risk factors such as type and grade, depth of myometrial invasion and extension to involve the cervix [2692,2714]. Myometrial invasion is thus an important issue, both as a prognostic factor in its own right and as a determinant of the extent of staging and of subsequent therapy in cases treated by hysterectomy. FIGO divides stage I tumours into IA (limited to the endometrium), IB (invasion of less than half of the myometrium), and IC (invasion of more than half of the myometrium), [51,2976]. Some oncologists, however, make treatment decisions based on thirds (inner, mid, outer) of myometrial invasion or distance in millimetres (mm) from the serosal surface. Thus, the pathologist can best satisfy the desires for all of this information by reporting the maximal depth of tumour invasion from the endometromyometrial junction and the thickness of the myometrium at that point (e.g. 7 mm tumour invasion into a 15 mm thick myometrium) [2686]. True myometrial invasion must be distinguished from carcinomatous extension (not invasion) into pre-existing “tongues” of endometrium penetrating the myometrium or into foci (sometimes deep-seated) of adenomyosis [2652,2688]. It should also be noted that tumour extension to the uterine serosa raises the stage to IIIA. Vascular or lymphatic space invasion is an unfavourable prognostic factor that should be reported [78]. Perivascular lymphocytic infiltrates may be the first clue to vascular invasion and, thus, should prompt deeper levels within the suspect block and/or the submission of more tissue sections for histological examination.

It is also important to evaluate cervical involvement in the hysterectomy specimen since extension to the cervix raises the stage to II. The distinction between stage IIA and IB is based on whether the extension involves the endocervical surface and/or underlying glands only or invades the cervical stroma. One should be aware that an adenocarcinoma involving glands only might be an entirely separate adenocarcinoma in situ primary in the endocervix.

Non-histological factors may also play a role in determining the prognosis of endometrial carcinoma. It is unclear at the present time, however, what the cost/benefit ratio of performing additional studies might be since the prognosis and treatment are currently based on the combination of tumour type, grade, where appropriate, and extent, as discussed above. Nevertheless, patients with carcinomas of intermediate prognosis, such as stage I well differentiated endometrioid adenocarcinoma with focal deep myometrial invasion might benefit from additional information including such factors as tumour ploidy [1349,1441], hormone receptor status [575,1441], tumour suppressor genes [1309,1449], oncogenes [1205,1449], proliferation markers [966,1449,2012] and morphometry [2751]. Which, if any, of these or other studies will prove to be most useful is problematic at this time.
Mesenchymal tumours and related lesions

Definition
Uterine mesenchymal tumours are derived from the mesenchyme of the corpus consisting of endometrial stroma, smooth muscle and blood vessels or admixtures of these. Rarely, these tumours may show mesenchymal differentiation that is foreign to the uterus.

Epidemiology
The most common malignant mesenchymal tumours of the uterine corpus are leiomyosarcoma and endometrial stromal tumours, and both are more frequent in Black than in White women (1139, 1729).

Clinical features
Signs and symptoms
The most common presentation for mesenchymal tumours is uterine enlargement, abnormal uterine bleeding or pelvic pain.

Imaging
Non-invasive imaging, usually by ultrasound, but occasionally by magnetic resonance imaging (MRI), can be utilized in selected cases to distinguish between a solid ovarian tumour and a pedunculated leiomyoma or to distinguish leiomyomas from adenomyosis. On MRI leiomyomas present as well delineated lesions of low signal intensity on T1 and T2-weighted images. They may, however, undergo degenerative changes resulting in various, non-specific MRI appearances (1947,2971). On MRI the presence of a large, heterogeneous mass with irregular contours should raise concern for sarcoma.

Endometrial stromal and related tumours

Definition and historical annotation
Endometrial mesenchymal tumours in their better-differentiated forms are composed of cells resembling those of proliferative phase endometrial stroma. Numerous thin-walled small arteriolar type (plexiform) vessels are characteristically present. Endometrial stromal sarcomas (ESS) have been traditionally divided into low and high grade types based on mitotic count. However, since high grade endometrial sarcomas lack specific differentiation and bear no histological resemblance to endometrial stroma, it has been proposed that they be designated undifferentiated endometrial sarcoma (811). In this classification the distinction between low grade ESS and undifferentiated endometrial sarcoma is not made on the basis of mitotic count but on features such as nuclear pleomorphism and necrosis.

ICD-O codes
Endometrial stromal sarcoma, low grade 8931/3
Endometrial stromal nodule 8930/0
Undifferentiated endometrial sarcoma 8930/3

Histopathology
Endometrial stromal tumours are composed of cells resembling those of proliferative endometrial stroma and are far less frequent than smooth muscle tumours. Endometrial stromal tumours are subdivided into benign and malignant groups based on the type of tumour margin (1432,2054,2097,2883). Those with pushing margins are benign stromal nodules, whereas those with infiltrating margins qualify as stromal sarcomas. There is general agreement on the morphologic definition of typical cases of both low grade ESS and undifferentiated endometrial sarcoma. Characteristically, low grade ESS, a clinically indolent neoplasm, features a plexiform vasculature, minimal cytological atypia and infrequent mitotic figures. The usual undifferentiated sarcoma, a highly aggressive neoplasm, lacks a plexiform vasculature, features substantial cytological atypia and has frequent and often atypical mitotic figures. However, there is no valid evidence that the isolated finding of a mitotic index of 10 or more per 10 high power fields is an adverse prognostic finding in a neoplasm that is otherwise a typical low grade ESS. A small minority of cases share features of low grade ESS and undifferentiated sarcoma, and their classification is controversial.

Immunoprofile
The neoplastic cells of both the stromal nodule and low grade ESS are immunoreactive for vimentin, CD10

Fig. 4.25 Low grade endometrial stromal sarcoma (ESS). A Worm-like, soft, yellow masses focally replace the myometrium. B The myometrium is extensively infiltrated by basophilic islands of low grade ESS. C A tongue of low grade ESS protrudes into a vascular space.
endometrial stromal sarcoma
low grade

Definition
This tumour fits the definition of endome-
trial stromal tumour presented above and
is distinguished from the stromal nodule
on the basis of myometrial infiltration
and/or vascular space invasion.

Epidemiology
Low grade ESS is a rare tumour of the
uterus accounting for only 0.2% of all
genital tract malignant neoplasms [645,
1509,1745]. In general low grade ESSs
affect younger women than other uterine
malignancies; studies have demonstrat-
ed that the mean age ranges from 42-58
years, and 10-25% of patients are pre-
menopausal [437,645].

Clinical features
The clinical features have been dis-
cussed above.

Macroscopy
Low grade ESS may present as a solitary,
well delineated and predominantly intra-
mural mass, but extensive permeation of
the myometrium is more common, with
extension to the serosa in approximately
half of the cases. The sectioned surface
appears yellow to tan, and the tumour
has a softer consistency than the usual
leiomyoma. Cystic and myxoid degener-
ation as well as necrosis and haemor-
rhage are seen occasionally.

Localization
Metastases are rarely detected prior to
the diagnosis of the primary lesion
[29,684,3222]. Extratumoral extension is
present in up to a third of the women with
low grade ESS at the time of hysterecto-
my. The extension may appear as worm-
like plugs of tumour within the vessels of
the broad ligament and adnexa.

Histopathology
Low grade ESS is usually a densely cel-
lular tumour composed of uniform, oval
or spindle-shaped cells of endometrial
stromal-type; by definition significant
atypia and pleomorphism are absent.
Although most tumours are paucimor-
tic, mitotic rates of 10 or more per 10 high
power fields can be encountered, and a
high mitotic index does not in itself alter
the diagnosis. A rich network of delicate
small arterioles resembling the spiral
arterioles of the late secretory endometri-
um supports the proliferating cells. Cells
with foamy cytoplasm (tumour cells,
foamy histiocytes, or both) are prominent
in some cases. Endometrial type glands
occur in 11-40% of endometrial stromal
tumours [516,1343,2054]. Sex cord-like
structures may also be found [511].

Fig. 4.26 Low grade endometrial stromal sarcoma (ESS). A There is a proliferation of endometrial stromal cells lacking atypia around spiral arteriole-like blood ves-
sels. B Note a sex cord-like pattern in a low grade ESS.
areas are limited to less than 30% of the tumour. When the smooth muscle component comprises 30% or more of the tumour, the lesion is designated as a mixed endometrial stromal and smooth muscle tumour. Focal rhabdoid differentiation has been described in one case (1813).

The differential diagnosis includes stromal nodule, intravenous leiomyomatosis, adenomyosis with sparse glands and adenosarcoma. In a biopsy or curettage specimen it is often impossible to distinguish low grade ESS from a stromal nodule, a non-neoplastic stromal proliferation or a highly cellular leiomyoma.

**Histogenesis**
Extraterine primary endometrioid stromal sarcomas occur and often arise from endometriosis (280).

**Prognosis and predictive factors**
Low grade ESS is characterized by indolent growth and late recurrences; up to one-half of patients develop one or more pelvic or abdominal recurrences. The median interval to recurrence is 3-5 years but may exceed 20 years. Pulmonary metastases occur in 10% of stage I tumours (1311). The 5-year survival rate for low grade ESS ranges from 67% (2048) to nearly 100% with late metastases and a relatively long-term survival despite tumour dissemination (427,811,2263). The surgical stage is the best predictor of recurrence and survival for ESSs (300,437).

Both recurrent and metastatic ESSs may remain localized for long periods and are amenable to successful treatment by resection, radiation therapy, progestin therapy or a combination thereof (300,1750,3089). Conservative management has been advocated for some patients with low grade ESS (1677). In some studies that have utilized progestin therapy, 100% survival rates have been achieved even for patients with stage III tumours (2263).

**Endometrial stromal nodule**

**Definition**
A benign endometrial stromal tumour characterized by a well delineated, expansive margin and composed of neoplastic cells that resemble proliferative phase endometrial stromal cells supported by a large number of small, thin-walled arteriolar-type vessels.

**Clinical features**
Women with a stromal nodule range in age from 23-75 years with a median of 47 years (2883). About one-third of the women are postmenopausal. Two-thirds of the women present with abnormal uterine bleeding and menorrhagia. Pelvic and abdominal pain occur less frequently.

**Macroscopy**
The tumour is characteristicallu solitary, well delineated, round or oval, fleshy nodule with a yellow to tan sectioned surface. The median tumour diameter is 4.0 cm (range 0.8-15 cm) (2883). About two-thirds are purely intramural without any apparent connections to the endometrium, 18% of the lesions are polypoid, and others involve both the endometrium and myometrium.

**Histopathology**
The histological appearance is identical to that described above for low grade ESS except for the absence of infiltrative margins [292,437,2097,2098,2101,2102,2883]. Rare, focal marginal irregularity in the form of finger-like projections that do not exceed 3 mm is acceptable. Smooth and skeletal muscle along with sex cord differentiation may be present focally (1685).

The differential diagnosis includes low grade ESS and highly cellular leiomyoma. The presence of at least focal typical neoplastic smooth muscle bundles, large, thick walled vessels and strong immunoreactivity with desmin and h-caldesmon and the absence of reactivity with CD10 help distinguish a highly cellular leiomyoma from a stromal nodule.
Endometrial stromal nodules are benign \cite{437,2101,2883}. A hysterectomy may be required if the lesion has not been completely excised.

**Undifferentiated endometrial sarcoma**

**Definition**
A high grade endometrial sarcoma that lacks specific differentiation and bears no histological resemblance to endometrial stroma.

**Synonym**
Undifferentiated uterine sarcoma.

**Macroscopy**
Macroscopically, undifferentiated uterine sarcomas are characterized by one or more polypoid, fleshy, grey to yellow endometrial masses and often show prominent haemorrhage and necrosis.

**Histopathology**
Histologically, undifferentiated endometrial sarcomas show marked cellular atypia and abundant mitotic activity, often including atypical forms. They lack the typical growth pattern and vascularity of low grade ESS \cite{651,811} and displace the myometrium in contrast to the infiltrative pattern of low grade ESS. They resemble the sarcomatous component of a carcinosarcoma, and the possibility of carcinosarcoma and other specific sarcomas should be excluded with adequate sampling. These sarcomas are most often aneuploid with an S-phase fraction greater than 10% \cite{292} and negative for estrogen and progesterone receptors.

**Prognosis and predictive factors**
These tumours are aggressive, and death occurs from tumour dissemination within three years after hysterectomy in most cases.

**Smooth muscle tumours**

**Definition**
Benign or malignant neoplasms composed of cells demonstrating smooth muscle differentiation.

**ICD-O codes**
- Leiomyosarcoma, NOS \text{8890/3}
- Epithelioid variant \text{8891/3}
- Myxoid variant \text{8896/3}
- Smooth muscle tumour of uncertain malignant potential \text{8897/1}
- Leiomyoma, NOS \text{8890/0}
- Leiomyoma, histological variants
  - Cellular leiomyoma \text{8892/0}
  - Epithelioid leiomyoma \text{8891/0}
  - Myxoid leiomyoma \text{8896/0}
  - Atypical leiomyoma \text{8893/0}

**Table 4.05**
Diagnostic criteria for leiomyosarcoma.

<table>
<thead>
<tr>
<th>Standard smooth muscle differentiation</th>
<th>Epithelioid differentiation</th>
<th>Myxoid differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fascicles of cigar-shaped spindled cells with scanty to abundant eosinophilic cytoplasm</td>
<td>Rounded cells with central nuclei and clear to eosinophilic cytoplasm</td>
<td>Spindle-shaped cells set within an abundant myxoid matrix</td>
</tr>
<tr>
<td><strong>Criteria for leiomyosarcoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any coagulative tumour cell necrosis</td>
<td>Any coagulative tumour cell necrosis</td>
<td>Any coagulative tumour cell necrosis</td>
</tr>
<tr>
<td>In the absence of tumour cell necrosis the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of ( \geq 10 \text{mf}/10 \text{hpf} ). When the mitotic index is less than 10 \text{mf}/10 \text{hpf}, the chance of recurrence is low (less than a 2-3%) and the tempo of recurrence is slow. This group is labelled ‘atypical leiomyoma with low risk of recurrence’.</td>
<td>In the absence of tumour cell necrosis the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of ( \geq 5 \text{mf}/10 \text{hpf} ).</td>
<td>In the absence of tumour cell necrosis, the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of ( \geq 5 \text{mf}/10 \text{hpf} ).</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the absence of coagulative tumour cell necrosis and significant atypia a high mitotic index is compatible with a benign clinical course. When the mitotic index exceeds 15 \text{mf}/10 \text{hpf} the term ‘mitotically active leiomyoma with limited experience’ can be used.</td>
<td>Focal epithelioid differentiation may be mimicked by cross-sectioned fascicles of standard smooth muscle</td>
<td>The very common perinodular hydropic degeneration should not be included in this group</td>
</tr>
<tr>
<td>The category ‘leiomyoma with limited experience’ is also used for smooth muscle neoplasms that have focal moderate to severe atypia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mf/10hpf = mitotic figure(s) per 10 high power fields. See ref. \cite{211} for discussion of mitosis counting techniques.
Leiomyosarcoma

Definition
A malignant neoplasm composed of cells demonstrating smooth muscle differentiation.

Epidemiology
Leiomyosarcoma represents the most common pure uterine sarcoma and comprises slightly over 1% of all uterine malignancies [1139]. The incidence of leiomyosarcoma is reported to be 0.3-0.4/100,000 women per year [1139]. Leiomyosarcoma arises nearly exclusively in adults. The median age of patients with leiomyosarcoma was 50-55 years in larger studies [947,1745], and 15% of the patients were younger than 40 years. The risk factors for endometrial carcinomas such as nulliparity, obesity, diabetes mellitus and hypertension are not known to relate to leiomyosarcoma.

Clinical features
Leiomyosarcomas localized to the uterus and leiomyomas produce similar symptoms. Although a rapid increase in the size of the uterus after menopause may raise the possibility of leiomyosarcoma, in fact sarcoma is not more prevalent (less than 0.5%) in women with "rapidly growing" leiomyomas [1622,2187]. Leiomyosarcoma may spread locally, regionally or by haematogenous dissemination. This fact of natural history has implications for both diagnosis and management. Local and regional extension may produce an abdominal or pelvic mass and gastrointestinal or urinary tract symptoms. Haematogenous dissemination is most often to the lungs. Leiomyosarcoma is only infrequently diagnosed on endometrial samplings [1622].

Macroscopy
Leiomyosarcomas are characteristically solitary intramural masses and are usually not associated with leiomyomas. Leiomyosarcomas average 8.0 cm in diameter and are fleshy with poorly defined margins. Zones of haemorrhage and necrosis characteristically interrupt their grey-yellow or pink sectioned surface.
Histopathology

The usual leiomyosarcoma is a cellular tumour composed of fascicles of spindle-shaped cells that possess abundant eosinophilic cytoplasm. Typically, the nuclei are fusiform, usually have rounded ends and are hyperchromatic with coarse chromatin and prominent nucleoli. Tumour cell necrosis is typically prominent but need not be present. The mitotic index usually exceeds 15 figures per 10 high power fields. Vascular invasion is identified in up to 25% of leiomyosarcomas. Giant cells resembling osteoclasts occasionally are present in otherwise typical leiomyosarcomas, and, rarely, xanthoma cells may be prominent (1058,1776).

A diagnosis of leiomyosarcoma should be made with great caution in women less than 30 years of age and only after exclusion of exposure to Leuprolide, which sometimes induces a pattern of necrosis identical to coagulative tumour cell necrosis (664).

Epithelioid variant

Epithelioid leiomyosarcomas combine an “epithelioid” phenotype with the usual features of malignancy, i.e. high cellularity, cytological atypia, tumour cell necrosis and a high mitotic rate (130,1538, 2292). Specifically, epithelioid differentiation denotes tumour cells that have a rounded configuration with eosinophilic to clear cytoplasm. When the cytoplasm is totally clear the label “clear cell” is used. Most malignant epithelioid smooth muscle tumours are of the leiomyoblastoma type, although clear cell leiomyosarcoma has been reported.

Myxoid variant

Myxoid leiomyosarcoma is a large, gelatinous neoplasm that often appears to be circumscribed on macroscopic examination (131,1465). The smooth muscle cells are widely separated by myxoid material. The characteristic low cellularity largely accounts for the presence of only a few mitotic figures per 10 high power fields in most myxoid leiomyosarcomas. In almost all instances myxoid leiomyosarcomas show cellular pleomorphism and nuclear enlargement. They commonly show myometrial and, sometimes, vascular invasion.

Prognosis and predictive factors

Leiomyosarcoma is a highly malignant neoplasm (1745,2096). The variation in survival rates reported historically is largely the result of the use of different criteria for its diagnosis. Overall 5-year survival rates range from 15-25% (185,231,377,812,1585,3109). The 5-year survival rate is 40-70% in stage I and II tumours (291,947,1585,1745,1765,1797,2045,2049,2200,3139). Premenopausal women have a more favourable outcome in some series (947,1381,1585,1797,2045,3139) but not in others (185,1148). Most recurrences are detected within 2 years (231,377,1148,1381). The prognosis of leiomyosarcoma depends chiefly upon the extent of spread. For tumours confined to the uterine corpus, some investigators have found that the size of the neoplasm is an important prognostic factor (812,1364, 2049) with the best demarcation occurring at 5 cm. Several recent series, including the large Gynecologic Oncology Group study of early stage leiomyosarcoma, have found the mitotic index to be of prognostic significance (811,947,1585,1745), whereas others have not (812). The utility of grading leiomyosarcomas is controversial, and no universally accepted grading system exists. Pathologists should comment on the presence or absence of extratumour extension and/or vascular space involvement, the maximum tumour diameter and the mitotic index.

Smooth muscle tumour of uncertain malignant potential

Definition

A smooth muscle tumour that cannot be diagnosed reliably as benign or malignant on the basis of generally applied criteria.

Histopathology

This category of smooth muscle tumour of uncertain malignant potential should...
be used sparingly and is reserved for smooth muscle neoplasms whose appearance is ambiguous for some reason, and the relevant diagnostic possibilities differ in their clinical implications [211]. Examples include cases in which the subtype of smooth muscle differentiation is in doubt, i.e. standard smooth muscle, epithelioid or myxoid, and application of the competing classification rules would lead to different clinical predictions. On other occasions the assessment of a diagnostic feature, e.g. the type of necrosis or the interpretation of mitotic figures, is ambiguous, and the competing alternative interpretations would lead to different clinical predictions.

**Leiomyoma**

**Definition**
A benign neoplasm composed of smooth muscle cells with a variable amount of fibrous stroma.

**Macroscopy**
Leiomyomas are typically multiple, spherical and firm. The sectioned surface is white to tan and has a whorled trabecular texture. Leiomyomas bulge above the surrounding myometrium from which they are easily shelled out. Submucosal leiomyomas distort the overlying endometrium and, as they enlarge, they may bulge into the endometrial cavity and produce bleeding. Rare examples become pedunculated and prolapse through the cervix. Intramural leiomyomas are the most common. Subserosal leiomyomas can become pedunculated, and on torsion with necrosis of the pedicle the leiomyoma may lose its connection with the uterus. Very rarely, some become attached to another pelvic structure (parasitic leiomyoma). The appearance of a leiomyoma often is altered by degenerative changes. Submucosal leiomyomas frequently are ulcerated and haemorrhagic. Haemorrhage and necrosis are observed in some leiomyomas, particularly in large ones in women who are pregnant or who are undergoing high-dose progesterin therapy. Dark red areas represent haemorrhage and sharply demarcated yellow areas reflect necrosis. The damaged smooth muscle is replaced eventually by firm white or translucent collagenous tissue. Cystic degeneration also occurs, and some leiomyomas become extensively calcified.

**Histopathology**
Most leiomyomas are composed of easily recognized smooth muscle featuring whorled, anastomosing fascicles of uniform, fusiform cells. Characteristically, the spindle-shaped cells have indistinct borders and abundant, often fibrillar, eosinophilic cytoplasm. Sometimes, particularly in cellular leiomyomas, the cytoplasm is sparse, and the fascicular arrangement of the cells may be muted.

Nuclei are elongated with blunt or tapered ends and have finely dispersed chromatin and small nucleoli. Mitotic figures usually are infrequent. Most leiomyomas are more cellular than the surrounding myometrium. Leiomyomas lacking increased cellularity are identified by their nodular circumscription and by the disorderly arrangement of the smooth muscle fascicles within them, out of alignment with the surrounding myometrium. Degenerative changes are common in leiomyomas. Hyaline fibrosis, oedema and, on occasion, marked hydropic change can be present [525]. Haemorrhage, necrosis, oedema, myxoid change, hypercellular foci and cellular hypertrophy occur in leiomyomas in women who are pregnant or taking progestins. Not infrequently, there is increased mitotic activity near the areas of necrosis. On the other hand, the coagulative tumour cell necrosis common in leiomyosarcoma is not associated very often with acute inflammation and haemorrhage. Progestational agents are associated with a slight increase in mitotic activity, but not to the level observed in a leiomyosarcoma. In addition, the mitotic figures seen in conjunction with inflammatory necrosis have a normal histologi-

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition or comment</th>
</tr>
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<tbody>
<tr>
<td>Necrosis</td>
<td>Death of a portion of tissue</td>
</tr>
<tr>
<td>Coagulative tumour</td>
<td>Abrupt transition from viable tumour to necrotic tumour, ghost outlines of cells usual, haemorrhage and inflammation uncommon.</td>
</tr>
<tr>
<td>Cell necrosis</td>
<td>Intervening zone of collagen or granulation tissue between nonviable and viable tumour, haemorrhage common, cellular outlines often not visible.</td>
</tr>
<tr>
<td>Hyaline necrosis</td>
<td>Assessed at scanning power</td>
</tr>
<tr>
<td>Diffuse vs. focal</td>
<td>Cells diffusely present in most fields examined vs. scattered widely spaced aggregates of cells</td>
</tr>
<tr>
<td>None to mild</td>
<td>Pleomorphic type: Nuclear pleomorphism appreciated at scanning power</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>Uniform type: Cells lack pleomorphism but exhibit uniform but marked nuclear chromatin abnormalities</td>
</tr>
<tr>
<td>Mitotic index</td>
<td>Expressed in mitotic figures per 10 high power fields in the mitotically most active areas</td>
</tr>
<tr>
<td></td>
<td>Only unequivocal mitotic figures are counted [211]</td>
</tr>
</tbody>
</table>

**Table 4.06**
Definition of terms used in the diagnosis of uterine smooth muscle neoplasms.

Fig. 4.33 MRI showing an enlarged uterus with multiple leiomyomas.
cal appearance. The margins of most leiomyomas are histologically circumscribed, but occasional benign tumours demonstrate interdigitation with the surrounding myometrium, which may rarely be extensive.

Immunoprofile
Smooth muscle neoplasms react with antibodies to muscle-specific actin, alpha-smooth muscle actin, desmin and h-caldesmon. Anomalous expression of cytokeratin immunoreactivity is observed frequently both in the myometrium and in smooth muscle tumours, the extent and intensity of reactivity depending on the antibodies used and the fixation of the specimen. Epithelial membrane antigen is negative in smooth muscle tumours. CD10 reactivity may focally be present.

Histological variants
Most subtypes of leiomyoma are chiefly of interest in that they mimic malignancy in one or more aspects.

Mitotically active leiomyoma
Mitotically active leiomyomas occur most often in premenopausal women. They have the typical macroscopic and histological appearances of a leiomyoma with the exception that they usually have 5 or more mitotic figures per 10 high power fields [211,2293]. Occasionally, these smooth muscle tumours contain >15 mitotic figures per 10 high power fields, in which case the term mitotically active leiomyoma with limited experience is used. The clinical evolution is benign, even if the neoplasm is treated by myomectomy. It is imperative that this diagnosis not be used for neoplasms that exhibit moderate to severe nuclear atypia, contain abnormal mitotic figures or demonstrate zones of coagulative tumour cell necrosis.

Cellular leiomyoma
Cellular leiomyoma accounts for less than 5% of leiomyomas, and by definition their cellularity is “significantly” greater than that of the surrounding myometrium [211,2101]. The isolated occurrence of hypercellularity may suggest a diagnosis of leiomyosarcoma, but cellular leiomyomas lack tumour cell necrosis and moderate to severe atypia and have infrequent mitotic figures. A cellular leiomyoma comprised of small cells with scanty cytoplasm can be confused with an endometrial stromal or pure sex cord-like tumour.

Haemorrhagic cellular leiomyoma and hormone induced changes
A haemorrhagic cellular or “apoplectic” leiomyoma is a form of cellular leiomyoma that is found mainly in women who are taking oral contraceptives or who either are pregnant or are postpartum [1960,2050]. Macroscopic examination reveals multiple stellate haemorrhagic areas. Coagulative tumour cell necrosis is generally absent. Normal mitotic figures are present and are usually confined to a narrow zone of granulation.

Fig. 4.34 Leiomyomas. The sectioned surface shows typical circumscribed, rubbery, white nodules.

Fig. 4.35 Epithelioid leiomyoma with sex cord-like features. The presence of smooth muscle rules out an endometrial stromal or pure sex cord-like tumour.

Fig. 4.36 Epithelioid leiomyoma. Both tumour cells on the right and normal myometrium on the left are immunoreactive for desmin.

Fig. 4.37 Atypical leiomyoma. This cellular neoplasm exhibits nuclear pleomorphism but no mitotic figures or tumour cell necrosis.
tissue in relation to areas of haemorrhage.

**Epithelioid leiomyoma**

Epithelioid leiomyomas are composed of epithelial-like cells [130, 1538, 2292]. They are yellow or grey and may contain visible areas of haemorrhage and necrosis. They tend to be softer than the usual leiomyoma, and most are solitary. Histologically, the epithelioid cells are round or polygonal, they are arranged in clusters or cords, and their nuclei are round, relatively large and centrally positioned. There are three basic subtypes of epithelioid leiomyoma: leiomyoblastoma, clear cell leiomyoma and plexiform leiomyoma. Mixtures of the various patterns are common, hence the designation "epithelioid" for all of them. Small tumours without cytological atypia, tumour cell necrosis or an elevated mitotic index can be safely regarded as benign. Plexiform tumourlets invariably are benign. Epithelioid leiomyomas with circumscribed margins, extensive hyalinization and a predominance of clear cells generally are benign. The behaviour of epithelioid leiomyomas with two or more of the following features is not well established:

1. Large size (greater than 6 cm).
2. Moderate mitotic activity (2–4 mitotic figures per 10 high power fields),
3. Moderate to severe cytological atypia
4. Necrosis

Such tumours should be classified in the uncertain malignant potential category, and careful follow-up is warranted. Neoplasms with 5 or more mitotic figures per 10 high power fields metastasize with sufficient frequency that all should be regarded as epithelioid leiomyosarcoma.

**Myxoid leiomyoma**

Myxoid leiomyomas are benign smooth muscle tumours in which myxoid material separates the tumour cells [131, 1465]. They are soft and translucent. Histologically, abundant amorphous myxoid material is present between the smooth muscle cells. The margins of a myxoid leiomyoma are circumscribed, and neither cytological atypia nor mitotic figures are present.

**Atypical leiomyoma (pleomorphic, bizarre or symplastic leiomyoma)**

When unassociated with either coagulative tumour cell necrosis or a mitotic index in excess of 10 mitotic figures per 10 high power fields, cytological atypia, even when severe, is an unreliable criterion for identifying clinically malignant uterine smooth muscle tumours. These atypical cells have enlarged hyperchromatic nuclei with prominent chromatin clumping (often smudged). Large cytoplasmic pseudonuclear inclusions often are present. The atypical cells may be distributed throughout the leiomyoma (diffuse) or they may be present focally (possibly, multifocally). When the atypia is at most multifocal and the neoplasm has been completely sampled, such tumours are designated "atypical leiomyoma with minimal, if any, recurrence potential." Such lesions have behaved benignly except for a single reported case.

**Lipoleiomyoma**

Scattered adipocytes in an otherwise typical leiomyoma are a relatively common finding; a leiomyoma that contains a striking number of these cells is called a lipoleiomyoma [2357, 2671].

**Growth pattern variants**

Growth pattern variants may produce unusual clinical, macroscopic and/or histological features.

**Diffuse leiomyomatosis**

Diffuse leiomyomatosis is an unusual condition in which numerous small smooth muscle nodules produce symmetrical, sometimes substantial, enlargement of the uterus [518]. The hyperplastic smooth muscle nodules range from histologically to 3 cm in size, but most are less than 1 cm in diameter. They are composed of uniform, bland, spindle-shaped smooth muscle cells and are less circumscribed than leiomyomas. The clinical course may be complicated by haemorrhage, but the condition is benign.

**Dissecting leiomyoma**

Dissecting leiomyoma refers to a benign smooth muscle proliferation with a border marked by the dissection of compressive tongues of smooth muscle into the surrounding myometrium and, occasionally, into the broad ligament and pelvis [2469]. This pattern of infiltration may also be seen in intravenous leiomyomatosis. When oedema and congestion are prominent, a uterine dissecting leiomyoma with extraterine extension may resemble placental tissue; hence the name cotyledonoid dissecting leiomyoma [2470].
Intravenous leiomyomatosis
Intravenous leiomyomatosis is a very rare smooth muscle tumour featuring nodular masses and cords of histologically benign smooth muscle growing within venous channels outside the confines of a leiomyoma (1928,2051). Intravenous leiomyomatosis should be distinguished from the common vascular intrusion within the confines of a leiomyoma. Macroscopically, Intravenous leiomyomatosis consists of a complex, coiled or nodular myometrial growth often with convoluted, worm-like extensions into the uterine veins in the broad ligament or into other pelvic veins. On occasion, the growth extends into the vena cava, and sometimes it extends into the right heart. Histologically, tumour is found within venous channels that are lined by endothelium. The histological appearance is highly variable, even within the same tumour. The cellular composition of some examples of intravenous leiomyomatosis is similar to a leiomyoma, but most contain prominent zones of fibrosis or hyalinization. Smooth muscle cells may be inconspicuous and difficult to identify. Any variant smooth muscle histology, i.e. cellular, atypical, epithelioid or lipoleiomyomatous, may be encountered in intravenous leiomyomatosis.

Benign metastasizing leiomyoma
Benign metastasizing leiomyoma is an ill-defined clinicopathological condition which features "metastatic" histologically benign smooth muscle tumour deposits in the lung, lymph nodes or abdomen that appear to be derived from a benign uterine leiomyoma (798,2923). Reports of this condition often are difficult to evaluate. Almost all cases of benign metastasizing leiomyoma occur in women who have a history of pelvic surgery. The primary neoplasm, typically removed years before the extraterine deposits are detected, often has been inadequately studied. Most examples of "benign metastasizing leiomyoma," however, appear to be either a primary benign smooth muscle lesion of the lung in a woman with a history of uterine leiomyoma or pulmonary metastases from a histologically non-informative smooth muscle neoplasm of the uterus. The findings of a recent cytogenetic study were most consistent with a monoclonal origin of both uterine and pulmonary tumours and the interpretation that the pulmonary tumours were metastatic (2923). The hormone dependence of this proliferation is suggested by the finding of estrogen and progesterone receptors in metastatic deposits and the regression of tumour during pregnancy, after the menopause and after oophorectomy.

Somatic genetics
Uterine leiomyomas often have chromosomal abnormalities detectable by cytogenetic analysis, most frequently involving the HMGIC (12q15) and HMGIIY (6p21) genes (2204a).

Miscellaneous mesenchymal tumours
Definition
A diverse group of mesenchymal tumours of the uterus that do not show predominantly smooth muscle or stromal differentiation.

Mixed endometrial stromal and smooth muscle tumour
Definition and historical annotation
These neoplasms, previously designated stromyomyoma, are composed of an admixture of endometrial stromal and smooth muscle elements (1448,2098, 2550,2860). Small areas of smooth muscle differentiation are commonly seen in otherwise typical endometrial stromal neoplasms and vice versa, but a minimum of 30% of the minor component is recommended for the designation of mixed endometrial stromal-smooth muscle neoplasm (2098).

Macroscopy
These neoplasms may have a predominant intramural, submucosal or subserosal location. Some have been described as well circumscribed, whereas others have been multinodular or have had infiltrating margins. Some neoplasms contain areas with a whorled appearance admixed with tan foci that are softer than typical leiomyomas (2098).

Histopathology
A population of small cells with round to ovoid nuclei and inconspicuous cytoplasm characterizes the endometrial stromal component. Numerous small arterioles are a characteristic feature. The endometrial stromal component usually exhibits minimal cytological atypia, and the mitotic rate is variable. Areas exhibiting sex cord-like differentiation and perivascular hyalinization may be present in the endometrial stromal component (2098). A case has been described with an associated glandular component consisting of benign endometrial glands surrounded by endometrial stroma (1812). The smooth muscle component is usually benign in appearance and is often arranged in nodules with a prominent central area of hyalinization creating a starburst appearance. However, in some cases the smooth muscle component may exhibit any one or a combination of

![Fig. 4.40 Perivascular epithelioid cell tumour. A Low power image shows a "tongue-like" growth pattern, similar to low grade endometrial stromal sarcoma. B High power image shows epithelioid cells with clear to pale granular cytoplasm without significant atypia or mitotic figures. C HMB-45 stain is positive.](image-url)
cytological atypia, tumour cell necrosis and conspicuous mitotic activity. The smooth muscle component is positive for desmin and alpha-smooth muscle actin. However, there may be positivity of the endometrial stromal component with these antibodies, and they cannot be used to reliably distinguish between endometrial stroma and smooth muscle. Studies have shown that markers such as CD10 that stain endometrial stroma but are focally positive in many smooth muscle neoplasms and h-caldesmon and calponin that stain smooth muscle may be of value in distinguishing the two components (44,486,1821,2065). Sex cord-like areas may exhibit immunohistochemical staining with alpha-inhibin and other sex cord-stromal markers (1521, 1808).

**Prognosis and predictive factors**
The limited literature on these rare neoplasms suggests that they should be evaluated and reported in the same way as endometrial stromal neoplasms; i.e. malignant if there is vascular or myometrial invasion, benign otherwise (2008, 2311).

**Perivascular epithelioid cell tumour**

**Definition**
A tumour composed predominantly or exclusively of HMB-45-positive perivascular epithelioid cells with eosinophilic granular cytoplasm. It is a member of a family of lesions thought to be composed, at least in part, of perivascular epithelioid cells. Other members of this group include some forms of angiomyolipoma and lymphangioleiomyomatosis, as well as clear cell 'sugar' tumour.

**Synonym**
PEComa.

**Epidemiology**
The age of patients ranged from 40-75 years with a mean of 54 (2998).

**Clinical features**
Most patients present with abnormal uterine bleeding.

**Macroscopy**
A mass is present in the uterine corpus.

**Histopathology**
The tumours are divided into two groups (2998). The first demonstrates a tongue-like growth pattern similar to that seen in low grade ESS. These tumours are composed of cells that have abundant clear to eosinophilic pale granular cytoplasm and stain diffusely for HMB-45 and also variably express muscle markers. The second group is composed of epithelioid cells with less prominent clear cell features and a smaller number of cells that are HMB-45 positive. These tumours exhibit more extensive muscle marker expression and a lesser degree of tongue-like growth than the first group.

**Genetic susceptibility**
One-half of the patients in the second group had pelvic lymph nodes involved by lymphangioleiomyomatosis, and one-fourth had tuberous sclerosis.

**Prognosis and predictive factors**
Hysterectomy is the usual treatment. Some uterine cases have exhibited aggressive behaviour. Uterine perivascular epithelioid cell tumour should be considered of uncertain malignant potential until long-term outcome data for a larger number of patients become available (2998).

**Adenomatoid tumour**

**Definition**
A benign tumour of the uterine serosa and myometrium originating from mesothelium and forming gland-like structures.

**ICD-O code** 9054/0

**Clinical features**
They are usually an incidental finding in a hysterectomy specimen. Occasionally, they may be multiple or associated with a similar lesion in the fallopian tube.

**Macroscopy**
Macroscopically, adenomatoid tumours may resemble leiomyomas, being well circumscribed intramural masses. However, in many cases they are less well defined and of softer consistency. They may occur anywhere within the myometrium but are often located towards the serosal surface.

**Histopathology**
On low power examination adenomatoid tumour is usually composed of multiple small, often slit-like, interconnecting spaces within the myometrium. On higher power these are composed of tubules lined by a single layer of cells that may be cuboidal or attenuated. The lesion often has an infiltrative appearance. Sometimes the spaces are dilated resulting in a cystic pattern that was confused with lymphangioma in the past, and in other cases a more solid growth pattern is apparent. There is little nuclear atypia or mitotic activity, and there is no stromal desmoplastic response. Occasional tumours may exhibit signet-ring cell histology, focally or diffusely, which may
cause obvious diagnostic problems. Sometimes a papillary pattern may be apparent. Ultrastructural examination shows the long slender microvilli characteristic of mesothelial cells.

**Immunoprofile**
Immunohistochemical positivity with anticytokeratin antibodies and anti-mesothelial antibodies, such as HBME-1 and calretinin, is usual. This finding may be useful in the distinction between adenomatoid tumour and lymphangioma. There is no reactivity with Ber-EP4, helping to exclude a carcinoma in those cases that have signet-ring cell morphology (211, 2101,2123).

**Histogenesis**
The histogenesis has been debated in the past, but immunohistochemical and ultrastructural studies have shown these neoplasms to be of mesothelial origin. When located within the uterus (654, 2041,2311,2768,2924), they are probably derived from the serosal mesothelium.

**Prognosis and predictive factors**
Adenomatoid tumours are invariably benign with no risk of recurrence or metastasis.

**Rare mesenchymal tumours**
Definition
A variety of mesenchymal tumours, both malignant and benign, occurring within the uterus that are not endometrial stromal, smooth muscle or mesothelial in type. These are rare and are identical histologically to their counterparts arising in more usual sites.

**Malignant tumours**
In cases of malignancy the neoplasm should be extensively sampled in order to exclude sarcomatous overgrowth in a MMMT or an adenosarcoma. The most common of these neoplasms to arise in the uterus is *rhabdomyosarcoma* (716, 1149,1814,2112). The latter is usually of embryonal type in young females and of pleomorphic type in the middle aged or elderly. Occasional cases of uterine alveolar rhabdomyosarcoma have also been described (475). Occasional residual entrapped benign endometrial glands may be present, especially towards the surface of these neoplasms. That finding should not be taken as evidence of an adenosarcoma. Other malignant mesenchymal neoplasms described in the uterus include malignant fibrous histiocytoma (1404), angiosarcoma (including the epithelioid variant) (2551,2853), liposarcoma (180), osteosarcoma (784, 1137,1844), chondrosarcoma (1489), alveolar soft part sarcoma (2219), Ewing tumour, malignant peripheral nerve sheath tumour, malignant pigmented neuroectodermal tumour of infancy (2580) and peripheral primitive neuroectodermal tumour (638,1894,2017). In general, these are all bulky neoplasms, frequently high stage at presentation, and the histology is similar to their counterparts elsewhere. Immunohistochemical studies may assist in establishing a definitive diagnosis.

**Haemangiopericytoma** has also been described in the uterus, but it is likely that most of the reported cases represent vascular endometrial stromal neoplasms (2693).

**Malignant rhabdoid tumours** have also been described (948,1255). Since a rhabdoid component may rarely be found in an otherwise typical endometrial stromal neoplasm (1813), it is possible that some rhabdoid tumours represent an unusual histological variant of an endometrial stromal or some other neoplasm. As with other extrarenal rhabdoid tumours, the uterine neoplasm may represent a peculiar histological growth pattern that may be found in a variety of neoplasms; therefore, extensive sampling should be undertaken to exclude a diagnosis of rhabdoid differentiation in another more common neoplasm. Only when other elements are not identified should a diagnosis of uterine malignant rhabdoid tumour be considered.

**Benign tumours**
Benign tumours include lipoma, haemangioma, lymphangioma and rhabdomyoma (466,686). Occasional uterine myxomas have been described in Carney syndrome (2654). Before diagnosing these entities, a lipo leiomyoma should be excluded in the case of lipoma, a vascular leiomyoma in the case of haemangioma, an adenomatoid tumour in the case of lymphangioma and a myxoid smooth muscle neoplasm in the case of myxoma. A single case of postoperative spindle cell nodule of the endometrium that occurred following a uterine curettage has been described (504).
Mixed epithelial and mesenchymal tumours

Definition
Tumours of the uterine corpus composed of an epithelial and a mesenchymal component.

ICD-O codes
- Carcinosarcoma 8980/3
- Adenosarcoma 8933/3
- Carcinofibroma 8934/3
- Adenofibroma 9013/0
- Adenomyoma 8932/0
- Atypical polypoid variant 8932/0

Carcinosarcoma

Definition
A neoplasm composed of an admixture of malignant epithelial and mesenchymal components.

Synonyms
Malignant müllerian mixed tumour, malignant mesodermal mixed tumour, metaplastic carcinoma.

These tumours are still classified as "mixed" by convention, although there is increasing evidence that they are monoclonal and should be considered subsets of endometrial carcinoma.

Epidemiology
Carcinosarcoma is the most common neoplasm of this group (703). Carcinosarcomas usually occur in elderly postmenopausal women, although occasional cases may occur in younger women and rarely even in young girls. The median age of patients presenting with carcinosarcoma is 65 years, higher than that of patients with leiomyosarcoma (813.1745). Less than 5% of patients are younger than 50 years.

Aetiology
An occasional case is secondary to prior pelvic irradiation. In recent years an association between long term tamoxifen therapy and the development of uterine carcinosarcoma has been suggested (813.1811,2947).

Clinical features
Signs and symptoms
Vaginal bleeding is the most frequent presenting symptom of patients with carcinosarcoma, followed by an abdominal mass and pelvic pain (703). Carcinosarcomas may be polypoid and may prolapse through the cervix to present as an upper vaginal mass. The most important diagnostic method is uterine curettage, but in 25% of cases the diagnosis is made following hysterectomy (2965).

Imaging
Magnetic resonance imaging (MRI) of women with a typical carcinosarcoma usually shows an enlarged uterus with a widened endometrial cavity and evidence of deep myometrial invasion. Whereas a carcinosarcoma cannot be distinguished from endometrial carcinoma by means of MRI, the presence of a large tumour with extensive myometrial invasion as well as the presence of ovarian or intraperitoneal metastases should raise suspicion (1060,2838).

Macroscopy
At the time of presentation uterine carcinosarcomas are usually polyoid, bulky, necrotic and haemorrhagic neoplasms that fill the endometrial cavity and deeply invade the myometrium, often extending beyond the uterus. If cartilage or bone forms a significant portion of the neoplasm, the neoplasm may have a hard consistency. Occasionally, these neoplasms may arise within a benign endometrial polyp.

Tumour spread and staging
Intra-abdominal and retroperitoneal nodal metastases are frequent (1745).

Histopathology
The malignant epithelial element is usually glandular, although rarely it may be non-glandular, most commonly consisting of squamous or undifferentiated carcinoma. The glandular component may be either endometrioid or non-endometrioid, such as serous or clear cell in type. The sarcomatous elements may be either homologous or heterologous. In homologous neoplasms the mesenchymal component usually consists of undifferentiated sarcoma, leiomyosarcoma or endometrial stromal sarcoma and is usually, although not always, high grade. Heterologous mesenchymal elements most commonly consist of malignant cartilage or malignant skeletal muscle in the

Table 4.07
Nomenclature of mixed epithelial and mesenchymal tumours defined by phenotypes of epithelial and mesenchymal components.

<table>
<thead>
<tr>
<th>Benign mesenchyme</th>
<th>Malignant mesenchyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenofibroma</td>
<td>Carcinofibroma</td>
</tr>
<tr>
<td>Adenomyoma</td>
<td>Carcinoid sarcoma</td>
</tr>
<tr>
<td>(including atypical)</td>
<td></td>
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</table>

Fig. 4.42 Carcinosarcoma. Sagittal section of the uterus shows a solid, polyoid tumour within the fundus.
Tumours of the uterine corpus form of rhabdomyoblasts, although other elements such as osteosarcoma and liposarcoma may rarely occur.

In general, both carcinomatous and sarcomatous elements are easily identifiable, although in some cases one or other element may form a minor component that may be only identified following extensive sampling of the neoplasm. Any uterine neoplasm composed of high grade sarcoma, especially when heterologous elements are present, should be extensively sampled in order to rule out a carcinosarcoma or sarcomatous overgrowth in an adenosarcoma. In most instances the two elements are sharply demarcated, but in some they appear to merge with transitional forms between the two elements. Eosinophilic hyaline inclusions are commonly seen, especially in the sarcomatous elements (2359). Occasionally, a carcinosarcoma may be identified in an otherwise benign endometrial polyp. A uterine carcinosarcoma with a component of yolk sac tumour has been described in a patient with an elevated serum alpha-fetoprotein level (2665). Occasional tumours with a rhabdoid phenotype (190) or a malignant neuroectodermal component (931) have also been described. Occasional uterine carcinosarcomas of mesonephric origin have been reported (3171). Other unusual histological features include melanocytic (77) and neuroendocrine differentiation (537).

Immunoprofile

In general, the epithelial elements are immunoreactive with anti-cytokeratin antibodies and the mesenchymal elements with vimentin. The mesenchymal elements often show focal staining with anti-cytokeratin antibodies supporting an epithelial origin of this component. The usual concordance of TP53 stains between the epithelial and mesenchymal components supports a common monoclonal origin for both elements (1796, 2827). Desmin, myoD1, myoglobin and sarcomeric actin staining may highlight a rhabdomyosarcomatous mesenchymal component. Cartilaginous elements usually stain with S-100 protein.

Histogenesis

It should be noted that clinical, immunohistochemical, ultrastructural and molecular studies have all suggested that carcinosarcomas are really metaplastic carcinomas in which the mesenchymal component retains at least some epithelial features in the vast majority of cases (1809). Though still classified as “mixed” by convention, these tumours are perhaps better considered subsets of endometrial carcinoma and certainly should not be grouped histogenetically or clinically with uterine sarcomas (1810). On the other hand, the tumours other than carcinosarcoma in this group are considered to be true mixed tumours.
Prognosis and predictive factors
The clinical course of uterine carcinosarcoma is generally aggressive with a poor overall prognosis, considerably worse than that of a poorly differentiated endometrial carcinoma. The pattern of spread is generally similar to that of high grade endometrial carcinoma, and deep myometrial invasion and extraterine spread are often observed at the time of presentation. The clinical staging is the same as that for endometrial carcinoma. Some studies have found no independent prognostic factors other than tumour stage, whereas others have found that the characteristics of the epithelial component such as high grade carcinoma, including serous or clear cell components, are associated with a worse prognosis [2692]. Previously, it was thought that the presence of heterologous mesenchymal components indicated a worse outcome; however, recent larger studies have suggested that the histological features of the mesenchymal component bear no relationship to the overall prognosis [2692].

The biological behaviour of uterine carcinosarcomas is more akin to high grade endometrial carcinomas than to uterine sarcomas [282,2692]. Carcinosarcomas primarily spread via lymphatics, whereas pure uterine sarcomas commonly spread haematogenously. Detailed studies of uterine carcinosarcoma have shown that metastatic foci and foci within lymphatic or vascular spaces are commonly carcinomatous with pure sarcomatous elements being rare [282,2692,2767]. Although the tumour stage is the most important prognostic factor, recurrences may be encountered even in those rare cases lacking myometrial infiltration. However, tumours confined to an otherwise benign polypl appear to have a somewhat better outcome [188,1382].

Adenosarcoma

Definition
Adenosarcoma is a biphasic neoplasm containing a benign epithelial component and a sarcomatous mesenchymal component.

Epidemiology
Adenosarcoma occurs in women of all ages, ranging from 15-90 years with a median age at diagnosis of 58. Adenosarcomas have been reported in women undergoing tamoxifen therapy for breast cancer [509] and occasionally after prior pelvic radiation [515]. There is no association of adenosarcoma with obesity or hypertension.

Clinical features
Typical symptoms of patients with adenosarcoma are abnormal vaginal bleeding, an enlarged uterus and tissue protruding from the external os. The tumour may not be correctly diagnosed as adenosarcoma until re-excision of a recurrent polypoid lesion [515].

Macroscopy
Adenosarcomas typically grow as exophytic polypoid masses that extend into the uterine cavity. Rarely, they may arise in the myometrium, presumably from adenomyosis. Although the tumour is usually a single polypoid mass, it sometimes may present as multiple papillary masses. On sectioning, the surface is tan brown with foci of haemorrhage and necrosis. Small cysts are frequently present. Most adenosarcomas do not invade the myometrium.

Histopathology
Under low magnification a leaf-like pattern closely resembling phyllodes tumour of the breast is observed. Isolated glands, often dilated and compressed into thin slits, are dispersed throughout the mesenchymal component. Characteristically, there is stromal condensation surrounding the glands and clefts. It is in these areas where the greatest degree of stromal atypia and mitotic activity is present. By definition the epithelium is benign and may show focal metaplastic changes. The mesenchymal component of an adenosarcoma is generally a low grade homologous stromal sarcoma containing varying amounts of fibrous tissue and smooth muscle. Mesenchymal mitotic figures, usually stated to be more than one per 10 high power fields, are required in the hypercellular cuffs. Cytological atypia is typically only mild, but is occasionally moderate. Sex cord-like components resembling those in endometrial stromal sarcomas are found in less than 10% of adenosarcomas. Heterologous components consisting of striated muscle (most commonly), cartilage, fat and other components are present in approximately 10-15% of tumours. The diagnosis of sarcomatous overgrowth is made if the pure component assumes 50% or more of the tumour mass.

Fig. 4.44 Adenosarcoma. A The tumour is composed of tubular and convoluted, cleft-like glands of endometrioid type surrounded by a cuff of cellular mesenchyme. B A polypoid structure compresses a glandular lumen producing a leaf-like pattern similar to that of a mammary phyllodes tumour. The epithelial component is cytologically bland, and the mesenchymal component is cellular and fibromatous without significant nuclear atypia but contained abundant mitoses.
sarcomatous component, usually of high grade, occupies 25% or more of the total tumour volume.

**Immunoprofile**
As might be expected, the epithelial component reacts with a broad spectrum of antibodies to cytokeratins. The mesenchymal component usually reacts focally with antibodies to CD10. Variable degrees of staining for smooth muscle markers, desmin and caldesmon, can also be observed.

**Differential diagnosis**
The differential diagnosis includes adenofibroma and in children sarcoma botryoides (embryonal rhabdomyosarcoma).

**Prognosis and predictive factors**
Adenosarcoma is considered a low grade neoplasm but recurs in approximately 25-40% of cases, typically in the pelvis or vagina, and distant metastasis has been reported in 5% of cases [515]. The metastases almost always are composed of a sarcomatous element only, but rarely epithelium has been reported. Factors in the primary tumour that are predictive of a poor outcome are extrauterine spread, deep myometrial invasion into the outer half of the myometrium and sarcomatous overgrowth. Vascular invasion is usually not identified but, if present, is a poor risk factor. Rhabdomyosarcomatous differentiation was an adverse prognostic factor in one series [1388]. There appears to be no correlation between the prognosis and the level of mitotic activity. Long-term follow-up is necessary because recurrences may manifest after many years. Most tumour deaths occur more than five years after the diagnosis.

**Carcinofibroma**

**Definition**
A neoplasm composed of an admixture of a malignant epithelial element and a benign mesenchymal component.

**Epidemiology**
These are extremely uncommon neoplasms with few cases reported in the literature [1286,2228,2916].

**Histopathology**
Adenofibromas have a papillary or club-like growth pattern. They are composed of benign epithelial and mesenchymal components, the epithelial component forming a lining on the underlying mesenchymal core. Cleft-like spaces are often present. The epithelial component may be endometrioid or ciliated in type but often is non-descript cuboidal or columnar. Rarely, there are foci of squamous metaplasia. The mesenchyme is usually of a non-specific fibroblastic type, although rarely it may contain endometrial stromal or smooth muscle components. Stromal atypia, mitotic activity and periglandular cuffing are absent or inconspicuous. Rarely, adipose tissue or skeletal muscle components are present, and such lesions have been designated lipoadenofibroma or adenomyofibroma [1239,2711].

**Differential diagnosis**
If there is a stromal mitotic count of >1 mitosis per 10 high power fields, marked stromal hypercellularity with periglandular cuffing and/or more than mild stromal atypia, a diagnosis of low grade adenosarcoma should be made.

**Prognosis and predictive factors**
Adenofibromas are benign lesions, although they may recur following “polypectomy” [2625]. Occasional...
Mixed epithelial and mesenchymal tumours may superficially invade the myometrium, but metastases have not been reported. Invasion of myometrial veins has also been described (514). Occasional cases have been focally involved by adenocarcinoma, but the association is probably incidental (1873).

Adenomyoma including atypical polypoid adenomyoma

Definition
A lesion composed of benign epithelial (usually endometrial glands) and mesenchymal components in which the mesenchymal component is fibromyomatous. Atypical polypoid adenomyoma is a variant of adenomyoma in which the glandular component exhibits architectural complexity with or without cytological atypia.

Epidemiology
Adenomyoma may occur at any age, whereas atypical polypoid adenomyoma characteristically occurs in premenopausal women (1690, 1801, 3228).

Macroscopy
Adenomyomas and atypical polypoid adenomyomas usually are polypoid submucosal lesions but may rarely be intramural or subserosal (1002). They have a firm sectioned surface. Atypical polypoid adenomyoma usually involves the lower uterine segment or upper endocervix.

Histopathology
Adenomyoma is composed of an admixture of benign endometrial glands (there may be minor foci of tubal, mucinous or squamous epithelium) with minimal cytological atypia and architectural complexity embedded in a benign fibromyomatous mesenchyme. Often endometrial type stroma surrounds the endometrial glandular component, and the former is in turn surrounded by smooth muscle (1002).

Atypical polypoid adenomyoma
In atypical polypoid adenomyoma the glands characteristically show marked architectural complexity; there is no endometrial type stroma around the distorted glands. There is often also cytological atypia that varies from mild to marked. Foci may be present that architecturally resemble well differentiated adenocarcinoma, and such tumours have been designated “atypical polypoid adenomyoma of low malignant potential” (1690). Extensive squamous or morular metaplasia of the glandular elements, with or without central necrosis, is a common finding. The mesenchymal component is composed of swirling and interlacing fascicles of benign smooth muscle.

Differential diagnosis
It should be noted that many simple endometrial polyps contain a minor component of smooth muscle within the stroma; however, this finding alone is not sufficient for the diagnosis of adenomyoma. The designation adenomyoma has also been used for a localized adenomyosis that forms a discrete mass, but such usage is confusing and not recommended. Differentiation from a well differentiated endometrioid adenocarcinoma invading the myometrium may be difficult, especially on a curettage or biopsy specimen. However, the usual lack of pronounced cellular atypia and the absence of a stromal desmoplastic response would be against a diagnosis of adenocarcinoma. Additional features against a diagnosis of carcinoma are the usual youth of the patient and the presence of normal endometrial fragments in the sample.

Genetic susceptibility
Atypical polypoid adenomyomas may occur in women with Turner syndrome (517).

Prognosis and predictive factors
Adenomyoma is generally cured by simple polypectomy, but if associated with myometrial adenomyosis, symptoms may persist. Atypical polypoid adenomyoma may recur, especially following incomplete removal. In addition, superficial myometrial infiltration is often identified in hysterectomy specimens, a finding that may be more common in those cases with marked glandular architectural complexity (1690). A small number of cases are associated with an underlying endometrioid adenocarcinoma with a transition zone between the two components (1882, 2813).
Gestational trophoblastic disease

Definition
A heterogeneous group of gestational and neoplastic conditions arising from trophoblast, including molar gestations and trophoblastic tumours.

Epidemiology
Gestational trophoblastic disease (GTD) varies widely among various populations with figures as high as 1 in 120 pregnancies in some areas of Asia and South America compared to 0.6-1.1 per 1000 in the United States (1162). The incidence of hydatidiform moles is greater in women older than 40 years (161) and is also increased in those younger than 20 years. Patients who have had prior GTD are more at risk of having a second GTD after subsequent pregnancies. Other risk factors include: a diet low in vitamin A, lower socioeconomic status and blood group A women married to group 0 men (161,162,244,363).

Aetiology
Hydatiform moles arise from abnormal conceptions. Partial moles result from diandry (fertilization of an empty ovum). Up to 50% of choriocarcinomas and 15% of placental site trophoblastic tumours follow complete moles.

Clinical features

Signs and symptoms
A complete molar pregnancy usually presents with first trimester bleeding, a uterus larger than expected for gestational age and the absence of fetal parts on ultrasound in association with a markedly elevated beta-human chorionic gonadotropin (β-hCG) level (568). Other signs include hyperemesis, toxemia during the first or second trimester, theca lutein cysts and hyperthyroidism. Patients with partial molar gestations usually present as spontaneous abortions, sometimes with increased β-hCG levels. GTD should always be considered when a patient has continued vaginal bleeding following delivery or abortion.

Imaging
A characteristic pattern of multiple vesi- cles (snowstorm pattern) is commonly seen with complete molar pregnancy. The diagnosis of partial molar pregnancy by ultrasonography is more difficult.

Tumour spread and staging
Choriocarcinoma spreads haematoge- nously and may involve the lung (57-80%), vagina (30%), pelvis (20%), brain (17%), and liver (10%) (168,243). Since β-hCG titres accurately reflect the clinical disease, histological verification is not required for diagnosis. Staging should be based on history, clinical examination and appropriate laboratory and radiological studies.

Metastatic GTD is also categorized by the WHO scoring system as low, medium, and high risk (51,2976). Since β-hCG titres accurately reflect the clinical disease, histological verification is not required for diagnosis. Staging should be based on history, clinical examination and appropriate laboratory and radiological studies.

Metastatic GTD is also categorized by the WHO scoring system as low, medium, and high risk (51,2976). The individual scores for each prognostic factor are added together to obtain a total score. A total prognostic score less than or equal to 4 is considered low risk, a total score of 5-7 is considered middle risk, and a total score of 8 or greater is considered high risk. (See TNM and FIGO classification of gestational trophoblastic diseases at the beginning of the chapter).

Somatic genetics
Overexpression of TP53 protein may be associated with more aggressive behaviour in gestational trophoblastic disease since it is more commonly observed in complete moles and choriocarcinoma (937,1616,2307), but TP53 mutations are uncommon (471). Overexpression of the p21 gene has also been detected in complete moles and choriocarcinoma (469). No correlation between p21 and TP53 expression has been detected in gestational trophoblastic disease.

Both complete mole and choriocarcino- ma exhibit overexpression of several growth factors including c-Myc, epidermal growth factors receptor (EGFR), c-erbB-2, Rb, mdm2, and bcl-2 as compared to normal placenta and partial mole (938,2966). Expression of c-fms protein does not differ between normal placenta and gestational trophoblastic diseases (938). In one study strong immunostaining of c-erbB-3 and epidermal growth factor receptor in extravillous trophoblast of complete mole was signifi- cantly correlated with the development of persistent gestational trophoblastic tumour (2966). The molecular pathogen- esis of gestational trophoblastic diseases may involve these and potentially other growth-regulatory factors.

Prognosis and predictive factors
Major adverse prognostic variables for GTD are:

1. Age >39
2. Prior term pregnancy
3. Interval from antecedent pregnancy of >12 months
4. β-hCG >105 IU/litre
5. Tumour mass >5cm
6. Disease in liver and brain
7. Failure of 2 or more prior chemotherapies

The above factors are included in a prognostic score (see the TNM and FIGO classification of gestational trophoblastic tumours at the beginning of the chapter). The patients are separated into low risk and high risk groups for different treat- ments (1123,3111). The prognosis of patients with low risk disease is very close to 100% survival, whilst patients with high risk disease have a survival of 85-95%, depending on the number of patients with ultra high risk disease in the patient population.

Table 4.08
The U.S. National Institutes of Health staging classi- fication for gestational trophoblastic disease (GTD).

<table>
<thead>
<tr>
<th>I</th>
<th>Benign GTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Complete hydatidiform mole</td>
</tr>
<tr>
<td>B</td>
<td>Partial hydatidiform mole</td>
</tr>
<tr>
<td>II</td>
<td>Malignant GTD</td>
</tr>
</tbody>
</table>

| A | Non-metastatic GTD |
| B | Metastatic GTD |

1. Good prognosis:
   - absence of any risk factor
2. Poor prognosis:
   - presence of any risk factor
   - Duration of GTD >4 months
   - Pre-therapy serum β-hCG >40,000 mIU/mL
   - Brain or liver metastasis
   - GTD after term gestation
   - Failed prior chemotherapy for GTD
**Trophoblastic tumours**

**Definition**
Neoplasms derived from trophoblast.

**ICD-O codes**
- Choriocarcinoma 9100/3
- Placental site trophoblastic tumour 9104/1
- Epithelioid trophoblastic tumour 9105/3

**Gestational choriocarcinoma**

**Definition**
A malignant neoplasm composed of large sheets of biphasic, markedly atypical trophoblast without chorionic villi.

**Clinical features**
Gestational choriocarcinoma may occur subsequent to a molar pregnancy (50% of instances), an abortion (25%), a normal gestation (22.5%) or an ectopic pregnancy (2.5%) (1203).
In rare cases an intraplacental choriocarcinoma is diagnosed immediately following pregnancy from placental pathological examination [343,722,907,1923].

**Histopathology**
Choriocarcinoma consists of an admixture of syncytiotrophoblast, cytotrophoblast and intermediate trophoblast as single cells and clusters of cells with prominent haemorrhage, necrosis and vascular invasion (775a,1593,1801a,1802a,2011,2024a,2077a). Choriocarcinoma does not possess tumour stroma or vessels; correspondingly, the diagnostic viable tumour is located at the periphery of haemorrhagic foci. Extraordinarily, choriocarcinomas have developed and been diagnosed as intraplacental tumours [112,343,722,907,1962,1923,2103].

**Immunoprofile**
All trophoblastic cell types are strongly immunoreactive for cytokeratins [640]. In addition, the syncytiotrophoblast is strongly immunoreactive for β-hCG and weakly immunoreactive for human placental lactogen (hPL); intermediate trophoblast shows the opposite immunoprofile [935].

**Differential diagnosis**
The differential diagnosis of choriocarcinoma in endometrial curettings includes previllous trophoblast from an early gestation, persistent molar tissue following hydatidiform mole, placental site trophoblastic tumour, epithelioid tro-

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**Fig. 4.46** A Gestational choriocarcinoma. Note the plexiform pattern with triphasic differentiation into cytotrophoblast, syncytiotrophoblast and intermediate trophoblast and marked cytological atypia. B Intraplacental choriocarcinoma. There is a distinct interface between malignant biphasic trophoblast in the maternal intervillous space seen on the lower right and mature chorionic villi on the left.

**Fig. 4.47** A Placental site trophoblastic tumour. Coronal section shows the neoplasm diffusely infiltrating the uterine wall. B Tumour cells show marked cytological atypia and numerous mitotic figures.
phoblastic tumour and undifferentiated carcinoma.

**Somatic genetics**
Recent studies using cDNA microarray analysis have demonstrated decreased expression of heat shock protein-27 in choriocarcinoma, a finding which has been associated with chemotherapy responsiveness in other cancers [3014].

**Placental site trophoblastic tumour**

**Definition**
A monophasic neoplasm composed of intermediate trophoblast and cytotrophoblast without a significant component of syncytiotrophoblast.

**Histopathology**
The tumour cells are medium to large sized and mononuclear or multinucleated with mild to marked nuclear atypia, prominent nucleoli, eosinophilic to clear cytoplasm, scattered mitoses and occasional intranuclear inclusions [746,747, 842, 861, 933, 1018, 1019, 1177, 1237, 1511, 1540, 1543, 1589, 2967, 3202, 3227]. They permeate the myometrium and vessels in a manner reminiscent of the implantation site trophoblast.

**Differential diagnosis**
The differential diagnosis of placental site trophoblastic tumour includes placental site nodule, exaggerated implantation site, epithelioid leio myosarcoma, epithelioid trophoblastic tumour and poorly differentiated carcinoma. Extensive sampling and immunohistochemistry for keratin, β-hCG and hPL are helpful in distinguishing among the above lesions [2658, 2659].

**Somatic genetics**
A Y-chromosomal locus and/or new (paternal) alleles not present in adjacent normal uterine tissue was demonstrated in all cases of placental site trophoblastic tumour studied confirming the placental origin of these neoplasms [2747].

**Prognosis and predictive factors**
Placental site trophoblastic tumours are rare, and their biological behaviour is variable. The major prognostic variable is a long interval from the last known antecedent pregnancy. All patient deaths from placental site trophoblastic tumour in the Charing Cross series occurred when the interval from the last known pregnancy was greater than 4 years. An elevated mitotic index predicts a poor outcome [842].

**Epithelioid trophoblastic tumour**

**Definition**
A tumour composed of a monomorphic population of intermediate trophoblastic cells closely resembling those of the chorion laeve (membranous chorion).

**Histopathology**
The epithelioid trophoblastic tumour is a relatively uncommon, recently described neoplasm that differs from the placental site trophoblastic tumour in that the tumour cells of the epithelioid trophoblastic tumour are smaller and less pleomorphic and grow in a nodular as opposed to a diffusely infiltrative pattern. Because they are frequently found in the cervix, they may be confused with hyalinizing squamous cell carcinomas. Epithelioid trophoblastic tumours are focally immunoreactive for placental-like alkaline phosphatase (PLAP) and hPL but strongly and diffusely immunoreactive for E-cadherin and epidermal growth factor receptor [2658].

**Somatic genetics**
A Y-chromosomal locus and/or new (paternal) alleles not present in adjacent normal uterine tissue was demonstrated in all cases of epithelioid trophoblastic tumour studied confirming the placental origin of this neoplasm [2747].

**Prognosis and predictive factors**
Based on available data, the behaviour of epithelioid trophoblastic tumour resembles that of placental site trophoblastic tumour.

**Hydatidiform mole**

**Definition**
An abnormal placenta with villous hydrops and variable degrees of trophoblastic proliferation.

**ICD-O codes**
Hydatidiform mole, NOS 9100/0
Complete 9100/0
Partial 9103/0
Invasive 9100/1

**Complete hydatidiform mole**

**Definition**
A hydatidiform mole involving most of the...
Gestational trophoblastic disease

chorionic villi and typically having a diploid karyotype.

Histopathology
The villous hydrops of a complete mole is characterized by extensive cavititation. The trophoblastic proliferation differs from normal villi by its circumferential distribution, hyperplasia and cytological atypia (978,1203). Intermediate trophoblast of the molar implantation site characteristically displays marked cytologic atypia (1901). A gestational sac, amnion, umbilical cord and fetal tissue are not found (481). It has recently been suggested that villous stromal nuclear negative staining for the paternally imprinted gene product p57 may be diagnostically useful for confirming the diagnosis of a complete mole (425). The extent of trophoblastic atypia and hyperplasia do not correlate with the behaviour in complete mole (776,978).

In the past most complete hydatidiform moles were diagnosed early in the second trimester at an average gestational age of 14 weeks (1924). Currently, with the widespread use of routine ultrasonography in pregnancy, complete moles are diagnosed between 8 and 12 weeks of gestational age (1924). Moles diagnosed at this "early" stage differ histologically from moles diagnosed in the second trimester (1426,1924). Although villous cavititation may be minimal in an "early" mole, other characteristic villous stromal features are present, including hypercellularity and a myxoid basophilic stroma (resembling that of a myxoid fibroadenoma). In addition, unusual villous shapes with complex bulbous protrusions ("cauliflower-like" villi) and trophoblastic atypia are present.

Somatic genetics
Complete and partial molar pregnancies have distinctly different cytogenetic origins. Complete moles generally have a 46,XX karyotype, and the molar chromosomes are completely of paternal origin (1385). Most complete moles appear to arise from an anuclear empty ovum fertilized by a (23X) haploid sperm that then replicates its own chromosomes (3172). Whereas most complete moles have a 46,XX chromosomal pattern, about 10% of complete moles have a 46,XY karyotype (2197). The 46,XY complete mole arises from fertilization of an anuclear empty egg by two sperm. While all chromosomes in a complete mole are entirely of paternal origin.
origin, the mitochondrial DNA is of maternal origin [146].

**Partial hydatidiform mole**

**Definition**

A hydatidiform mole having two populations of chorionic villi, one of normal size and the other hydropic, with focal trophoblastic proliferation. The lesion typically has a triploid karyotype.

**Histopathology**

Histologically, partial moles are characterized by the concurrence of four features (977,1319,1593,2170,2348,2365,2828,2829):

1. Two populations of villi, one hydropic and one "normal";
2. Minimal trophoblastic hyperplasia involving syncytiotrophoblast;
3. Enlarged cavitated villi;
4. Other villi with scalloped borders, often containing trophoblastic inclusions. Stromal blood vessels often contain nucleated fetal red blood cells; other evidence suggesting fetal development is common, including portions of the chorionic sac wall, amnion, umbilical cord and embryonic/fetal tissue.

The differential diagnosis of partial hydatidiform mole includes:

1. Complete mole.
2. Hydroptic abortus.
3. Several rare sporadic genetic syndromes with focal placental hydrops and a fetus, such as the Beckwith-Weidemann syndrome [1558] and placental angiomatous malformation [2522], which collectively have been termed "placental mesenchymal dysplasia" [1337].

In instances in which the histological diagnosis is uncertain, cytogenetic analysis or flow cytometry may be of assistance (549,682,933,1485,1557-1563,2170).

**Somatic genetics**

In contrast to complete moles, partial moles generally have a triploid karyotype that results from fertilization of an apparently normal ovum by two sperm [2828]. The reported incidence of triploidy in partial moles varies from 90-93% respectively (1560,1593). When fetuses are identified with partial moles, they usually have stigmata of triploidy including multiple congenital anomalies and growth retardation.

**Invasive hydatidiform mole**

**Definition**

Invasive hydatidiform mole is defined as villi of hydatidiform mole within the myometrium or its vascular spaces.

**Histopathology**

Most invasive moles follow complete hydatidiform mole and have the characteristic histological appearance of that lesion. Rare examples of invasive partial mole have also been described (33,942,1065,2841,3131). A hysterectomy is usually required for the histological diagnosis.

**Metastatic hydatidiform mole**

**Definition**

Metastatic hydatidiform mole is defined as extraterine molar villi within blood vessels or tissues, most commonly the vagina or the lung.

**Non-neoplastic, non-molar trophoblastic lesions**

**Placental site nodule or plaque**

The placental site nodule or plaque (1260,3203) is a well circumscribed lesion with abundant hyalinized stroma infiltrated by scattered, degenerated-appearing intermediate trophoblastic cells; these cells show no significant cytological atypia, but rare mitoses may be present.

**Exaggerated placental site**

The exaggerated implantation site represents a non-neoplastic exaggeration of the normal implantation process, usually found concurrently with immature villi.
Sex cord-like, neuroectodermal and neuroendocrine tumours, lymphomas and leukaemias

**Sex cord-like tumours**

**Definition**
Tumours of the uterine corpus that closely resemble some true ovarian sex cord tumours.

**Epidemiology**
Among these rare tumours the most numerous are the sex cord-like tumours [511], which closely resemble some true ovarian sex cord tumours.

**Histopathology**
These are diagnosed only when they are not found within otherwise classical endometrial stromal or smooth muscle tumours. Histologically, sex cord elements are represented by trabecular ribbons and nodules or isolated cells with luteinized or foamy cytoplasm that are histologically and immunohistochemically identical to ovarian steroid-producing cells, being strongly positive for alpha-inhibin, calretinin and CD99 [167, 1521, 1808]. They may be capable of hormone-secreting activity [2034]. They have a prominent epithelial component that can be tubular, retiform [3247] or glomeruloid. They also show frequent positivity for cytokeratins, vimentin, smooth muscle actin and, occasionally, epithelial membrane antigen (EMA) [930].

**Neuroectodermal tumours**

**Definition**
A variety of tumours of the uterine corpus that show neuroectodermal differentiation.

**Epidemiology**
Different types of neuroectodermal tumours are found in the uterus. When pure, they usually present in young patients [1188]; however, when mixed with carcinoma or carcinosarcoma they are usually found in older women [638, 931, 2710]. Recently, peripheral primitive neuroectodermal tumour/Ewing tumour has been reported in both young [1597] and postmenopausal patients [2710].

**Histopathology**
Well differentiated variants with an appearance similar to low grade astrocytoma [3201] should be differentiated from non-neoplastic fetal parts implanted in the endometrium following abortion. Most often, the tumour cells differentiate into neuroblastic, neuroepithelial, glial and neuronal elements [1188]. Peripheral primitive neuroectodermal tumour/Ewing tumour shows a characteristic immunophenotype positive for neuron-specific enolase, vimentin and CD99 as well as the presence of EWS/FLI-1 fusion transcripts.

**Prognosis and predictive factors**
All neuroectodermal tumours except the well differentiated astrocytic forms behave in a highly malignant fashion.

**Melanotic paraganglioma**

**Definition**
A tumour morphologically identical to paraganglioma, but functionally producing mainly melanin pigment instead of neuroendocrine granules.

**Epidemiology**
Only two examples of melanotic paraganglioma have been described in the uterus in women 31 and 46 years of age [2866].

**Macroscopy**
Both were incidental findings in uteri removed for unrelated benign lesions. The larger lesion was 1.5 cm and appeared as a black pigmented lesion on macroscopic examination; the other was a histological finding.

**Histopathology**
Both lesions were well circumscribed and composed of large nests of round or angulated polygonal cells with abundant clear or granular pale eosinophilic cytoplasm. Both cases had psammoma bodies, and large amounts of coarse melanin.
granules were present in many cells. The large cells do not stain with S-100 protein. At the ultrastructural level intracellular melanosomes and premelanosomes abound, and a few neuroendocrine granules are present; the cells lack microvilli or dendritic processes.

Prognosis and predictive factors

Both women were free of any recurrences at 2.2 and 3.2 years after the discovery of the tumour [2866].

Lymphomas and leukaemias

Definition

A malignant lymphoproliferative or haematopoietic neoplasm that may be primary or secondary.

Clinical findings

The patients typically present with vaginal bleeding [2354].

Tumour spread and staging

Most lymphomas and leukaemias that involve the uterine corpus are a manifestation of disseminated disease. On rare occasions the corpus is the first known site of a malignant lymphoma.

Histopathology

The majority of cases are of the large B cell type [114]. Lymphomas of the uterine corpus must be distinguished from an atypical lymphoma-like inflammatory lesion of the endometrium. The latter is characterized by a massive infiltrate of lymphoid cells, some of which are immature. The presence of other inflammatory cells including plasma cells and neutrophils within the infiltrate and the typical absence of myometrial invasion or a macroscopic mass are helpful in the differential diagnosis [851]. Cases of uterine leiomyoma massively infiltrated by lymphocytes may also mimic a lymphoma [488].

Rare tumours

Definition

A variety of benign or malignant tumours of the uterine corpus that are not otherwise categorized.

Histopathology

Germ cell tumours such as teratomas and yolk sac tumours can develop in the endometrium, either in a pure form [398, 2196,2763,2836] or associated with endometrioid tumours [103,2665]. Extrarenal Wilms tumours (nephroblastomas) have also been reported in the uterus [1783,1934]. Their histological appearance is similar to that of the tumours occurring in other sites.
Secondary tumours of the uterine corpus

Definition
Tumours of the uterine corpus that originate from, but are discontinuous with, a primary extrauterine tumour or a tumour in the cervix or elsewhere in the uterus.

Clinical features
Signs and symptoms
The mean age of patients with extragenital tumour metastasis to the uterus is 60 years. Patients have abnormal uterine bleeding since most neoplasms metastatic to the uterus infiltrate the endometrium diffusely.

Imaging
Imaging studies are non-specific [1240, 1282, 1576, 3184].

Macroscopy
Metastases may appear as solitary or multiple tumours or be diffusely infiltrating.

Histopathology
The majority of metastases to the uterus are confined to the myometrium. However, approximately one-third involve the endometrium and thus can be detected in biopsy specimens [1529]. Metastatic carcinoma within the endometrium and/or myometrium characteristically infiltrates as single cells, cord or glands. The appearance is particularly striking in lobular carcinoma of the breast, which usually retains its single-file pattern, and with metastatic signet-ring cell carcinoma of the stomach or colon. Metastatic colon carcinoma of the usual type may form large tumour masses and can mimic an endometrial carcinoma of mucinous or endometrioid type. Metastatic carcinoma in the endometrium should be suspected if one or more of the following features are present [1539].

1. A tumour with an unusual macroscopic or histological pattern for primary endometrial carcinoma.
2. Diffuse replacement by tumour of endometrial stroma with sparing of occasional normal endometrial glands.
3. Lack of premalignant changes in endometrial glands.
4. Lack of tumour necrosis For specific identification of certain primary tumours immunohistochemical studies are frequently required.

Origin and histogenesis
In most instances the primary tumour is well known, or disseminated disease is clinical evident. Occasionally, a tumour diagnosed by curettage or hysterectomy represents the first sign of an extraterine primary tumour.

Secondary tumours of the uterine corpus can be divided into two major groups: tumours of the genital and extragenital organs. Neoplasms of neighbouring organs such as cervix, fallopian tubes, ovaries, bladder and rectum can metastasize to the uterine corpus via lymphatics or blood vessels but mostly represent local direct extension. Haematogenous or lymphatic uterine metastases from any extragenital primary tumour may occur but are extremely rare. Reported primary tumours include carcinomas of the breast, stomach, colon, pancreas, gallbladder, lung, urinary bladder and thyroid and melanoma [192, 1452, 1455, 1529, 1531, 1620, 1720]. Mammary lobular carcinoma, gastric signet-ring cell carcinoma and colonic carcinoma are the most frequently reported extragenital primary tumours [1529, 1531].

Prognosis and predictive factors
When uterine metastases are present, the patient usually has widely disseminated disease. However, in one series the average survival was 20 months after the diagnosis of uterine metastases. The reason for this relatively favourable outcome might be the predominance of cases of metastatic breast carcinoma [1529].

Fig. 4.59 Metastatic colon carcinoma to the myometrium. A Note the tumour cells in lymphatic vessels in the right upper portion of the field with a plexiform pattern on the left. B The neoplastic glands are positive for cytokeratin 20.

Fig. 4.60 Metastatic melanoma to the endometrium. Tumour cells containing melanin pigment surround an atrophic endometrial gland.