Tumours of the ovary represent about 30% of all cancers of the female genital system. Age-adjusted incidence rates are highest in the economically advanced countries where they are almost as common as cancers of the corpus uteri and invasive cancer of the cervix. Carcinomas of surface epithelial-stromal origin account for 90% of these cancers in North America and Western Europe. In some Asian countries, including Japan, germ cell tumours account for a significant proportion (20%) of ovarian malignancies. High parity and the use of oral contraceptives are consistently associated with a reduced risk of developing surface epithelial-stromal tumours while long-term estrogen replacement therapy appears to increase the risk in postmenopausal women.
## WHO histological classification of tumours of the ovary

<table>
<thead>
<tr>
<th>Surface epithelial-stromal tumours</th>
<th>Metaplastic variant</th>
<th>Squamous cell tumours</th>
<th>Epidermoid cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous tumours</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Malignant Adenocarcinoma 8441/3</td>
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<tr>
<td>Surface papillary adenocarcinoma 8461/3</td>
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<tr>
<td>Adenocarcinofibroma (malignant adenofibroma) 9014/3</td>
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<tr>
<td>Borderline tumour 8442/1</td>
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<tr>
<td>Papillary cystic tumour 8462/1</td>
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<tr>
<td>Surface papillary tumour 8463/1</td>
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<tr>
<td>Adenofibroma, cystadenofibroma 9014/1</td>
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<tr>
<td>Benign Cystadenoma 8441/0</td>
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<tr>
<td>Papillary cystadenoma 8460/0</td>
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<tr>
<td>Surface papilloma 8461/0</td>
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<tr>
<td>Adenofibroma and cystadenofibroma 9014/0</td>
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<tr>
<td>Malignant Mucinous tumours</td>
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<tr>
<td>Adenocarcinoma 8480/0</td>
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<td>Borderline tumour 8472/1</td>
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<tr>
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<tr>
<td>Adenofibroma and cystadenofibroma 9015/0</td>
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<tr>
<td>Malignant Mucinous cystic tumour with mural nodules</td>
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<tr>
<td>Malignant Mucinous cystic tumour with pseudomyxoma peritonei 8480/3</td>
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<td>Endometrioid tumours including variants with squamous differentiation</td>
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<tr>
<td>Adenocarcinofibroma (malignant adenofibroma) 8381/3</td>
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<td>Malignant müllerian mixed tumour 8950/3</td>
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<td>Adenosarcoma 8932/3</td>
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<td>Borderline tumour 8380/1</td>
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<tr>
<td>Cystadenoma 8380/0</td>
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<td>Adenofibroma and cystadenofibroma 8381/0</td>
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<td>Benign Cystadenoma 8380/0</td>
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<td>Adenofibroma and cystadenofibroma 8381/0</td>
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<td>Clear cell tumours</td>
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<tr>
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<tr>
<td>Adenocarcinofibroma (malignant adenofibroma) 8313/3</td>
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<tr>
<td>Borderline tumour 8310/1</td>
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<tr>
<td>Cystadenoma 8310/0</td>
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<tr>
<td>Adenofibroma and cystadenofibroma 8313/0</td>
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<tr>
<td>Benign Cystadenoma 8310/0</td>
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<tr>
<td>Adenofibroma and cystadenofibroma 8313/0</td>
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<td>Transitional cell tumours</td>
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<td>Malignant Transitional cell carcinoma (non-Brenner type) 8120/3</td>
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<tr>
<td>Malignant Brenner tumour 9000/3</td>
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<tr>
<td>Borderline Borderline Brenner tumour 9000/1</td>
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<td>Proliferating variant 9000/1</td>
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<tr>
<td>Benign Brenner tumour 9000/0</td>
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<td>Steroid cell tumours</td>
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<tr>
<td>Malignant Leydig cell tumour group (androblastomas) 8610/0</td>
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<tr>
<td>Leydig cell tumour group</td>
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<tr>
<td>Hilus cell tumour 8660/0</td>
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<tr>
<td>Leydig cell tumour, non-hilar type 8650/1</td>
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<tr>
<td>Steroid cell tumour, not otherwise specified 8670/0</td>
<td></td>
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<td></td>
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<tr>
<td>Well differentiated 8670/0</td>
<td></td>
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<tr>
<td>Malignant 8670/3</td>
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<tr>
<td>Germ cell tumours</td>
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<tr>
<td>Malignant Primitive germ cell tumours</td>
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<td></td>
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<tr>
<td>Dysergeminoma 9060/0</td>
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<tr>
<td>Yolk sac tumour 9071/3</td>
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<tr>
<td>Polyvesicular vitelline tumour</td>
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<tr>
<td>Glandular variant</td>
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<tr>
<td>Hepatoïd variant</td>
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<tr>
<td>Embryonal carcinoma 9070/3</td>
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</tr>
</tbody>
</table>
Polyembryoma
Non-gestational choriocarcinoma
Mixed germ cell tumour (specify components)
Biphasic or triphasic teratoma
Immature teratoma
Mature teratoma
Solid
Cystic
Dermoid cyst
Fetiform teratoma (homunculus)

Monodermal teratoma and somatic-type tumours associated with dermoid cysts
Thyroid tumour group
Struma ovarii
Benign
Malignant (specify type)
Carcinoid group
Insular
Trabecular
Mucinous
Struma carcinoid
Mixed
Neuroectodermal tumour group
Ependymoma
Primary neuroectodermal tumour
Medulloepithelioma
Glioblastoma multiforme
Others
Carcinoma group
Squamous cell carcinoma
Adenocarcinoma
Others
Melanocytic group
Malignant melanoma
Melanocytic naevus
Sarcoma group (specify type)
Sebaceous tumour group
Sebaceous adenoma
Sebaceous carcinoma
Pituitary-type tumour group
Retinal anlage tumour group
Others

Monodermal teratoma and somatic-type tumours associated with dermoid cysts

Tumours of the rete ovarii
Adenocarcinoma
Adenoma
Cystadenoma
Cystadenofibroma

Miscellaneous tumours
Small cell carcinoma, hypercalcaemic type
Small cell carcinoma, pulmonary type
Large cell neuroendocrine carcinoma
Hepatoid carcinoma
Primary ovarian mesothelioma
Wilms tumour
Gestational choriocarcinoma
Hydatidiform mole
Adenoid cystic carcinoma
Basal cell tumour
Ovarian wolfian tumour
Paraganglioma
Myxoma
Soft tissue tumours not specific to the ovary
Others

Germ cell sex cord-stromal tumours
Gonadoblastoma
Variant with malignant germ cell tumour
Mixed germ cell-sex cord-stromal tumour
Variant with malignant germ cell tumour

Other tumours
Germ cell sex cord-stromal tumours
Gonadoblastoma
Variant with malignant germ cell tumour
Mixed germ cell-sex cord-stromal tumour
Variant with malignant germ cell tumour

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.

WHO histological classification of tumours of the peritoneum

<table>
<thead>
<tr>
<th>Peritoneal tumours</th>
<th>Tumour of uncertain origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesotheial tumours</td>
<td>Desmoplastic small round cell tumour</td>
</tr>
<tr>
<td>Diffuse malignant mesothelioma</td>
<td>Epithelial tumours</td>
</tr>
<tr>
<td>Well differentiated papillary mesothelioma</td>
<td>Primary peritoneal serous adenocarcinoma</td>
</tr>
<tr>
<td>Multicystic mesothelioma</td>
<td>Primary peritoneal borderline tumour (specify type)</td>
</tr>
<tr>
<td>Adenomatoid tumour</td>
<td>Others</td>
</tr>
<tr>
<td>Smooth muscle tumour</td>
<td>Leiomyomatosis peritonealis disseminata</td>
</tr>
</tbody>
</table>

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 tumours of the ovary

<table>
<thead>
<tr>
<th>TNM Categories</th>
<th>FIGO</th>
<th>Stages</th>
</tr>
</thead>
<tbody>
<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>T1</td>
<td>Tumour limited to the ovaries</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>IA Tumour limited to one ovary; capsule intact, no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>IB Tumour limited to both ovaries; capsule intact, no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>IC Tumour limited to one or both ovaries with any of the following: capsule ruptured, tumour on ovarian surface, malignant cells in ascites or peritoneal washings</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>II Tumour involves one or both ovaries with pelvic extension</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>IIA Extension and/or implants on uterus and/or tube(s); no malignant cells in ascites or peritoneal washings</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>IIB Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings</td>
<td></td>
</tr>
<tr>
<td>T2c</td>
<td>IIC Pelvic extension (2a or 2b) with malignant cells in ascites or peritoneal washings</td>
<td></td>
</tr>
<tr>
<td>T3 and/or N1</td>
<td>III Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA Microscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>IIB Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension</td>
<td></td>
</tr>
</tbody>
</table>

| T3c and/or N1  | IIC Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis |
| M1             | IV Distant metastasis (excludes peritoneal metastasis) |

**Stage Grouping**

- 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 IIC: T2c N0 M0
- Stage IIIA: T3a N0 M0
- Stage IIIB: T3b N0 M0
- Stage IIIC: T3c N0 M0
- Stage IV: Any T Any N M1

---

1. [http://tnm.uicc.org](http://tnm.uicc.org)
3. The classification applies to malignant surface epithelial-stromal tumours including those of borderline malignancy.
4. Non-epithelial ovarian cancers may also be classified using this scheme.
5. The regional lymph nodes are the hypogastric (obturator), common iliac, external iliac, lateral sacral, para-aortic, and inguinal nodes.
**Definition**

Surface epithelial-stromal tumours are the most common neoplasms of the ovary. They originate from the ovarian surface epithelium or its derivatives and occur in women of reproductive age and beyond. They are histologically composed of one or more distinctive types of epithelium, admixed with a variable amount of stroma. Their biological behaviour varies with histological type.

**Epidemiology**

Cancer of the ovary represents about 30% of all cancers of the female genital organs. In developed countries it is about as common as cancers of the corpus uteri (35%) and invasive cancer of the cervix (27%). The age-adjusted incidence rates vary from less than 2 new cases per 100,000 women in most of Southeast Asia and Africa to over 15 cases in Northern and Eastern Europe. The economically advanced countries of North America, Europe, Australia, New Zealand and temperate South America show the highest rates. In the United States more women die from ovarian cancer today than from all other pelvic gynaecological cancer sites combined (1066). Incidence rates have been either stable or have shown slow increases in most western countries, whereas they have risen steadily in parts of Eastern Asia.

**Aetiology**

Two factors consistently associated with a reduced risk of the disease are high parity and the use of oral contraceptives (1295,2474). Three recent studies have shown an increased risk of ovarian cancer in postmenopausal women treated with high-dose estrogen replacement therapy for 10 years or greater (963, 2373,2399). Very little is known of the aetiology of non-familial cases. The protective effects of pregnancies and of oral contraception suggest a direct role for ovulation in causing the disease, but no convincing mechanism linking the risk factors with malignant transformation has been proposed. Several dietary factors have been related to ovarian cancer (819). There is emerging evidence that the Western lifestyle, in particular, obesity, is associated with an increased risk (388).

**Clinical features**

**Signs and symptoms**

Women with ovarian cancer have a poor prognosis. The mean 5-year survival rate in Europe is 32% (256). This unfavourable outcome is largely ascribed to a lack of early warning symptoms and a lack of diagnostic tests that allow early detection. As a result, approximately 70% of patients present when this cancer is in an advanced stage, i.e. it has metastasized to the upper abdomen or beyond the abdominal cavity (394). It is now recognized that the overwhelming majority of women diagnosed with ovarian cancer actually have symptoms, but they are subtle and easily confused with those of various benign entities, particularly those related to the gastrointestinal tract (1024,2106).

Physical signs associated with early stage ovarian cancer may be limited to palpation by pelvic examination of a mobile, but somewhat irregular, pelvic mass (stage I). As the disease spreads into the pelvic cavity, nodules may be found in the cul-de-sac, particularly on bimanual rectovaginal examination (stage II). Ascites may occur even when the malignancy is limited to one or both ovaries (stage IC). As the disease involves the upper abdomen, ascites may be evident. A physical examination of the abdomen may demonstrate flank bulging and fluid waves associated with the ascites. Metastatic disease is commonly found in the omentum, such that the latter may be readily identified in the presence of advanced stage (stage III) ovarian cancer as a ballottable or palpable mass in the mid-abdomen, usually superior to the umbilicus and above the palpable pelvic mass. Finally, the
disease may spread through lymphatics to either the inguinal or left supraclavicular lymph nodes, which may be readily palpable. It may advance into the pleural cavity as a malignant effusion, usually on the right side or bilateral, in which case the lung bases exhibit dullness to percussion and decreased breath sounds and egophony to auscultation (stage IV).

**Advanced intra-abdominal ovarian carcinomatosis** may also present with signs of intestinal obstruction including nausea, vomiting and abdominal pain.

**Imaging**

Due to its wide availability, ultrasound (US) is the imaging method of choice to assess an ovarian lesion and to determine the presence of solid and cystic elements. The distinction between benign, borderline and malignant tumours is generally not possible by US, either alone or in combination with magnetic resonance imaging (MRI) or computed tomography (CT). None of these methods has a clearly established role in preoperative tumour staging. Surgical exploration remains the standard approach for staging [1116,1417,1522,1795,2898].

**Tumour spread and staging**

About 70-75% of patients with ovarian cancer have tumour spread beyond the pelvis at the time of diagnosis [1770]. Ovarian cancers spread mainly by local extension, by intra-abdominal dissemination and by lymphatic dissemination, but rarely also through the bloodstream. The International Federation of Gynecology and Obstetrics (FIGO) Committee on Gynecologic Oncology is responsible for the staging system that is used internationally today [217]. The pTNM-system is based on the postoperative pathological staging for histological control and confirmation of the disease. [51,2976].

**Histogenesis**

The likely origin of ovarian surface epithelial-stromal tumours is the mesothelial surface lining of the ovaries and/or invaginations of this lining into the superficial ovarian cortex that form inclusion cysts [838].

**Genetic susceptibility**

**Familial clustering**

Numerous epidemiological investigations of ovarian cancer have attempted to quantify the risks associated with a positive family history. Whereas ovarian cancer has not been as extensively studied as breast cancer, several studies point to familial clustering. The relative risk of ovarian cancer for first degree relatives varies from 1.94 to 25.5, the latter if both a mother and sister are affected [1029,2557,2801].

**BRCA1/2**

A number of specific genes have been identified as playing a role. The most important of these, BRCA1 and BRCA2, are discussed in chapter 8. In contrast to breast cancer in which only a minority of the familial clustering could be explained by known major susceptibility loci such as BRCA1 and BRCA2, it is likely that the majority of the familial risk of ovarian cancer is explained by BRCA1 and to a lesser extent BRCA2, MLH1 and MSH2. Using statistical modelling and the results from BRCA1 and BRCA2 mutation testing in 112 families with at least two cases of ovarian cancer (allowing for insensitivity of the mutation detection assay), BRCA1 and BRCA2 accounted for nearly all of the non-chance familial aggregation [973].

**HNPCC**

Ovarian cancer is a minor feature of the hereditary nonpolyposis colon cancer syndrome caused by mutations in genes associated with DNA base mismatch repair, the most frequent of which are MLH1 and MSH2.

---

**Fig. 2.02** Serous adenocarcinoma. The sectioned surface of the tumour shows two solid nodules within a multiloculated cyst.

**Fig. 2.03** Serous adenocarcinoma. A The tumour is composed of closely packed papillae most of which lack fibrous cores lined by cells with atypical nuclei and high nuclear to cytoplasmic ratios. B This poorly differentiated tumour shows relatively solid papillary aggregates without fibrovascular cores and scattered bizarre, pleomorphic nuclei. Cherry red nucleoli are apparent in some nuclei.
Association with endometrial cancer
Several studies provide evidence of associations between ovarian and other cancers, particularly endometrial (715, 1029). The relative risk of developing endometrial cancer is about 1.5 among mothers and sisters of ovarian cancer cases, although in both studies the risk fell just short of statistical significance.

Serous tumours

Definition
Ovarian tumours characterized in their better-differentiated forms by cell types resembling those of the fallopian tube.

ICD-O codes
- Serous adenocarcinoma 8441/3
- Serous borderline tumour 8442/1
- Benign serous tumours
  - Serous papillary cystadenoma 8460/0
  - Serous cystadenoma 8441/0
  - Serous surface papilloma 8461/0
  - Serous adenofibroma, cystadenofibroma 9014/0

Serous adenocarcinoma
Definition
An invasive ovarian epithelial neoplasm composed of cells ranging in appearance from those resembling fallopian tube epithelium in well differentiated tumours to anaplastic epithelial cells with severe nuclear atypia in poorly differentiated tumours.

Macroscopy
The tumours range from not being macroscopically detectable to over 20-cm in diameter and are bilateral in two-thirds of all cases, but only in one-third of stage I cases. Well differentiated tumours are solid and cystic with soft papillae within the cystic spaces or on the surface. The papillae tend to be softer and more confluent than in cases of borderline tumours. Rare tumours are confined to the ovarian surface. Poorly differentiated tumours are solid, friable, multinodular masses with necrosis and haemorrhage.

Histopathology
The architecture of the tumour varies from glandular to papillary to solid. The glands are typically slit-like or irregular. The papillae are usually irregularly branching and highly cellular. In poorly differentiated tumours solid areas are usually extensive and composed of poorly differentiated cells in sheets with small papillary clusters separated by myxoid or hyaline stroma. Psammoma bodies may be present in varying numbers. The stroma may be scanty or desmoplastic. Serous carcinomas may contain a variety of other cell types as a minor component (less than 10%) that may cause diagnostic problems but do not influence the outcome. Serous psammocarcinoma is a rare variant of serous carcinoma characterized by massive psammoma body formation and low grade cytological features. The epithelium is arranged in small nests with no areas of solid epithelial proliferation, and at least 75% of the epithelial nests are associated with psammoma body formation (1001).

Immunoprofile
Serous carcinomas are always cytokeratin 7 positive and cytokeratin 20 negative. They are also positive for epithelial membrane antigen, CAM5.2, AE1/AE3, B72.3 and Leu M1 and for CA125 in 85% of the cases, but negative for calretinin and other mesothelial markers.

Grading
Various grading systems have been proposed for serous carcinomas. The utilization of a three-tiered grading system is recommended since the tumour grade has important prognostic and therapeutic implications (2687).

Somatic genetics
The prevailing view of the pathogenesis of serous adenocarcinoma is that it arises directly from the ovarian surface epithelium, invaginations or epithelial inclusions and progresses rapidly (205). At present, serous carcinoma is regarded as a relatively homogeneous group of tumours from the standpoint of pathogenesis. Thus, although these neoplasms are graded as well, moderately and poorly differentiated, they are thought to represent a spectrum of differentiation reflecting progression from a low grade to a high grade malignancy. Whereas in colorectal carcinoma a
tumour progression model in which sequential accumulation of molecular genetic alterations leading to morphologically recognizable stages is well established [1468], a similar model for ovarian serous carcinoma has not been proposed because well defined precursor lesions have not been identified. It has been reported that even the earliest histological serous carcinomas are already high grade and morphologically resemble their advanced stage counterparts [205]. The histological similarities are paralleled by recent molecular genetic findings demonstrating TP53 mutations in very small stage I serous carcinomas and in the adjacent “dysplastic” surface epithelium [2275]. Most studies have shown that approximately 60% of advanced stage ovarian serous carcinomas have mutant TP53 [230,3095]. Thus, although the molecular genetic findings in these early carcinomas are preliminary, they suggest that serous carcinoma in its very earliest stage of development resembles advanced stage serous carcinoma at the molecular level. This would support the view that there are no morphologically recognized intermediate steps in the progression of the conventional type of ovarian serous carcinoma. Serous borderline tumours (SBTs), non-invasive and invasive micropapillary types, frequently display KRAS mutations but rarely mutant TP53. Increased allelic imbalance of chromosome 5q is associated with the progression from typical SBT to micropapillary SBT and increased allelic imbalance of chromosome 1p with the progression from micropapillary SBT to invasive serous carcinoma [2706]. In contrast, KRAS mutations are very rare in conventional serous carcinoma, but TP53 mutations occur in approximately 60%. Recently, mutations were also identified in the BRAF gene, a downstream mediator of KRAS, BRAF and KRAS mutations appear to be mutually exclusive. These mutations were only detected in low grade ovarian serous carcinomas [2707]. Thus, there appears to be more than one pathway of tumorigenesis for serous carcinoma. In one pathway, conventional serous carcinoma, a high grade neoplasm, develops “de novo” from the surface epithelium of the ovary, grows rapidly and is highly aggressive [205]. These tumours, even at their earliest stage, display TP53 mutations but not KRAS mutations. In the other pathway a SBT progresses in a “stepwise” fashion through a non-invasive micropapillary stage before becoming invasive [2706] or through microinvasion in a background of typical SBT. The indolent micropapillary tumours frequently display KRAS mutations, but TP53 mutations are only rarely detected.

Genetic susceptibility
The neoplasms that develop in women with germline BRCA1 mutations are mostly serous carcinomas of the ovary, fallopian tube and peritoneum.

Prognosis and predictive factors
The overall 5-year survival is approximately 40%; however, many of those alive at 5 years are alive with disease. Up to 85% of cases present with widespread metastatic disease. Survival at 5 years in this group is 10-20%. Patients with disease confined to the ovary or pelvis have a 5-year survival of 80%. Patients with serous psammocarcinoma have a protracted clinical course and a relatively favourable prognosis; their clinical behaviour more closely resembles that of SBT than serous carcinoma of the usual type.

Serous borderline tumour with microinvasion

Definition
An ovarian serous tumour of low malignant potential exhibiting early stromal invasion characterized by the presence in the stroma of individual or clusters of neoplastic cells cytologically similar to those of the associated non-invasive tumour. One or more foci may be present; none should exceed 10 mm².

Synonyms
Serous tumour of low malignant potential with microinvasion, serous tumour of borderline malignancy with microinvasion.

Epidemiology
Present in about 10-15% of SBTs, microinvasion occurs in women ranging in age from 17-83 years with a median age of 34.5 years [203,2867].

Clinical features
Most symptomatic women present with a pelvic mass or pain. About 28% of the 39 women in the 2 major series were pregnant at the time of presentation [203,2867].

Macroscopy
The macroscopic features are similar to those of SBT without microinvasion.

Tumour spread and staging
At presentation about 60% of the neoplasms are stage IA, 13% stage IB, 5% stage IC, 8% stage IIC, 10% stage III (mostly IIIC) and 2.5% stage IV (liver metastases).

Histopathology
The hallmark of serous borderline tumours with microinvasion is the presence within the tumour stroma of single cells and cell clusters with generally abundant eosinophilic cytoplasm morphologically identical to those of the adjacent non-invasive tumour. The microinvasive foci form micropapillary, solid or rarely cribriform arrangements without or with only minimal stromal or cellular reaction. These cells are often

Table 2.01
Histological criteria for the diagnosis of serous borderline tumours.

- Epithelial hyperplasia in the form of stratification, tufting, cribriform and micropapillary arrangements
- Atypia (usually mild to moderate)
- Detached cell clusters
- Variable and usually minimal mitotic activity
- Absence of destructive stromal invasion

Fig. 2.05 Serous borderline tumour. The sectioned surface shows a solid and cystic neoplasm with numerous papillary excrescences.
Surface epithelial-stromal tumours located within empty stromal spaces, but vascular space invasion occurs in 10% of cases. In 87% of the 39 reported cases the invasive cells were of the eosinophilic cell type [203,2867]. The lymph nodes were rarely assessed as part of staging for these tumours. Tumour cells, mainly of the eosinophilic cell type, were found in three nodes (obturator, external iliac, and para-aortic) from two women [203,2867].

Prognosis and predictive factors
The behaviour of SBTs with microinvasion is similar to that of SBTs without microinvasion. In one series long-term follow-up was available in 11 cases with a 5-year survival of 100% and a 10-year survival of 86% [2285]. Unilateral salpingo-oophorectomy is currently acceptable therapy for young women who wish to preserve fertility.

Serous borderline tumour
Definition
An ovarian tumour of low malignant potential exhibiting an atypical epithelial proliferation of serous type cells greater than that seen in their benign counterparts but without destructive stromal invasion.

Synonyms
Serous tumour of low malignant potential, serous tumour of borderline malignancy. The designation “atypical proliferative serous tumour” is not recommended because it discourages complete surgical staging [2285] and because long term follow up indicates that some patients with typical SBT do not follow a benign course [3946].

Epidemiology
Patients with SBT are approximately 10-15 years younger than those with serous carcinoma (i.e. 45 years vs. 60 years). About 30-50% of SBTs are bilateral.

Clinical features
Signs and symptoms
The tumour is often asymptomatic but may rarely present with abdominal enlargement or pain due to rupture of a cystic tumour or torsion. In younger women SBT has been associated with a high rate of infertility [2894a].

Macroscopy
The tumour may be cystic with a variable number of excrescences, form a solid purely surface papillary growth or have a combination of these appearances. In
contrast to carcinomas, SBTs generally lack areas of necrosis and haemorrhage. The cysts usually contain serous fluid, but occasionally it is mucinous.

**Tumour spread and staging**
Stage I SBTs are confined to the inner surface of the cyst with no spread beyond the ovary. The staging of SBT follows the TNM/FIGO system for carcinomas (51, 2976).

**Histopathology**
The hallmarks of SBT that distinguish it from a cystadenoma are the presence of epithelial hyperplasia forming papillae (with fibrodermatous stalks), micropapillae associated with “detached” or “floating” cell clusters and mild to moderate nuclear atypia. It is distinguished from serous carcinoma by the lack of destructive stromal invasion. The proliferating cells vary from uniform, small cells with hyperchromatic nuclei to larger cells displaying eosinophilic cytoplasm with variable and generally low mitotic activity. Psammoma bodies may be present but are less abundant than in serous carcinomas. SBTs are divided into typical and micropapillary types. The typical type makes up the vast majority (90%) of SBTs and has a classic branching papillary architecture and epithelial tufts overlying the papillae. The micropapillary type accounts for a small proportion (5-10%) of tumours. This type shows focal or diffuse proliferation of the tumour cells in elongated, thin micropapillae with little or no stromal support emerging directly from the lining of a cyst, from large papillae in a non-hierarchical pattern or from the surface of the ovary. The micropapillae are at least five times as wide as they are long, arising directly from papillae with a thick fibrous stalk (non-hierarchical branching creating a “Medusa head-like appearance”). Less common patterns are cribriform and almost solid proliferations of non-invasive cells overlying papillary stalks. A continuous 5-mm growth of any of these three patterns is required for the diagnosis of micropapillary SBT.

Up to 30% of SBTs are associated with tumour on the outer surface of the ovary, and about two-thirds are associated with peritoneal implants (376,2615).

**Serous surface borderline tumour**
In this variant, polypoid excrescences formed by fine papillae with features of SBT occupy the outer surface of the ovary. Serous surface borderline adenofibroma and cystadenofibroma
In this variant, the epithelial lining of the glands and/or cysts of the adenofibroma or cystadenofibroma has the features of SBT instead of benign epithelium.

**Peritoneal implants**
Two prognostically different types of peritoneal implants have been identified, non-invasive and invasive. The former is further subdivided into desmoplastic and epithelial types. Whereas the non-invasive implants (regardless of their type) have almost no negative influence on the
implants are heterogeneous, and various involved by SBT in about 20% of cases; show the typical appearance of tubal the pathologist must assess multiple samples of macroscopically "normal" appearing omentum to ascertain adequate sampling. Invasive implants should be distinguished from benign epithelial inclusions and foci of endosalpingiosis. The latter are uncommon, occurring between a fifth and a tenth as often as implants [207]. Benign epithelial inclusions are characterized by small, generally round glands lined by a single layer of flat to low columnar cells without atypia or mitotic activity, often associated with a fibrous stroma. Small rounded glands also characterize endosalpingiosis, but the latter may be papillary and the lining cells show the typical appearance of tubal epithelium (ciliated, secretory and intercalated cells).

Lymph node involvement
Pelvic and para-aortic lymph nodes are involved by SBT in about 20% of cases; this finding appears to be without clinical significance. These lesions may be true metastases in peripheral sinuses, mesothelial cells in sinuses misinterpreted as tumour cells or independent primary SBTs arising in nullian inclusion glands that are present in 25-30% of pelvic and para-aortic lymph nodes.

Somatic genetics
The pattern of genetic alterations described in SBTs (for review see [1159]) differs from that of invasive carcinomas, e.g. TP53 mutations are most often absent in typical [838,1408] and micropapillary SBTs [1408], but are present in up to 88% of cases of invasive serous carcinoma. Loss of heterozygosity on the long arm of the inactivated X chromosome (464) is characteristic for SBT and rare in carcinomas (for review see [838]). Chromosomal imbalances have been identified in 3 of 9 SBTs, 4 of 10 micropapillary SBTs and 9 of 11 serous carcinomas by comparative genomic hybridization; some changes in micropapillary SBT are shared with SBT and others with serous carcinomas only suggesting a relationship among them [2771]. The genetic profile indicates that SBTs are a separate category with little capacity to transform into a malignant phenotype. The situation concerning micropapillary SBTs has to be clarified.

Prognosis and predictive factors

Clinical criteria
Stage 1 SBTs do not progress and have an indolent clinical course with a 5-year survival rate of up to 99% [1542] and a 10-year survival which is not much worse. In stage III SBTs, i.e. distributed throughout the abdominal cavity with peritoneal implants (for details see below), the 5-year survival rate ranges between 55-75%, and the probability of a 10-year survival is not significantly worse.

Histopathological criteria
Compared to typical SBTs, it has been suggested that micropapillary SBTs have a higher frequency of bilaterality (59-71% vs. 25-30%) (754,2727), an increased risk of recurrence among higher stage lesions (2727), more frequent ovarian surface involvement (50-65% vs. 36%) and probably a higher frequency of advanced stage at presentation (48-66% vs. 32-35%) at least among referral cases [376,754]. Several reports based on large series of cases, however, have demonstrated no difference in survival among patients with typical SBT and those with a micropapillary pattern among specific stages (658, 754,1000,1412,2285,2727), indicating a need for further investigation of the significance of the micropapillary pattern. In addition to its indolent course, micropapillary SBT differs from conventional serous carcinoma by its lack of responsiveness to platinum-based chemotherapy [210].

Cytophotometric predictive factors
The most reliable approach is the application of DNA-cytophotometry (preferably the static variant) according to the guidelines of the 1997 ESACP consensus report [1011,1141]. About 95% of SBTs display a diploid DNA-histogram with only a few cells in the 4c region indicating their low proliferative activity and only minor genetic alterations associated with an excellent clinical outcome [1380]. On the other hand, aneuploid SBTs characterized by a stemline deviation have a high recurrence rate, and the patients die frequently of their disease. For peritoneal implants DNA-cytophotometry is also of prognostic importance because aneuploid implants were found
Tumours of the ovary and peritoneum to be associated with a poor prognosis (652,2145). Although rare, transformation of a SBT into a bona fide frankly invasive carcinoma may occur.

Benign serous tumours

Definition
Benign tumours composed of epithelium resembling that of the fallopian tube or in some cases the surface epithelium of the ovary.

Epidemiology
Benign serous tumours account for approximately 16% of all ovarian epithelial neoplasms. The majority of benign serous tumours arise in adults in the fourth to sixth decades, although they may occur in patients younger than twenty or older than eighty years.

Localization
Benign serous tumours arise preferentially in the cortex of the ovary or on its surface (8%). They are usually bilateral, especially in older women. Often the tumours are metachronous with intervals that range from three to fourteen years.

Clinical features

Signs and symptoms
The most common symptoms are pain, vaginal bleeding and abdominal enlargement, but usually the tumour is asymptomatic and discovered incidentally during ultrasound investigation of another gynaecological disorder.

Macroscopy
Benign serous tumours are usually 1-10 cm in diameter but occasionally reach up to 30 cm or more. They are typically unilocular or multilocular cystic lesions, the external surface is smooth, and the inner surface may contain small papillary projections. The cyst contents are watery and very rarely opaque or bloody. Adenofibromas are solid and have a spongy sectioned surface with minute, colourless fluid-containing cysts. Cystadenofibromas contain both solid areas and cysts. Surface papillomas appear as warty excrescences of different sizes on the surface of the ovary.

Histopathology
Benign serous tumours typically are lined by an epithelium similar to that of the fallopian tube with ciliated and less frequently nonciliated secretory cells. Of special diagnostic interest are the cysts with flattened lining, some of which may represent benign serous neoplasms with a desquamated lining. The only effective method to establish their nature is the application of scanning electron microscopy, which easily detects the ciliated cells, allowing a definitive diagnosis to be made.

Histogenesis
Benign serous tumours result from the proliferation of the surface epithelium of the ovary, producing surface papillary excrescences or invaginating into the cortex of the ovary, forming so-called inclusion cysts. Some morphological data support the possibility that a number of benign serous tumours arise from remnants in the hilar region of the ovary, possibly from rete cysts (726,1403,1823).

Prognosis and predictive factors
Serous cystadenomas are benign.

Mucinous tumours

Definition
Ovarian tumours some or all of whose epithelial cells contain intracytoplasmic mucin. They may resemble those of the endocervix, gastric pylorus or intestine.

ICD-O codes
- Mucinous adenocarcinoma 8480/3
- Mucinous cystadenocarcinofibroma 9015/3
- Mucinous borderline tumour 8472/1
- Mucinous cystadenoma 8470/0
- Mucinous adenofibroma 9015/0

Mucinous adenocarcinoma and related tumours

Definition
A malignant epithelial tumour of the ovary that in its better differentiated areas resembles intestinal or endocervical epithelium. Ovarian mucinous adenocarcinomas differ from borderline tumours by having evidence of ovarian stromal invasion.

Macroscopy
Mucinous carcinomas are usually large, unilateral, smooth surfaced, multilocular or unilocular cystic masses containing watery or viscous mucoid material. They are bilateral in approximately 5% of cases. Haemorrhagic, necrotic, solid or papillary areas are relatively frequent, and some tumours may be predominantly solid (1613,2605). Because areas of malignancy may be limited, generous sampling of all mucinous cystic tumours to include up to one histological section per 1-2 cm of tumour diameter with sam-
pling of all macroscopically suspicious areas has been recommended.

**Histopathology**

In the absence of obvious infiltration of the stroma, invasion is assumed if there are complex papillary areas or back-to-back glands lined by malignant-appearing cells with little or no discernible intervening stroma. To qualify as frankly invasive, such areas should be at least 10 mm² and at least 3 mm in each of 2 linear dimensions [1613]. Alternatively, invasion may be in the form of infiltrative glands, tubules, cords or cell nests. The stroma may resemble ovarian stroma or be desmoplastic. In most cases there are also areas that are benign or borderline in appearance (1147,1150,1228,2047,2401). Rarely, mucinous tumours contain areas of mucinous adenofibroma with malignant epithelial cells and foci of stromal invasion.

**Differential diagnosis**

The most important differential diagnosis of mucinous ovarian carcinoma is with metastatic mucinous carcinoma that may present clinically as a primary ovarian tumour. Most of these originate in the large intestine, appendix, pancreas, or cervix [237,639,1587,1703,2377,2406,3200]. Since this problem has been emphasized relatively recently, it is likely that early reports of the histological appearance and behaviour of ovarian mucinous carcinomas have been contaminated by metastatic carcinomas masquerading as primary ovarian neoplasms (see Table 2.03). Common features that favour a primary mucinous carcinoma are an expansile pattern of invasion and a complex papillary pattern [1614]. Common features favouring a metastatic mucinous carcinoma are bilaterality, a multinodular growth pattern microscopically, histological surface involvement by epithelial cells (surface implants) and vascular space invasion [1614].

**Histopathological criteria**

With the exception of one recent series [3769], grading of mucinous carcinomas has not been shown to be predictive of behaviour or response to therapy independent of the surgical stage [1076,1228,1458,1613,2377,3069]. Infiltrative stromal invasion proved to be biologically more aggressive than expansile invasion. If individual invasive foci are all less than 10 mm², they have been termed “microinvasive,” and cases with this finding have had a favourable outcome [1453,1613,1967,2047,2401,2713].

**Mucinous borderline tumour, intestinal type**

**Definition**

Ovarian tumours of low malignant potential exhibiting an epithelial proliferation of mucinous type cells greater than that seen in their benign counterparts but without evidence of stromal invasion. The epithelial component resembles intestinal epithelium, almost always contains goblet cells, usually contains neuroendocrine cells and rarely contains Paneth cells.

**Synonyms**

Mucinous tumour of low malignant potential, intestinal type; mucinous tumour of borderline malignancy, intestinal type.

**Epidemiology**

These account for 85-90% of mucinous borderline tumours.

**Macroscopy**

Mucinous borderline tumours of intestinal type are bilateral in approximately 5% of cases and usually are large, multilocular or unicellular cystic masses containing watery or viscous mucoid material.
Velvety excrescences may line the cysts. Haemorrhagic, necrotic, solid or papillary areas are occasionally present. Histopathology

Areas resembling mucinous cystadenoma are common. In the borderline areas the cells lining the cysts are stratified (usually to no more than 3 layers) and may form filiform intracystic papillae with at least minimal stromal support. Nuclei are slightly larger with more mitotic figures than in cystadenomas. Goblet cells and sometimes Paneth cells are present. The overall appearance resembles a hyperplastic or adenomatous colonic polyp (322, 653, 1076, 1147, 1150, 1613, 2377, 2491, 2605, 2713). Some or most of the epithelial cells lining the cysts of intestinal type borderline tumours may appear cytologically malignant and may be stratified to four or more layers in a solid, papillary or cribriform pattern. Whether tumours with such foci should be classified as non-invasive carcinomas or as borderline tumours has been a subject of controversy for many years. To provide for uniformity in reporting, it has been recommended that they be classified as borderline with intraepithelial carcinoma (2605).

Prognosis and predictive factors

When the tumour is confined to the ovaries at initial staging, the prognosis is excellent with only rarely reported recurrences (1150). It is likely that most tumours diagnosed as intestinal-type mucinous borderline tumour that are associated with pseudomyxoma peritonei are actually metastatic from a similar-appearing tumour in the appendix (see section on pseudomyxoma peritonei). In the remaining cases with advanced disease, the metastases are usually in the form of invasive pelvic or abdominal implants rather than pseudomyxoma peritonei. In these cases the prognosis is similar to that of ovarian mucinous carcinomas with metastases, and it is likely that areas of invasion within the ovarian tumour were not sampled (1076, 1147, 1150, 1613, 2401). Table 2.04 summarizes the differences in appearance and outcome among neoplasms having the appearance of mucinous borderline tumours.

Mucinous borderline tumour, endocervical-like

Definition

Ovarian tumours of low malignant potential exhibiting an epithelial proliferation of mucinous type cells greater than seen in their benign counterparts but without destructive stromal invasion. The mucinous epithelial cells resemble endocervical epithelium.

Synonyms

Mucinous tumour of low malignant potential, endocervical-like; mucinous tumour of borderline malignancy, endocervical-like; müllerian mucinous borderline tumour.

Epidemiology

These tumours make up 10-15% of mucinous borderline tumours (1613, 2497, 2713).
Histopathology
They differ from intestinal-type borderline tumours in that the intracystic growth is composed of broad bulbous papillae similar to those of serous borderline tumours. The epithelial cells lining the papillae are columnar mucinous cells and rounded cells with eosinophilic cytoplasm; the latter are often markedly stratified with detached cell clusters. The nuclei are only slightly atypical. Characteristically, there are many acute inflammatory cells within the papillae or free-floating in extracellular spaces.

Precursor lesions
Endocervical-like borderline tumours likely arise from endometriosis [2494]. At least in some cases the peritoneal implants may arise from independent foci of endometriosis with in situ transformation.

Prognosis and predictive features
Endocervical-like borderline tumours may be associated with abdominal or pelvic implants, some of which may appear invasive, but the clinical behaviour has been indolent in the relatively few cases that have been reported [2497,2713]. However, more cases in this category need to be studied.

Benign mucinous tumours

Definition
Benign mucinous tumours composed of epithelium resembling endocervical or gastrointestinal epithelium. The latter almost always contains goblet cells, usually contains neuroendocrine cells and rarely contains Paneth cells.

Macroscopy
Benign cystadenomas are usually large, unilateral, multicocular or unicocular cystic masses containing watery or viscous mucoid material. Cystadenofibromas and adenofibromas are partially to almost completely solid with only small cysts [200].

Histopathology
Benign mucinous tumours consist of cystadenomas, cystadenofibromas and adenofibromas These contain glands and cysts lined by mucinous columnar epithelium [2605]. Cellular stratification is minimal, and nuclei are basally located with only slight, if any, atypia. Cystadenomas may have mucin extravasation with or without a stromal reaction. An ipsilateral dermoid cyst is present in 3-5% of cases. The uncommon mucinous adenofibroma is composed predominantly of fibromatous stroma [200].

Mucinous cystic tumours with mural nodules

Rare mucinous cystic tumours contain one or more solid mural nodules in which the histological features differ markedly from the background of either an intestinal-type borderline tumour or carcinoma [2007,2288,2290,2605]. The nodules are yellow, pink or red with areas of haemorrhage or necrosis and range up to 12 cm in size. They may be malignant (anaplastic carcinoma, sarcoma or carcinosarcoma) or benign (sarcoma-like). Mucinous cystic tumours containing more than 1 type of mural nodule as well as mixed nodules have been described. Anaplastic carcinosomatous nodules usually contain a predominant population of cytokeratin-positive, large, rounded or spindle-shaped cells with abundant eosinophilic cytoplasm and high grade malignant nuclei. The few sarcomas that have been reported have been fibrosarcomas or rhabdomyosarcomas or have not been otherwise classified. Sarcoma-like nodules are sharply circumscribed and without vascular invasion but otherwise may appear alarming, containing pleomorphic cells with bizarre nuclei and many mitotic figures, often accompanied by spindle-shaped cells, epulis-type giant cells, acute and chronic inflammatory cells and foci of haemorrhage and necrosis. The sarcoma-like cells may be weakly or focally cytokeratin-positive, but this finding, in itself, does not indicate a carcinomatous component [2605]. The distinction is important because patients with anaplastic carcinoma in a mural nodule may follow a malignant course [2290], whereas the outcome of
those with only sarcoma-like nodules is the same as the corresponding category of mucinous tumour without the nodules [163]. Although the foci of anaplastic carcinoma are found more often in advanced stage tumours, it is now apparent that when they are confined to intact stage IA tumours, they are not necessarily associated with an adverse outcome [2401].

**Mucinous cystic tumours associated with pseudomyxoma peritonei**

Since there is strong evidence that ovarian mucinous tumours associated with pseudomyxoma peritonei (PP) are almost all metastatic rather than primary, it is important that such tumours are not diagnosed as stage II or III mucinous borderline tumours or carcinomas without first excluding an appendiceal or other gastrointestinal primary. Present evidence suggests that almost all genuine ovarian mucinous borderline tumours are stage 1. The number of stage 2 and 3 tumours in this category has been greatly exaggerated by including cases in which PP is associated with an undetected primary tumour in the appendix. Also, there is probably an unwarranted apparent increase in the number of high stage ovarian mucinous carcinomas because of undetected primary intestinal mucinous carcinomas associated with the clinical syndrome of PP. Pseudomyxoma peritonei is a clinical term used to describe the finding of abundant mucoid or gelatinous material in the pelvis and abdominal cavity surrounded by fibrous tissue. The mucus may be acellular or may contain mucinous epithelial cells. Mucinous ascites, the presence of free-floating mucinous fluid, in the peritoneal cavity, almost never leads to pseudomyxoma peritonei. Areas of pseudomyxoma peritonei should be thoroughly sampled and examined histologically. The degree of atypia (benign, borderline or malignant) of any epithelial cells that are present should be reported, as well as whether the mucin dissects into tissues with a fibrous response or is merely on the surface. Pseudomyxoma peritonei with epithelial cells that are benign or borderline-appearing has been termed "disseminated peritoneal adenomucinosis" by some authors [2409], and patients with this finding have had a benign or protracted clinical course. In cases where the epithelial cells of the pseudomyxoma peritonei appear malignant, termed "peritoneal mucinous carcinomatosis" [2409], the source has usually been the appendix or colon, and the clinical course has usually been fatal. Pseudomyxoma peritonei may be present in women without a cystic ovarian tumour or in men. In such cases the source is almost always a gastrointestinal mucinous neoplasm, most commonly from the appendix [2409]. In cases where there is an appendiceal tumour and a mucinous cystic ovarian tumour,
the origin of the pseudomyxoma peritonei has been disputed. A majority of investigators believe that the ovarian tumour(s) are secondary in almost all such cases [2294,2407,3199]. However, a synchronous origin in both organs has also been proposed [2623]. Clonality studies have demonstrated identical KRAS mutations or the lack of them in both the appendiceal and the simultaneous ovarian tumours [590, 2830]. LOH analysis has shown similar findings in three cases and divergent findings in three; this latter observation appears to indicate that some simultaneous tumours are independent primaries [590], though genetic progression of the metastatic tumours could also account for the disparity of these results. The ovarian tumours are usually classified as either mucinous cystadenomas or intestinal-type borderline tumours. The epithelial cells within them are often found floating in mucin that dissect into the ovarian stroma (pseudomyxoma ovarii). They are well differentiated and often have a tall columnar appearance with abundant mucinous cytoplasm that is positive for cytokeratin 7 in approximately one-half of the cases [1075, 2408]. The latter finding differs from that of primary ovarian mucinous cystadeno-ma or intestinal-type borderline tumours most of which are cytokeratin 7-positive. The appendiceal tumour may be quite small relative to the ovarian tumour(s) and may not be appreciated macroscopically. Thus, removal and thorough histological examination of the appendix is indicated in cases of pseudomyxoma peritonei with a mucinous cystic ovarian tumour. In cases where an appendiceal mucinous neoplasm is found, it should be considered as the primary site and the ovaries as secondary. If the appendix has not been examined histologically and the ovaries are bilateral, or unilateral in the absence of an ipsilateral dermoid cyst, the appendix should also be considered primary. If an appendiceal mucinous neoplasm is not found after thorough histological examination, the appendix has been removed previously in the absence of pseudomyxoma peritonei or if the ovarian tumour is accompanied by a dermoid cyst in the absence of either a macroscopic or histological appendiceal lesion, the ovarian tumour may be considered to be the source of the pseudomyxoma peritonei [1613]. In equivocal cases cytokeratin 7 negativity in the ovarian tumour strongly suggests that it is metastatic.

**Table 2.04**

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Macroscopy</th>
<th>Histopathology</th>
<th>Appearance of extraovarian disease</th>
<th>Usual behaviour in cases with extraovarian disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal type MBT</td>
<td>Large, smooth surfaced multilocular cyst, bilateral in 5%</td>
<td>Cysts lined with slightly stratified intestinal type cells with mild nuclear atypia and no detached cell clusters Usually CK7 positive</td>
<td>Invasive peritoneal implants without PP This is a rare finding</td>
<td>Prognosis is poor. Cases with invasive implants are likely due to unsampled invasive areas in the ovarian tumour.</td>
</tr>
<tr>
<td>Intestinal type MBT with intraepithelial carcinoma</td>
<td>Same</td>
<td>Same, with foci of malignant-appearing nuclei and often highly stratified, solid or cribriform areas</td>
<td>Invasive peritoneal implants without PP</td>
<td>Same as above</td>
</tr>
<tr>
<td>Endocervical-like MBT</td>
<td>Smaller with fewer cysts and may be associated with endometriosis, bilateral in 40%</td>
<td>Cysts composed of complex, bulbous papillae with highly stratified, benign-appearing mucinous and eosinophilic cells, detached cell clusters and numerous neutrophils</td>
<td>Invasive or noninvasive peritoneal implants</td>
<td>Benign</td>
</tr>
<tr>
<td>Mucinous ovarian tumours associated with PP</td>
<td>Bilateral in a high percentage of cases</td>
<td>Usually resembles intestinal type of MBT often with pseudomyxoma ovarii</td>
<td>PP Often primary appendiceal tumour</td>
<td>Variable, depending on the degree of atypia of the tumour cells in PP</td>
</tr>
</tbody>
</table>

**PP = Pseudomyxoma peritonei; MBT = mucinous borderline tumour**
Endometrioid tumours

Definition
Tumours of the ovary, benign, low malignant potential or malignant, that closely resemble the various types of endometrioid tumours (epithelial and/or stromal) of the uterine corpus. Although an origin from endometriosis can be demonstrated in some cases, it is not required for the diagnosis.

ICD-O codes
- Endometrioid adenocarcinoma, not otherwise specified 8380/3
- Variant with squamous differentiation 8570/3
- Ciliated variant 8383/3
- Oxyphilic variant 8290/3
- Secretory variant 8382/3
- Adenocarcinofibroma 8381/3
- Malignant müllerian mixed tumour 8950/3
- Adenosarcoma 8933/3
- Endometrioid stromal sarcoma 8930/3
- Endometrioid borderline tumour 8380/1
- Cystadenoma 8380/0
- Adenofibroma; cystadenofibroma 8381/0

Endometrioid adenocarcinoma

Definition
A malignant epithelial tumour of the ovary that closely resembles the common variant of endometrioid carcinoma of the uterine corpus. Although an origin from endometriosis can be demonstrated in some cases, it is not required for the diagnosis.

Epidemiology
Endometrioid carcinomas account for 10-20% of ovarian carcinomas (1409, 2489) and occur most commonly in women in the fifth and sixth decades of life (2773).

Aetiology
Up to 42% of the tumours are associated with endometriosis in the same ovary or elsewhere in the pelvis (676,932,1927, 2489,2287a) and 15-20% are associated with endometrial carcinoma (1477,1479, 1683,3239). These associations suggest that some endometrioid ovarian carcinomas may have the same risk factors for their development as endometrial carcinomas (613). Patients whose tumours occur in association with endometriosis are 5-10 years younger on average than patients without associated ovarian endometriosis (2800).

Clinical features
Like most ovarian carcinomas, many endometrioid carcinomas are asymptomatic. Some present as a pelvic mass, with or without pain and may be associated with endocrine symptoms secondary to steroid hormone secretion by the specialized ovarian stroma (1790). Serum CA125 is elevated in over 80% of the cases (946,1603).

Macroscopy
The tumours, typically measuring 10-20 cm in diameter, are solid, soft, friable or cystic with a fungating mass protruding into the lumen. They are bilateral in 28% of the cases.

Tumour spread and staging
Stage I carcinomas are bilateral in 17% of the cases (2233). The stage distribution of endometrioid carcinomas differs from that of serous carcinomas. According to the FIGO annual report, 31% of the tumours are stage I; 20%, stage II; 38%, stage III; and 11%, stage IV (2233).

Histopathology
Ovarian endometrioid carcinomas closely resemble endometrioid carcinomas of the uterine corpus. The well differentiated form shows round, oval or tubular glands lined by stratified nonmucin-containing epithelium. Cribriform or villoglandular patterns may be present. Squamous differentiation occurs in 30-50% of the cases, often in the form of morules (cytologically benign-appearing squamous cells) (341,2605). The designation “endometrioid carcinoma with squamous differentiation” (rather than adenocarcinoma and adenosquamous carcinoma) is favoured (2604,2605). Aggregates of spindle-shaped epithelial cells are an occasional finding in endometrioid carcinoma (2942). Occasionally, the spindle cell nests undergo a transition to clearly recognizable squamous cells suggesting that the former may represent abortive squamous differentiation (2605). Rare examples of mucin-rich, secretory, ciliated cell and oxyphilic types have been described (759,1187,2258). In the mucin-rich variant glandular lumens and the apex of cells are occupied by mucin (2605). The secretory type contains vacuolated cells resembling those of an
early secretory endometrium [2605]. The oxyphilic variant has a prominent component of large polygonal tumour cells with abundant eosinophilic cytoplasm and round central nuclei with prominent nucleoli [2258]. Occasional tumours contain solid areas punctuated by tubular or round glands or small rosette-like glands (microglandular pattern) simulating an adult granulosa cell tumour [3206]. In contrast to Call-Exner bodies, however, the microglands contain intraluminal mucin. The nuclei of endometrioid carcinomas are usually round and hyperchromatic, whereas those of granulosa cell tumours are round, oval, angular, pale, and grooved. Rare cases of endometrioid carcinomas of the ovary show focal to extensive areas resembling Sertoli and Sertoli-Leydig cell tumours [2111,2466,3206]. They contain small, well differentiated hollow tubules, solid tubules or, rarely, thin cords resembling sex cords. When the stroma is luteinized, this variant may be mistaken for a Sertoli-Leydig cell tumour, particularly in cases in which the patient is virilized. Nevertheless, typical glands of endometrioid carcinoma and squamous differentiation are each present in 75% of the tumours, facilitating their recognition as an endometrioid carcinoma [3206]. Furthermore, immunostains for alpha-inhibin are positive in Sertoli cells but negative in the cells of endometrioid carcinoma [1789].

Grading
Grading of endometrioid carcinoma uses the same criteria as endometrial adenocarcinoma [3238] (see chapter 4).

Histogenesis
Most endometrioid carcinomas are thought to arise from surface epithelial inclusions, and up to 42% are accompanied by ipsilateral ovarian or pelvic endometriosis [676,932,1927,2489] that may display the entire spectrum of endometrial hyperplasia (simple, complex, typical and atypical). Atypical (ipsilateral) endometriosis occurs in up to 23% of endometrioid carcinomas [932] and may have a role in the evolution of some endometrioid carcinomas [2618].

Somatic genetics
Somatic mutations of beta-catenin (CTNNB1) and PTEN are the most common genetic abnormalities identified in sporadic endometrioid carcinomas. The incidence of CTNNB1 mutations ranges from 38-50% [1909,2153]. Mutations have been described in exon 3 (codons 32, 33, 37, and 41) and involve the phosphorylation sequence for glycogen synthase kinase 3β. These mutations probably render a fraction of cellular beta-catenin insensitive to APC-mediated down-regulation and are responsible for its accumulation in the nuclei of the tumour cells. Beta-catenin is immunohistochemically detectable in carcinoma cells in more than 80% of the cases. Endometrioid carcinomas with beta-catenin mutations are characteristically early stage tumours associated with a good prognosis [965]. PTEN is mutated in approximately 20% of endometrioid ovarian tumours and in 46% of those with 10q23 loss of heterozygosity (LOH) [2075]. PTEN mutations occur between exons 3 to 8. The majority of endometrioid carcinomas with PTEN mutations are well differentiated and stage I tumours, suggesting that in this subset of ovarian tumours PTEN inactivation is an early event [2075]. The finding of 10q23 LOH and PTEN mutations in endometriotic cysts that are adenoid cent to endometrioid carcinomas with similar genetic alterations provides additional evidence for the precursor role of endometriosis in ovarian carcinogenesis [2543].

Microsatellite instability (MI) also occurs in sporadic endometrioid carcinomas of the ovary although less frequently than in uterine endometrioid carcinomas. The reported frequency of MI in the former tumours ranges from 12.5-19% [1055, 1909]. Like endometrial carcinomas, many ovarian carcinomas with MI follow the same process of MLH1 promoter methylation and frameshift mutations at coding mononucleotide repeat microsatellites [1055].

Simultaneous endometrioid carcinomas of the ovary and endometrium
Endometrioid carcinoma of the ovary is associated in 15-20% of the cases with carcinoma of the endometrium [767,822,1479,2651,3239]. The very good prognosis in those cases in which the tumour is

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**Fig. 2.30** Well differentiated endometrioid adenocarcinoma of the ovary. A. Confluent growth of glands is evident with replacement of stroma. B. Note the squamous differentiation in the form of squamous morules and keratin pearls.
limited to both organs provides strong evidence that these neoplasms are mostly independent primaries arising as a result of a müllerian field effect (822). Less frequently, one of the carcinomas represents a metastasis from the other tumour. The criteria for distinguishing metastatic from independent primary carcinomas rely mainly upon conventional clinical-pathologic findings, namely stage, size, histological type and grade of the tumours, the presence and extent of blood vessel, tubal and myometrial invasion, bilaterality and pattern of ovarian involvement, coexistence with endometrial hyperplasia or ovarian endometriosis and, ultimately, patient follow-up (762, 2286, 2978). By paying attention to these findings, the precise diagnosis can be established in most cases. Occasionally, however, the differential diagnosis may be difficult or impossible as the tumours may show overlapping features. In difficult cases comparative analysis of the immunohistochemical and DNA flow cytometric features of the two neoplasms may be of some help (822, 2286). The presence of identical aneuploid DNA indexes in two separate carcinomas suggests that one of them is a metastasis from the other (2286). In contrast, when the two neoplasms have different DNA indexes, the possibility of two independent primaries has to be considered (2286). The latter results, however, do not completely exclude the metastatic nature of one of the tumours, since metastatic tumours or even different parts of the same tumour may occasionally have different DNA indexes reflecting tumour progression (2728). Molecular pathology techniques can also be helpful (1788). These include LOH, (782, 923, 1664, 2641), gene mutation (923, 1664, 1909) and clonal X-inactivation analyses (926). Although LOH pattern concordance in two separate carcinomas is highly suggestive of a common clonal origin (i.e. one tumour is a metastasis from the other), the finding of different LOH patterns does not necessarily indicate that they represent independent tumours. Some studies have shown varying LOH patterns in different areas of the same tumour as a consequence of tumour heterogeneity (287). Discordant PTEN mutations and different microsatellite instability (MI) patterns in the two neoplasms are suggestive of independent primary carcinomas; nevertheless, metastatic carcinomas may also exhibit gene mutations that differ from those of their corresponding primary tumours as a result of tumour progression (923). Alternatively, two independent primary carcinomas may present identical gene mutations reflecting induction of the same genetic abnormalities by a common carcinogenic agent acting in two separate sites of a single anatomic region (1786, 1788). In other words, the genetic profile can be identical in independent tumours and different in metastatic carcinomas (1788). Therefore, clonality analysis is useful in the distinction of independent primary carcinomas from metastatic carcinomas provided the diagnosis does not rely exclusively on a single molecular result and the molecular data are interpreted in the light of appropriate clinical and pathologic findings (1786, 1788, 2283).

According to FIGO when the site of origin remains in doubt after pathological examination, the primary site of the tumour should be determined by its initial clinical manifestations.

Genetic susceptibility
Most endometrioid carcinomas occur sporadically, but occasional cases develop in families with germline mutations in DNA mismatch repair genes, mainly MSH2 and MLH1 (Muir-Torre syndrome) (535). This syndrome, thought to be a variant of the hereditary nonpolyposis colon cancer syndrome, is characterized by an inherited autosomal dominant susceptibility to develop cutaneous and visceral neoplasms (796).

Prognosis and predictive factors
The 5-year survival rate (FIGO) of patients with stage I carcinoma is 78%; stage II, 63%; stage III, 24%; and stage...
IV, 6% [2233]. Patients with grade 1 and 2 tumours have a higher survival rate than those with grade 3 tumours [1479]. Peritoneal foreign body granulomas to keratin found in cases of endometrioid carcinoma with squamous differentiation do not seem to affect the prognosis adversely in the absence of viable appearing tumour cells on the basis of a small series of cases [1459]. Endometrioid carcinomas with a mixed clear cell, serous or undifferentiated carcinoma component are reported to have a worse prognosis [2041].

**Malignant müllerian mixed tumour**

**Definition**
A highly aggressive neoplasm containing malignant epithelial and mesenchymal elements.

**Synonyms**
Carcinosarcoma, malignant mesodermal mixed tumour, metaplastic carcinoma.

**Epidemiology**
Malignant müllerian mixed tumours (MMMTs) are rare, representing less than 1% of ovarian malignancies. They occur most commonly in postmenopausal women of low parity, the median age being around 60.

**Clinical features**
The clinical presentation is similar to that of carcinoma of the ovary.

**Aetiology**
An increased incidence has been reported in women who have had pelvic irradiation [3080].

**Macroscopy**
The neoplasms form large (10-20 cm diameter), partly solid and partly cystic, or, less commonly, solid, grey-brown, unilateral or bilateral, bosselated masses with foci of haemorrhage and necrosis [479]. The sectioned surface is fleshy and friable, and cartilage and bone may be apparent. The tumours are bilateral in 90% of cases.

**Tumour spread and staging**
There is extraovarian spread to the pelvic peritoneum, omentum, pelvic organs and regional lymph nodes in more than 75% of cases at the time of diagnosis.

**Histopathology**
The histological and immunoprofile are similar to those of its uterine counterpart and those occurring elsewhere in the female genital system (see chapter 4).

**Histogenesis**
MMMT is believed to develop from the ovarian surface epithelium or from foci of endometriosis and, therefore, may be regarded as a high grade carcinoma with metaplastic sarcomatous elements. The positive tumour response to chemotherapy directed at ovarian carcinoma also supports this viewpoint.

**Somatic genetics**
There is evidence that MMMTs are monoclonal [26,2748] as the phenotypically different elements share similar allelic losses and retentions [925] and a cell line developed from an MMMT expresses both mesenchymal and epithelial antigens [195]. Furthermore, a heterogenous pattern of allelic loss at a limited number of chromosomal loci in either the carcinomatous or sarcomatous component of the neoplasm is consistent with either genetic progression or genetic diversion occurring during the clonal evolution of the tumour.

**Genetic susceptibility**
There is anecdotal evidence of *BRCA2* mutation [2748].

**Prognosis and predictive factors**
Improved cytoreductive surgery and platinum based chemotherapy has resulted in a median survival of 19 months [2715] and an overall 5-year survival of 18-27% [120,1182]. The survivors almost invariably have early stage disease at the time of diagnosis, and low stage is a statistically significant indicator of outcome [120,436,1182,2749]. No other histopathological factors are significant indicators of outcome.

**Adenosarcoma**

**Definition**
A biphasic tumour characterized by a proliferation of müllerian-type epithelium with a benign or occasionally markedly atypical appearance embedded in or
overlying a dominant sarcomatous mesenchyme.

Clinical features
Most of the tumours reported so far have been unilateral, occurring in the 4th and 5th decades. Abdominal discomfort and distension are the usual complaints.

Macroscopy and histopathology
The tumour is frequently adherent to the surrounding tissue (512,604,929). The macroscopic and histological features are described in detail in the uterine counterpart (see chapter 4).

Prognosis and predictive factors
Occasional reports have linked the spread of adenosarcomas into the abdominal cavity with a poor clinical outcome (510). Age greater than 53 years, tumour rupture, high grade and the presence of high grade sarcomatous overgrowth appear to be associated with recurrence or extraovarian spread. Ovarian adenosarcoma has a worse prognosis than its uterine counterpart, presumably because of the greater ease of peritoneal spread (760). Unfortunately, there exist no established morphological criteria to predict such biological behaviour. However, if during the course of the disease sarcomatous overgrowth develops, signifying invasive potential, the patient requires careful monitoring. In a series of 40 cases, the 5-year survival was 64%, the 10-year survival 46% and the 15-year survival 30% (760). Age greater than 53 years, tumour rupture, high grade and the presence of high grade sarcomatous overgrowth appear to be associated with recurrence or extraovarian spread. Ovarian adenosarcoma has a worse prognosis than its uterine counterpart, presumably because of the greater ease of peritoneal spread (760). Therapeutically, an aggressive surgical approach with wide excision is most often recommended (510). Chemotherapy and radiation may be applied in individual cases; however, no established protocols exist.

Endometrioid stromal and undifferentiated ovarian sarcoma

Definition
Endometrioid stromal sarcoma (ESS) is a monophasic sarcomatous tumour characterized by a diffuse proliferation of neoplastic cells similar to stromal cells of proliferative endometrium. At its periphery the tumour exhibits a typical infiltrative growth pattern. Those neoplasms that have moderate to marked pleomorphism, significant nuclear anaplasia and more cytoplasm than is found in endometrial stromal cells should be classified as undifferentiated ovarian sarcoma.

Clinical features
More than 70% of the tumours are unilateral. The age range is 11-76 years with the majority of tumours occurring around the 5th and 6th decade. The clinical symptoms do not differ from those recognized for other ovarian tumours.

Macroscopy
Most tumours are solid and firm, but some may show variably sized cysts, sometimes filled with mucoid or haemorrhagic fluid or debris. The sectioned surface appears yellow-white or tan, sometimes interspersed with grey fibrous bundles or septa.

Histopathology
Roughly half of the cases of ESS are associated with either endometriosis or a similar sarcomatous lesion of the endometrial stroma or both (2605). The dominant cell type of ESS consists of small, round to oval, or occasionally spindle shaped cells with round nuclei and scanty, sometimes barely visible pale cytoplasm. The cells may be arranged haphazardly in a diffuse pattern or may form parallel cell sheets mimicking fibro-ma. Hypocellular areas with a distinct oedematous appearance can be present. Lipid droplets may be present within tumour cells, which are often associated with foam cells. A hallmark of ESS is the presence of abundant small thick-walled vessels resembling spiral arteries of the late secretory endometrium. The vessels often are surrounded by whorls of neoplastic cells. Reticulin stain discloses delicate fibrils characteristically enveloping individual tumour cells. The cellularity can vary markedly within the same specimen. The tumour can be partly intersected by fibrous bands forming more or less distinct nodules. Sometimes, hyaline plaques are present. Rarely, cord-like or plexiform arrangements of tumour cells similar to the growth patterns seen in ovarian sex cord tumours such as granulosa cell tumours or thecomas are observed. In these areas reticulin fibrils are more or less absent. Rarely, glandular elements are interspersed, but they never represent a dominant feature. At its periphery the tumour exhibits a typical infiltrative growth pattern. In cases where the tumour has spread into extraovarian sites, a tongue-like pattern of invasion
into the adjacent tissue and intravascular growth appears. Most neoplasms are low grade, whereas approximately 10% of cases are high grade and are classified as undifferentiated ovarian sarcoma. In the past, tumours with less than 10 mitoses per 10 high power fields were classified as low grade ESS, whereas tumours with more than 10 mitoses per 10 high power fields were traditionally designated high grade (3208). However, there is no evidence that mitotic rate alone alters the outcome, and all tumours with an appearance resembling that of endometrial stroma should be designated endometrioid stromal sarcoma (438), whereas those that lack endometrial stromal differentiation should be diagnosed as undifferentiated ovarian sarcoma. The latter is a high grade neoplasm that is composed of pleomorphic mesenchymal cells with distinct variability in size and shape. The nuclei are highly atypical with prominent nucleoli and occasionally resemble rhabdomyosarcoma or fibrosarcoma.

Immunoprofile
Immunostaining demonstrates the expression of vimentin and CD10 in ESS. Muscle-associated proteins are only focally expressed. Alpha-inhibin was negative in all cases examined (1681).

Differential diagnosis
ESS must be differentiated from other ovarian lesions, including some small cell tumours. The major problem is to distinguish ESS from adult granulosa cell-tumour, foci of stromal hyperplasia, ovarian fibroma or ovarian thecoma.

On morphological grounds alone, it is not always possible to decide whether the ovarian lesion is a primary ESS of the ovary or a metastatic lesion from a uterine ESS. Thus, an ovarian ESS should never be diagnosed unless the uterus is carefully examined to exclude a uterine primary. Should ESS be found in both organs, it is more or less impossible to decide which tumour is the primary and which is metastatic. One criterion that establishes a primary site in the ovary is its continuity with endometriotic foci in the ovary.

Somatic genetics
Mutation of the TP53 tumour suppressor gene associated with overexpression of TP53 protein has been frequently observed in ovarian sarcomas. These mutations may occur on the basis of an impaired DNA repair system in these tumours (1681).

Prognosis and predictive factors
Since over one-half of the ESSs have already spread to pelvic or upper abdominal sites at the time of diagnosis, the tumour stage remains the major prognostic criterion (438). Whether the neoplasm is an ESS or undifferentiated ovarian sarcoma also influences the clinical course (3208). ESS often has a favourable outcome with survival in excess of 5 years even in the context of extraovarian spread. After 10 years, however, the tumour-related mortality increases, particularly if extraovarian manifestations were noted at the time of diagnosis. Tumour relapse represents an ominous prognostic sign. Undifferentiated ovarian sarcomas have a rapid course and a poor prognosis (3208). Radical panhysterectomy is the recommended therapy. Successful treatment with progesterone, non-hormonal cytotoxic drugs or radiation has been reported occasionally in ESS.

Endometrioid borderline tumour
Definition
An ovarian tumour of low malignant potential composed of atypical or histologically malignant endometrioid type glands or cysts often set in a dense fibrous stroma with an absence of stromal invasion.

Synonyms
Endometrioid tumour of low malignant potential, endometrioid tumour of borderline malignancy.

Epidemiology
Endometrioid tumours with atypical epithelial proliferations and lacking stromal invasion are rare. Their precise prevalence is not known because of variation in diagnostic criteria, but reportedly they account for 3-18% of malignant ovarian neoplasms (137,2490,2528).

Aetiology
These tumours appear to be predominantly derived from the surface epithelium of the ovary or endometriosis.

Clinical features
Patients range in age from 22-77 years (201,2737). A pelvic mass is palpable in a majority of patients, and others present with uterine bleeding. The tumours are
Tumours of the ovary and peritoneum

predominantly unilateral, but rare bilateral lesions occur.

Macroscopy
Tumours range in size from 2-40 cm, have a tan to grey-white sectioned surface that varies from solid to predominantly solid with cysts ranging from a few mm to 8 cm in diameter [201,2737]. Haemorrhage and necrosis are present mainly in larger tumours.

Histopathology
Three patterns have been described [201,2737]. The most common is adenofibromatous. Islands of crowded endometrioid glands or cysts lined by cells displaying grade 1 to, rarely, grade 3 cytological atypia proliferate in an adenofibromatous stroma. Stromal invasion is absent. Mitotic activity is usually low. Squamous metaplasia is common, and necrosis may develop in the metaplastic epithelium. The second pattern is villoglandular or papillary with an atypical cell lining similar to atypical hyperplasia of the endometrium again in a fibromatous background. The third form shows a combination of villoglandular and adenofibromatous patterns. Anywhere from 15% to over half of the patients have endometriosis in the same ovary as well as at extraovarian sites [201,2737].

Prognosis and predictive factors
The prognosis is excellent. Recurrences and metastases are rare. Even in the rare case of an extraovarian tumour node involving the colonic serosa [2737], no subsequent problems developed 9 years after surgery, radiation and chemotherapy. Since a few patients treated by unilateral salpingo-oophorectomy developed endometrioid carcinoma in the contralateral ovary, and 1 died from it, bilateral salpingo-oophorectomy would be prudent when retention of fertility is no longer an issue. Unilateral salpingo-oophorectomy along with follow-up for early detection of any subsequent ovarian or endometrial adenocarcinoma is acceptable for women of childbearing age.

Benign endometrioid tumours

Definition
Ovarian tumours with histological features of benign glands or cysts lined by well differentiated cells of endometrial type.

Epidemiology
Because of the rarity of these neoplasms no convincing epidemiological data can be quoted. The reported patients are mainly of the reproductive age.

Localization
Benign endometrioid tumours are usually unilateral, though in rare cases involvement of both ovaries is encountered.

Clinical features

Signs and symptoms
There are no specific clinical symptoms of benign endometrioid tumours. Small neoplasms are incidental findings, sometimes in the wall of an ovarian endometriotic cyst. Large tumours are manifested by pain and abdominal swelling.

Imaging
Imaging techniques, including US, CT and MRI, cannot effectively establish the specific nosological character of the process. They can visualize endometriotic foci and thus indirectly indicate the presumptive endometrioid nature of the neoplasm; otherwise the results of imaging technique show the formal characteristics, i.e. cystic or cystic-fibrous architecture of the lesion [234].

Histopathology
The histological diagnosis of endometrioid adenomas and cystadenomas is based on the presence of well differentiated, benign appearing glands or cysts lined by endometrial type cells with or without squamous differentiation. In the adenofibromatous variant fibrous stroma predominates. Though adenofibromas

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Fig. 2.38 Endometrioid borderline tumour of the ovary with microinvasion. Cystic tumour contains complex papillae. A small area has densely packed glands indicative of microinvasion (arrow).

Fig. 2.39 A Endometrioid cystadenoma. The cystic neoplasm forms villiform structures lined by well differentiated endometrioid type epithelium. B Endometrioid adenofibroma. A squamous morule bridges two endometrioid type glands lined by uniform cells set in a fibrous stroma.

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136 Tumours of the ovary and peritoneum
Surface epithelial-stromal tumours can have minimal periglandular endometrial stroma, cases in which endometrial stroma is present throughout the lesion are classified as endometriosis. The latter can have all forms of endometrial hyperplasia including those with atypia.

**Clear cell tumours**

**Definition**
Ovarian tumours, benign, borderline or malignant, with an epithelial component consisting most commonly of clear and hobnail cells, but often containing other cell types, which rarely predominate.

**Histopathology**
Clear cell tumours may by predominantly epithelial or may also contain a prominent fibromatous component. The epithelium may consist of one or more cell types. The most common cells are clear cells and hobnail cells. Other cells that may be present include cuboidal, flat, oxyphilic and rarely, signet-ring cells. Most clear cell tumours are carcinomas, and many have an adenofibromatous background. Benign and borderline clear cell tumours are rare and almost always adenofibromatous.

**ICD-O codes**
- Clear cell adenocarcinoma 8310/3
- Clear cell adenocarcinofibroma 8313/3
- Clear cell tumour of borderline malignancy 8310/1
- Clear cell adenofibroma of borderline malignancy 8313/1
- Clear cell cystadenoma 8310/0
- Clear cell cystadenofibroma 8313/0

**Clear cell adenocarcinoma**

**Definition**
A malignant ovarian tumour composed of glycogen-containing clear cells and hobnail cells and occasionally other cell types.

**Epidemiology**
The mean age of patients is 57 years.

**Aetiolog**
Tumours may arise directly from the ovarian surface epithelium, from inclusion cysts or from an endometriotic cyst.

**Clinical features**
Clear cell tumours among all surface epithelial cancers have the highest association of ovarian and pelvic endometriosis and paraendocrine hypercalcaemia [3204].

**Macroscopy**
The mean diameter of clear cell adenocarcinomas is 15 cm. The tumours may be solid, but more commonly the sectioned surface reveals a thick-walled unilocular cyst with multiple yellow fleshy nodules protruding into the lumen or multiloculated cysts containing watery or mucinous fluid. Tumours associated with endometriosis typically contain chocolate-brown fluid.

**Tumour spread and staging**
Patients with clear cell adenocarcinomas present as stage I disease in 33% of cases, as stage II in 19%, as stage III in 29% and as stage IV in 9% [2233].

**Histopathology**
Clear cell adenocarcinomas display tubulocystic, papillary and solid patterns that may be pure or mixed. The most common patterns are papillary and tubulocystic. Rarely, the tumour has a reticular pattern similar to that of a yolk sac tumour. Sheets of polyhedral cells with abundant clear cytoplasm separated by a delicate fibrovascular or hyalinized stroma are characteristic of the solid pattern. The tubulocystic pattern is characterized by varying-sized tubules and cysts lined by cuboidal to flattened epithelium and occasionally hobnail cells. The papillary pattern is characterized by thick or thin papillae containing...
fibrous tissue or abundant hyaline material. The most common cell types are the clear and hobnail cells. Clear cells tend to be arranged in solid nests or masses or lining cysts, tubules and papillae, whereas hobnail cells line tubules and cysts and cover papillary structures. The clear cells tend to be rounded or polygonal with eccentric nuclei, often containing some lipid. Mucin may be found, typically located in the lumens of tubules and cysts and is abundant within the cytoplasm of the signet-ring cells.

**Immunoprofile**

Clear cell adenocarcinomas stain strongly and diffusely for keratins, epithelial membrane antigen, Leu M1 and B72.3. Stains for carcinomaembryonic antigen are positive in 38% of cases and for CA125 (OC-125) in 50%. There have been a few reports of clear cell adenocarcinomas containing AFP. In a patient with clear cell adenocarcinoma who developed hypercalcaemia when the tumour recurred, immunostains for parathyroid hormone-related protein were strongly positive in the recurrent carcinoma but negative in the primary carcinoma (3209).

**Differential diagnosis**

The differential diagnosis includes germ cell tumours, particularly yolk sac tumour, dysgerminoma and, rarely, struma ovarii, endometrioid carcinoma with secretory change and steroid cell tumours that contain prominent areas of cells with clear cytoplasm. Metastatic clear cell neoplasms from outside the female genital system are very rare. Clinical information can be particularly helpful in the differential diagnosis as germ cell tumours occur in young women, and elevated serum alpha-feto-protein (AFP) levels are always found in patients with yolk sac tumours. Histologically, the papillary structures of clear cell carcinoma are more complex than those of yolk sac tumours and contain hyalinized cores. In contrast, yolk sac tumours display a variety of distinctive features including a prominent reticular pattern and Schiller-Duval bodies. Negative immunostains for AFP are useful in excluding yolk sac tumours, although rare examples of AFP-containing clear cell carcinomas have been reported. Positive staining for EMA and diffuse strong positivity for cytokeratins exclude dysgerminoma. Immunostains for thyroglobulin are very useful in ruling out struma ovarii.

Endometrioid carcinomas with secretory change typically are composed of cells that are columnar with subnuclear and supranuclear vacuolization resembling early secretory endometrium. In contrast, the clear cell changes in clear cell carcinoma are more diffuse, the cells are polygonal, and they typically display the other characteristic patterns of clear cell carcinoma. A metaplastic squamous component may be seen in endometrioid carcinoma and is not observed in clear cell carcinoma. In contrast to clear cell carcinomas, steroid cell tumours of the ovary that contain prominent clear cytoplasm are smaller, well circumscribed, have low grade nuclear features and stain strongly for alpha-inhibin.

**Grading**

Nuclei in clear cell carcinomas range from grade 1 to grade 3, but pure grade
1 tumours are extremely rare. Almost invariably high grade (grade 3) nuclei are identified. In view of this finding as well as the mixture of different architectural patterns, clear cell adenocarcinoma is not graded.

**Prognosis and predictive factors**

When controlled for stage, survival of women with clear cell adenocarcinoma may be slightly lower than that of patients with serous carcinoma. The five year survival is 69% for patients with stage I tumours, 55% for stage II, 14% for stage III and 4% for stage IV. There is no consensus in the literature about the value of pattern, cell type, mitotic index or grade as a prognostic indicator (395).

**Borderline clear cell adenofibromatous tumour**

**Definition**

An ovarian tumour of low malignant potential composed of atypical or histologically malignant glands or cysts lined by clear or hobnail cells set in a dense fibrous stroma with an absence of stromal invasion.

**Synonyms**

Clear cell adenofibromatous tumour of low malignant potential, clear cell adenofibromatous tumour of borderline malignancy.

**Epidemiology**

Of approximately 30 cases of neoplasms classified as borderline clear cell adenofibromatous tumour, the mean age of patients was 65 years.

**Macroscopy**

Adenofibromas with increasing atypia including intraepithelial carcinoma have a similar appearance to adenofibromas but in addition have areas that are softer and fleshier.

**Histopathology**

Borderline clear cell adenofibromatous tumours include those in which the epithelium is atypical or carcinomatous without invasion. Adenofibromatous tumours in which the glands are lined by malignant epithelium are best designated as "borderline clear cell adenofibromas with intraepithelial carcinoma". They are similar to borderline adenofibromas; however, nuclear atypia is more marked with coarse chromatin clumping, prominent nucleoli and increased mitotic activity. Occasionally, minute foci of invasion can be identified, and these tumours are designated "microinvasive".

**Prognosis and predictive factors**

With the exception of one case (202), borderline clear cell adenofibromatous tumours including those with intraepithelial carcinoma and micro-invasion have a benign course following removal of the ovary (583,1285,1435, 1897,2052).

**Clear cell adenofibroma**

**Definition**

An ovarian tumour composed of histologically benign glands or cysts lined by clear or hobnail cells set in a dense fibrous stroma.

**Epidemiology**

Among approximately twelve reported cases of benign clear cell adenofibroma, the mean age of patients was 45.

**Macroscopy**

Adenofibromas have a median diameter of 12 cm and display a smooth lobulated external surface. The sectioned surface has a fine honeycomb appearance with minute cysts embedded in a rubbery stroma.

**Histopathology**

Clear cell adenofibromas are characterized by tubular glands lined by one or two layers of epithelium that contains polygonal, hobnail or flattened cells. The cytoplasm may be clear, slightly granular or eosinophilic. Nuclear atypia and mitotic activity are minimal. The stroma is densely fibrous.
Transitional cell tumours

Definition
Ovarian tumours composed of epithelial elements histologically resembling urothelium and its neoplasms.

Histopathology
This group of tumours includes the following:
1. Benign Brenner tumours, distinguished by a prominent stromal component accompanying transitional cell nests.
2. Borderline and malignant Brenner tumours in which a benign Brenner tumour component is associated with exuberantly proliferative, variably atypical but non-invasive transitional epithelium in the former and unequivocal stromal invasion in the latter.
3. Transitional cell carcinoma in which a malignant transitional cell tumour is not associated with a benign or borderline Brenner component.

ICD-O codes
- Transitional cell carcinoma (non-Brenner): 8120/3
- Malignant Brenner tumour: 9000/3
- Borderline Brenner tumour: 9000/1
- Brenner tumour: 9000/0

Epidemiology
Transitional cell tumours account for 1-2% of all ovarian tumours.

Transitional cell carcinoma

Definition
An ovarian tumour that is composed of epithelial elements histologically resembling malignant urothelial neoplasms and does not have a component of benign or borderline Brenner tumour.

Epidemiology
Transitional cell carcinoma is the pure or predominant element in 6% of ovarian carcinomas (2676). The great majority of transitional cell carcinomas occur in women 50-70 years old (1110).

Clinical features
The presentation of women with transitional cell carcinoma is the same as with other malignant ovarian tumours, abdominal pain, swelling, weight loss, and bladder or bowel symptoms (139,2676).
Macroscopy
Transition cell carcinomas are bilateral in approximately 15% of cases [139] and are macroscopically indistinguishable from other surface epithelial-stromal tumours [139,2676].

Tumour spread and staging
At the time of diagnosis transition cell carcinomas have spread beyond the ovary in over two-thirds of cases [2676].

Histopathology
Transition cell carcinomas resemble those occurring in the urinary tract and lack a benign or borderline Brenner tumour component [139,2676]. Typically, they are papillary with multilayered transitional epithelium and a smooth luminal border ("papillary type"). A nested pattern characterized by malignant transitional cell nests irregularly distributed in fibrotic stroma ("malignant Brenner-like type") has been described [2464,2465]. As in urothelial carcinoma, foci of glandular and/or squamous differentiation may occur. Very commonly, transition cell carcinoma is admixed with other epithelial-stromal tumours of other types, particularly serous carcinoma. Transition cell carcinomas lack the prominent stromal calcification characteristic of some benign and malignant Brenner tumours.

Immunoprofile
Ovarian transition cell carcinomas have an immunoprofile that differs from transitional cell carcinomas of the urinary tract and closely resembles that of ovarian surface epithelial-stromal tumours. Ovarian transitional cell carcinomas are consistently uroplakin, thrombomodulin and cytokeratin 13 and 20 negative and CA125 and cytokeratin 7 positive [2115, 2371]. In addition, several immunohistochemical studies have demonstrated that the tumour lacks a urothelial phenotype [2115,2371]. Thus, the ovarian neoplasm shows histological but not immunohistochemical similarities to transitional cell carcinoma of the urinary bladder.

Grading
Transition cell carcinomas should be graded utilizing criteria for transitional cell carcinoma of the urinary tract.

Histogenesis
The term transitional cell carcinoma is not uniformly accepted, and overlapping features with other epithelial-stromal tumours, particularly serous carcinoma, are present. It is important that strict histological criteria be applied to establish the diagnosis [2465]. Not only an architectural but also a histological resemblance to transitional epithelium is required. The frequent association with epithelial-stromal tumours of other types strongly suggests a surface epithelial origin [2465]. In addition, several immunohistochemical studies have demonstrated that the tumour lacks a urothelial phenotype [2115,2371]. Thus, the ovarian neoplasm shows histological but not immunohistochemical similarities to transitional cell carcinoma of the urinary bladder.

Prognosis and predictive factors
The overall 5-year survival rate for transitional cell carcinoma is 35%. Some, but not all, investigators have reported greater chemosensitivity and higher 5-year survival in patients whose metastases are composed purely or predominantly of transitional cell carcinoma [564, 1232,2676].
**Malignant Brenner tumour**

**Definition**
An ovarian tumour containing invasive transitional cell aggregates as well as benign nests of transitional epithelium set in a fibromatous stroma.

**Epidemiology**
The great majority of malignant Brenner tumours occur in women 50-70 years old \{1110,1868,2676\}. Only 5% of Brenner tumours are malignant \(1110,1868\).

**Clinical features**
Most patients seek medical attention because of an abdominal mass or pain \{139,2460,2461\}. A few patients present with abnormal vaginal bleeding.

**Macroscopy**
Malignant Brenner tumours are typically large with a median diameter of 16-20 cm and typically have a solid component resembling benign Brenner tumour as well as cysts containing papillary or polypoid masses \{2461\}.

**Tumour spread and staging**
Malignant Brenner tumours are bilateral in 12% of cases \{139,452\}. About 80% of malignant Brenner tumours are stage 1 at the time of diagnosis.

**Histopathology**
In malignant Brenner tumours there is stromal invasion associated with a benign or borderline Brenner tumour component \{139\}. The invasive element is usually high grade transitional cell carcinoma or squamous cell carcinoma, although occasional tumours are composed of crowded, irregular islands of malignant transitional cells with low grade features \{2460\}. Glandular elements may be admixed, but pure mucinous or serous carcinomas associated with a benign Brenner tumour component should not be diagnosed as a malignant Brenner tumour. Foci of calcification are occasionally prominent.

**Immunoprofile**
The very small number of malignant Brenner tumours studied have exhibited a benign Brenner tumour immunoprofile in that component with a variable pattern of antigen expression in the invasive component; uroplakin immunopositivity has occurred in some \{2371\}.

**Prognosis and predictive factors**
When confined to the ovary, malignant Brenner tumours have an excellent prognosis. Patients with stage IA tumours have an 88% 5-year survival, and those with high stage malignant Brenner tumours have a better prognosis than stage matched transitional cell carcinomas \{139\}.

**Borderline Brenner tumour**

**Synonyms**
Brenner tumour of low malignant potential, proliferating Brenner tumour (for cases with low grade features).

**Definition**
An ovarian transitional cell tumour of low malignant potential with atypical or malignant features of the epithelium but lacking obvious stromal invasion.

**Epidemiology**
Only 3-5% of Brenner tumours are borderline \{1110,1868\}.

**Tumour spread and staging**
Borderline Brenner tumours are confined to the ovary and, with rare exceptions, have been unilateral \{1110,1868,2461,3144\}.

**Clinical features**
Most patients seek medical attention because of an abdominal mass or pain \{139,2460,2461\}. A few patients present with abnormal vaginal bleeding.

**Macroscopy**
Borderline Brenner tumours are typically large with a median diameter of 16-20 cm. They usually have a solid component resembling benign Brenner tumour as well as a cystic component containing a papillary or polypoid mass \{2461\}.

**Histopathology**
Borderline Brenner tumours show a greater degree of architectural complexity than benign Brenner tumours typified by branching fibrovascular papillae surfaced by transitional epithelium often protruding into cystic spaces. The transitional epithelium manifests the same spectrum of architectural and cytological features encountered in urothelial lesions of the urinary tract. By definition, there is no stromal invasion. A benign Brenner tumour component is typically present but may be small and easily overlooked. The mitotic rate is highly variable but may be brisk, and focal necrosis is common. Mucinous metaplasia may be a prominent feature. The diagnostic criteria and terminology applied to the intermediate group of transitional cell tumours is somewhat controversial \{2461,2605\}. Some have advocated categorizing tumours with low grade features as "proliferating" rather than borderline \{2461\}, and others designate those resembling grade 2 or 3 transitional cell carcinoma of the urinary tract as "borderline with intraepithelial carcinoma" \{2605\}.

**Prognosis and predictive factors**
No Brenner tumour in the intermediate category without stromal invasion has metastasized or caused the death of a patient \{1110,2461\}.

**Benign Brenner tumour**

**Definition**
An ovarian transitional cell tumour composed of mature urothelial-like cells arranged in solid or cystic circumscibed aggregates within a predominantly fibromatous stroma.

**Epidemiology**
Benign Brenner tumours account for 4-5% of benign ovarian epithelial tumours \{1409,1502,1970,2685\}. Most benign Brenner tumours (95%) are diagnosed in women 30-60 years old \{753,905,1868,2460,2461,2676,2685,3073,3186\}.

**Clinical features**
The majority of patients with benign Brenner tumours are asymptomatic; over 50% of tumours are less than 2 cm and are typically discovered incidentally in ovaries removed for some other reason \{753,905,2685,3073\}. In only 10% of cases is the tumour larger than 10 cm;
such patients may present with non-specific signs and symptoms referable to a pelvic mass. Occasionally, Brenner tumours are associated with manifestations related to the elaboration of estrogens or androgens by the stromal component of the tumour.

**Macroscopy**

The typical benign Brenner tumour is small, often less than 2 cm, but, regardless of size, is well circumscribed with a firm, white, sometimes gritty sectioned surface due to focal or extensive calcification. Small cysts are common, and a rare tumour is predominantly cystic. Brenner tumours are associated with another tumour type, usually mucinous cystadenoma, in 25% of cases.

**Tumour spread and staging**

Only 7-8% of benign Brenner tumours are bilateral (753).

**Histopathology**

Benign Brenner tumours are characterized by nests and islands of transitional type epithelial cells with centrally grooved, “coffee bean” nuclei, abundant amphophilic to clear cytoplasm and distinct cell membranes growing in a dominant fibromatous stroma. The nests may be solid or exhibit central lumina containing densely eosinophilic, mucin-positive material. The lumina may be lined by transitional type cells or mucinous, ciliated or nondescript columnar cells. Variably sized cysts lined by mucinous epithelium, either pure or overlying transitional epithelium are common in benign Brenner tumours. Benign Brenner tumours with crowded transitional nests and cysts with a prominent mucinous component, sometimes with complex gland formations, are termed “metaplastic Brenner tumour” by some and not mixed epithelial tumours (2461) since the epithelial components are admixed rather than separate. Their recognition avoids confusion with borderline or malignant Brenner tumours.

**Immunoprofile**

Benign Brenner tumours show some urothelial differentiation evidenced by uroplakin expression, but they do not express thrombomodulin and have been immunonegative for cytokeratin 20 in most, but not all, studies (2085, 2115, 2116, 2371, 2758). Benign Brenner tumours have an endocrine cell component demonstrable with immunostains for chromogranin A, serotonin and neuron specific enolase (45, 2530).

**Somatic genetics**

There is one report of a 12q14-21 amplification in a benign Brenner tumour (2207).

**Squamous cell lesions**

**Squamous cell carcinoma**

**Definition**

Malignant ovarian tumour composed of squamous epithelial cells that is not of germ cell origin.

**ICD-O code**

8070/3

**Epidemiology**

The age of women with squamous cell carcinoma, pure or associated with endometriosis, has ranged from 23-90 years.

**Macroscopy**

Most squamous cell carcinomas are solid, although in some instances cystic components predominate.

**Histopathology**

Histologically, squamous cell carcinomas are usually high grade and show a variety of patterns including papillary or polypoid, cystic, insular, diffusely infiltrative, verruciform or sarcomatoid. They must be distinguished from endometrioid adenocarcinomas with extensive squamous differentiation and from metastatic squamous cell carcinoma from the cervix and other sites (3198).

**Histogenesis**

Most squamous cell carcinomas arise from dermoid cysts and are classified in the germ cell tumour category. Less commonly, they occur in association with endometriosis (1624, 1828, 1973, 2255, 2902), as a component of malignant Brenner tumour (2460) or in pure form (2255) and are considered to be surface epithelial-stromal tumours. Some pure
squamous cell carcinomas have occurred in women with cervical squamous cell carcinoma in situ (1738).

Prognosis and predictive factors

Most tumours have spread beyond the ovary at the time of presentation, and the prognosis in the small number of reported cases is poor.

Epidemiology

The reported incidence of MET varies from 0.5-4% of surface epithelial-stromal tumours. This variability is due in part to problems in developing a standardized classification.

Tumour spread and staging

Mixed epithelial borderline tumours (MEBTs) are stage I in 93% of cases and show bilateral ovarian involvement in 22% (2496).

Histopathology

In cystadenomas the most frequent mixture is serous (ciliated) and mucinous epithelium. The mucinous epithelium should contain abundant intracytoplasmic mucin, not just apical or luminal mucin. MEBTs show papillae with detached cell clusters reminiscent of serous borderline tumours, but they generally contain a mixture of endocervical-like mucinous cells, endometrioid epithelium with focal squamous differentiation and indifferent eosinophilic epithelium. An acute inflammatory infiltrate may be seen rarely. Mixed Brenner-mucinous tumours are usually composed of a benign, and, occasionally, a borderline Brenner component; the mucinous component may be benign, borderline or malignant. A few mucinous glands within Brenner nests or histological areas of mucinous differentiation represent mucinous metaplasia in Brenner tumours, a common finding, and are not a MET. Rarely, the tumour macroscopically contains a myriad of small cysts lined by mucinous differentiation and the term metaplastic Brenner tumour is applied (2461). For cystadenocarcinomas frequent combinations are serous and endometrioid,

Mixed epithelial tumours

Definition

An ovarian epithelial tumour composed of an admixture of two or more of the five major cell types: serous, mucinous, endometrioid, clear cell and Brenner/transitional. The second or second and third cell types must comprise alone or together at least 10% of the tumour epithelium, or, in the case of a mixed Brenner-mucinous cystic tumour, both components should be macroscopically visible. A mixed epithelial tumour (MET) may be benign, borderline or malignant. Endometrioid tumours with squamous differentiation and neuroendocrine tumours associated with a surface epithelial-stromal tumour are not included in this definition.

ICD-O codes

Malignant mixed epithelial tumour 8323/3
Borderline mixed epithelial tumour 8323/1
Benign mixed epithelial tumour 8323/0

Histopathology

In cystadenomas the most frequent mixture is serous (ciliated) and mucinous epithelium. The mucinous epithelium should contain abundant intracytoplasmic mucin, not just apical or luminal mucin. MEBTs show papillae with detached cell clusters reminiscent of serous borderline tumours, but they generally contain a mixture of endocervical-like mucinous cells, endometrioid epithelium with focal squamous differentiation and indifferent eosinophilic epithelium. An acute inflammatory infiltrate may be seen rarely. Mixed Brenner-mucinous tumours are usually composed of a benign, and, occasionally, a borderline Brenner component; the mucinous component may be benign, borderline or malignant. A few mucinous glands within Brenner nests or histological areas of mucinous differentiation represent mucinous metaplasia in Brenner tumours, a common finding, and are not a MET. Rarely, the tumour macroscopically contains a myriad of small cysts lined by mucinous differentiation and the term metaplastic Brenner tumour is applied (2461). For cystadenocarcinomas frequent combinations are serous and endometrioid,

Epidermoid cyst

Definition

Benign ovarian cysts lined by squamous epithelial cells that are not clearly of germ cell origin.

Histopathology

Epidermoid cysts lined by benign keratinized squamous epithelium devoid of skin appendages and unaccompanied by teratomatous elements are rare in the ovary (823,3205). All are small (2-46 mm) and unilateral.

Histogenesis

The presence of small epithelial cell nests resembling Walthard cell nests in the walls of epidermoid cysts suggests an epithelial rather than a teratomatous origin (3205).
serous and transitional cell carcinoma and endometrioid and clear cell.

Grading
The least differentiated component determines the tumour grade.

Histogenesis
Endometriosis, occasionally with atypia, is found in association with 53% of MEBT (2406) and up to 50% of mixed clear cell-endometrioid tumours (2511). Some cases show a transition from endometriosis to neoplastic epithelium.

Somatic genetics
It is impossible to make broad statements, as studies are limited to a few cases. LOH on chromosome 17, common in serous tumours, has been found in two of five mixed endometrioid-serous tumours (959). PTEN mutation, which has been associated with the endometrioid type, has also been noted in a mixed mucinous-endometrioid tumour (2075). KRAS mutations, an early event in mucinous tumours, have been noted in three mixed Brenner-mucinous tumours (589). The mucinous cystadenocarcinoma and Brenner tumour components shared amplification of 12q 14-21 in one MET, suggesting clonal relatedness (2207).

Prognosis and predictive factors
The behaviour of MEBT is similar to that of endocervical-like mucinous borderline tumours. The dominant cell type generally dictates behaviour. An exception is mixed endometrioid and serous carcinoma, which, even when the serous component is minor, behaves more aggressively than pure endometrioid carcinoma and similarly to their serous counterpart. Mixed endometrioid and serous carcinoma may recur as serous carcinoma (2907). This finding stresses the importance of careful sampling of an endometrioid cystadenocarcinoma to rule out a mixed serous component.

Undifferentiated carcinoma
Definition
A primary ovarian carcinoma with no differentiation or only small foci of differentiation.

ICD-O code 8020/3

Epidemiology
When applying the WHO criteria, approximately 4-5% of ovarian cancers are undifferentiated carcinoma. The frequency of undifferentiated carcinoma was 4.1% when defined as carcinomas with solid areas as the predominant component representing over 50% of the tumour (2677).

Clinical features
In the only large series the age of the patients ranged from 39-72 (mean, 54 years) (2677).

Macroscopy
Macroscopically, undifferentiated carcinoma does not have specific features. The tumours are predominantly solid, usually with extensive areas of necrosis.

Tumour spread and staging
According to FIGO, 6% of the patients are discovered in stage I, 3% are in stage II, 74% in stage III and 17% in stage IV; thus 91% of the tumours are discovered in stages III and IV (2677).

Histopathology
Histologically, undifferentiated carcinoma consists of solid groups of tumour cells with numerous mitotic figures and significant cytological atypia. Areas with a spindle cell component, microcystic pattern and focal vascular invasion can be seen. It is unusual to see an undifferentiated carcinoma without any other component of müllerian carcinoma. Usually, areas of high grade serous carcinoma are present. Foci of transitional cell carcinoma can also be seen. Undifferentiated carcinoma of the ovary does not have a specific immunophenotype.

 Differential diagnosis
The main differential diagnoses are granulosa cell tumour of the adult type, transitional cell carcinoma, poorly differentiated squamous cell carcinoma, small cell carcinoma and metastatic undifferentiated carcinoma. Granulosa cell tumours may have a diffuse pattern; however, it is unusual not to have also areas with a trabecular pattern, Call-Exner bodies or areas showing sex cords. In addition, undifferentiated carcinoma is a more anaplastic tumour with a larger number of mitotic figures. Transitional cell carcinomas might have areas of undifferentiated tumour; however, either a trabecular pattern or large papillae are always identified in the former. Small cell carcinoma of the hypercalcaemic type typically occurs in young women and often contains follicle-like structures. The cells of small cell carcinoma of the pulmonary type show nuclear molding and have high nuclear to cytoplasmic ratios. Finally, metastatic undifferentiated carcinomas are uniform tumours without papillary areas.

All these differential diagnoses can usually be resolved when the tumour is well sampled, and areas with a different macroscopic appearance are submitted. Sampling will identify the different components of the tumour that are characteristic of primary ovarian lesions.

Prognosis and predictive factors
The five-year survival of patients with undifferentiated carcinoma is worse than that of ovarian serous or transitional cell carcinoma. Only 6% of these patients survive for 5 years.

Unclassified adenocarcinoma
Definition
A primary ovarian adenocarcinoma that cannot be classified as one of the specific types of müllerian adenocarcinoma because it has overlapping features or is not sufficiently differentiated. These tumours are uncommon.

ICD-O code 8140/3

Histopathology
Tumours in this category would include well or moderately differentiated tumours with overlapping features such as a mucinous tumour with cilia, or it might include a less differentiated tumour without distinctive features of one of the müllerian types of adenocarcinoma.

Prognosis and predictive factors
Since this group of tumours has not yet been specifically studied, the prognosis is not known.
Sex cord-stromal tumours

Definition
Ovarian tumours composed of granulosa cells, theca cells, Sertoli cells, Leydig cells and fibroblasts of stromal origin, singly or in various combinations. Overall, sex cord-stromal tumours account for about 8% of ovarian neoplasms.

Granulosa-stromal cell tumours

Definition
Tumours containing granulosa cells, theca cells or stromal cells resembling fibroblasts or any combination of such cells.

Granulosa cell tumour group

Definition
A neoplasm composed of a pure or at least a 10% population of granulosa cells often in a fibrothecomatous background. Two major subtypes are recognized, an adult and a juvenile type.

ICD-O codes
Granulosa cell tumour group
Adult granulosa cell tumour 8620/1
Juvenile granulosa cell tumour 8622/1

Epidemiology
Granulosa cell tumours account for approximately 1.5% (range, 0.6-3%) of all ovarian tumours. The neoplasm occurs in a wide age range including newborn infants and postmenopausal women. About 5% occur prior to puberty, whereas almost 60% occur after menopause [284,2588].

Aetiology
The aetiology of these tumours is unknown. Several studies suggest that infertile women and those exposed to ovulation induction agents have an increased risk for granulosa cell tumours [2458,2982,3125].

Clinical features
Signs and symptoms
Granulosa cell tumours may present as an abdominal mass, with symptoms suggestive of ovulation induction agents have an increased risk for granulosa cell tumours [2458,2982,3125].

Imaging
Cross sectional imaging, i.e. computed tomography and magnetic resonance imaging is of value in the surgical planning and preoperative determination of resectability of patients with granulosa cell tumours [859,1480,1728,1915,2131]. In contrast to epithelial ovarian tumours, granulosa cell tumours have been described as predominantly solid adnexal lesions; variable amounts of cystic components may, however, be present. Enlargement of the uterus and endometrial thickening might be seen as a result of the hormone production of the tumour [859,1480,1728,1915,2131].

Adolescent granulosa cell tumour

Epidemiology
More than 95% of granulosa cell tumours are of the adult type, which occurs in middle aged to postmenopausal women.

Macroscopy
Adult granulosa cell tumours (AGCTs) are typically unilateral (95%) with an average size of 12.5 cm and are commonly encapsulated with a smooth or lobulated surface. The sectioned surface of the tumour due to various types of endometrial hyperplasia or, rarely, well differentiated adenocarcinoma is the most common manifestation of hyperoestrogenism. A rare unicocular thin-walled cystic variant is often androgenic when functional [1971,2059].

Fig. 2.55 Granulosa cell tumour. Axial contrast-enhanced computed tomography image of the pelvis shows a large, well defined, multicystic mass.

Fig. 2.56 Adult granulosa cell tumour, microfollicular pattern. A An aggregate of neoplastic granulosa cells contains numerous Call-Exner bodies. B The Call-Exner bodies contain fluid and/or pyknotic nuclei; the tumour cells have scant cytoplasm and longitudinal nuclear grooves.
is yellow to tan with a variable admixture of cystic and solid areas \([906,2058]\). Haemorrhage is seen in larger tumours; necrosis is focal and uncommon. A small percentage is totally cystic, either uniloculated or multiloculated \([2058,2716]\). A solid or cystic tumour with a combination of yellow tissue and haemorrhage is highly suggestive of a granulosa cell tumour.

**Histopathology**

Histologically, there is a proliferation of granulosa cells often with a stromal component of fibroblasts, theca or luteinized cells. The granulosa cells have scant cytoplasm and a round to ovoid nucleus with a longitudinal groove. The mitotic activity rarely exceeds 1-2 per 10 high power fields. When luteinized, the cells develop abundant eosinophilic or vacuolated cytoplasm, and the nuclei become round and lose their characteristic groove. The rare presence of bizarre nuclei does not have an adverse effect on the prognosis \([2890,3210]\). The tumour cells grow in a variety of patterns. The best known of these is the microfollicular pattern characterized by the presence of Call-Exner bodies. Others include the macrofollicular, characterized by large spaces lined by layers of granulosa cells, insular, trabecular, diffuse (sarcomatoid) and the moiré silk (watered silk) patterns. A fibrothecomatous stroma often surrounds the granulosa cells.

**Immunoprofile**

Granulosa cell tumours are immunoreactive for CD99, alpha-inhibin, vimentin, cytokeratin (punctate), calretinin, S-100 protein and smooth muscle actin. The tumour cells are negative for cytokeratin 7 and epithelial membrane antigen \([482, 563, 889, 1815, 2124, 2379]\).

**Differential diagnosis**

Although endometrioid carcinomas may display an abundant rosette-like arrangement of nuclei mimicking Call-Exner bodies, they often show squamous metaplasia and lack nuclear grooves. Undifferentiated carcinomas and poorly differentiated adenocarcinomas may resemble the diffuse (sarcomatoid) pattern of granulosa cell tumours. These carcinomas have abundant mitotic figures and frequently have already extended beyond the ovary at presentation. The insular and trabecular patterns of granulosa cell tumour may be mistaken for a carcinoid and vice versa. Carcinoids have uniform round nuclei with coarse chromatin, lack nuclear grooves and show chromogranin positivity. Furthermore, primary carcinoids of the ovary are usually associated with other teratomatous elements, whereas the metastatic ones are generally multi-nodular and bilateral. The diffuse pattern of granulosa cell tumours may be confused with a benign thecoma, particularly when there is luteinization. A reticulin stain is helpful since granulosa cells typically grow in sheets or aggregates bound by reticulin fibres, whereas thecomas contain an abundance of intercellular fibrils surrounding individual cells. The distinction is important since granulosa cell tumours have an aggressive potential, whereas thecomas are with rare exceptions benign. Similarly, the presence of nuclear grooves and the absence of the characteristic vascular pattern of endometrioid stromal sarcoma distinguish AGCT from the former.

**Somatic genetics**

In contrast to older studies \([1635,2862]\), recent karyotypic and fluorescence in situ hybridization analyses have shown that trisomy and tetrasomy 12 are rarely present in granulosa cell tumours \([1635, 1653, 2221, 2635, 2862]\). The few available studies have shown trisomy 14 \([1043]\).
and structural changes in chromosome 6 with loss of 6q material [3021].

Prognosis and predictive factors
All granulosa cell tumours have a potential for aggressive behaviour. From 10-50% of patients develop recurrences. Some recurrences of AGCT develop as late as 20-30 years following the initial diagnosis [906,2058,2786], and long term follow-up is required.

The most important prognostic factor is the stage of the tumour [1815]. Nearly 90% of patients with granulosa cell tumour have stage I disease, however, and the prediction of tumour behaviour is most difficult in this group. Factors related to a relatively poor prognosis include age over 40 years at the time of diagnosis, large tumour size (>5cm), bilaterality, mitotic activity and atypia [906,1871,2786]. There is, however, disagreement on the precise significance of some of these factors. Among adults, survival is adversely affected by tumour rupture.

Juvenile granulosa cell tumour

Epidemiology
Accounting for nearly 5% of all granulosa cell tumours, juvenile granulosa cell tumour (JGCT) is encountered predominantly during the first 3 decades of life [3195].

Clinical features
In prepubertal girls, approximately 80% are associated with isosexual pseudo-precocity [277,3195,3242].

Macroscopy
The macroscopic appearance of JGCT is not distinctive and is similar in its spectrum of appearances to the adult variant.

Tumour spread and staging
JGCT presents almost always as stage I disease; less than 5% of tumours are bilateral, and only 2% have extraovarian spread.

Histopathology
JGCT is characterized by a nodular or diffuse cellular growth punctuated by macrofollicles of varying sizes and shapes. Their lumens contain eosinophilic or basophilic fluid. A fibrothecomatous stroma with variable luteinization and/or oedema is often evident. The typically rounded neoplastic granulosa cells have abundant eosinophilic and/or vaculated cytoplasm; and almost all nuclei lack grooves. Mitotic figures are abundant. Cytomegaly with macronuclei, multinucleation and bizarre multilobulated nuclei is occasionally observed [2890,3210].

Differential diagnosis
Only the entity of small cell carcinoma associated with hypercalcaemia, which also occurs in children and young women, poses a significant diagnostic problem. The clinical presentation of JGCT with estrogenic manifestations and that of small cell carcinoma with hypercalcaemia are important clues to the precise diagnosis. Dissemination beyond the ovary is evident in 20% of these small cell carcinomas at presentation, a feature that is most unusual for a JGCT. The presence of necrosis and more eccentric nuclei in the carcinomas are additional features that can help. The presence of mucinous epithelium in 10% of cases and clusters of larger cells in most small cell carcinomas provide further support. Finally, immunostains for alpha-inhibin are positive in granulosa cell tumours but completely negative in the carcinomas. Both tumours may be negative with a variety of epithelial markers.

Fig. 2.62 Juvenile granulosa cell tumour. Neoplastic cell aggregates form multiple round to oval follicles containing basophilic fluid.

Fig. 2.63 Juvenile granulosa cell tumour. A Solid nests of primitive granulosa cells alternate with macrofollicles lined by the same cell population. B Moderate to severe atypia is sometimes evident in both the solid and the cystic areas.
Genetic susceptibility
JGCTs may present as a component of a variety of non-hereditary congenital syndromes including Ollier disease (enchondromatosis) [2857,3015] and Maffucci syndrome (enchondromatosis and haemangiomatosis) [1102,2859]. Bilateral JGCT may develop in infants with features suggestive of Goldenhar (craniofacial and skeletal abnormalities) [2906] or Potter syndrome [2468].

Prognosis and predictive factors
Despite their more primitive histological appearance, only about 5% of JGCTs behave aggressively, and these usually do so within 3 years of presentation. The overall prognosis for JGCT is good with a 1.5% mortality associated with stage IA tumours; but it is poor in stage II or higher tumours [3195].

Thecoma-fibroma group

Definition
Tumours forming a continuous spectrum from those composed entirely of fibroblasts and producing collagen to those containing a predominance of theca cells.

<table>
<thead>
<tr>
<th>Thecoma</th>
<th>8600/0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteinized thecoma</td>
<td>8601/0</td>
</tr>
<tr>
<td>Fibroma, NOS</td>
<td>8810/0</td>
</tr>
<tr>
<td>Cellular fibroma</td>
<td>8810/1</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>8810/3</td>
</tr>
<tr>
<td>Stromal tumour with minor sex cord elements</td>
<td>8593/1</td>
</tr>
<tr>
<td>Sclerosing stromal tumour</td>
<td>8602/0</td>
</tr>
</tbody>
</table>

Thecoma

Definition
Thecomas are stromal tumours composed of lipid-containing cells resembling theca interna cells with a variable component of fibroblasts. Luteinized thecomas contain lutein cells in a background of thecoma or fibroma.

Epidemiology
Typical thecomas are about one-third as common as granulosa cell tumours. The great majority (84%) occur in postmenopausal women (mean age 59 years). Thecomas are rare before puberty, and only about 10% occur in women younger than 30 years [283]. The rare variant of luteinized thecoma associated with sclerosing peritonitis typically occurs in young women less than 30 years, only rarely occurring in older women [520].

Clinical features
Typical thecomas may be discovered incidentally or produce non-specific signs and symptoms of a pelvic mass. Symptoms related to estrogen production including abnormal uterine bleeding occur in about 60% of patients, and about 20% of postmenopausal women with thecoma have endometrial adenocarcinoma or rarely a malignant müllerian mixed tumour or endometrial stromal sarcoma (2300). Luteinized thecomas have a lower frequency of estrogenic manifestations than typical thecomas, and about 10% are associated with...
androgenic manifestations (3252). Patients with the rare variant of luteinized thecoma associated with sclerosing peritonitis present with abdominal swelling, ascites and symptoms of bowel obstruction (520).

**Macroscopy**

Thecomas may be small and non-palpable, but they usually measure 5-10 cm. The sectioned surface is typically solid and yellow, occasionally with cysts, haemorrhage or necrosis. Typical thecomas are almost invariably unilateral; only 3% are bilateral. Luteinized thecomas associated with sclerosing peritonitis are usually bilateral.

**Histopathology**

Typical thecomas are characterized by cells with uniform, bland, oval to spindle shaped nuclei with abundant, pale, vacuolated, lipid-rich cytoplasm. Individual cells are invested by reticulin. Mitoses are absent or rare. Rarely, the nuclei may be large or bizarre (3210). The fibromatous component commonly contains hyaline plaques and may be calcified. Extensively calcified thecomas tend to occur in young women (3194). Rarely, thecomas include a minor component of sex cord elements (3211). Luteinized thecomas contain lutein cells, individually or in nests, in a background often more fibromatous than thecomatous. Oedema and microcyst formation may be striking.

**Immunoprofile**

Thecomas are immunoreactive for vimentin and alpha-inhibin (482,562, 1499,1816,2181,2211).

**Somatic genetics**

Trisomy and tetrasomy 12 have been demonstrated in tumours in the thecoma-fibroma group by karyotypic analysis and fluorescence in situ hybridization (1635,1653,2221,2635,2862). This chromosomal abnormality is not, however, specific to tumours in this group since it has also been found in some benign and borderline epithelial tumours, as well as in occasional granulosa cell tumours (2209,2221).

**Prognosis and predictive factors**

Rarely, a typical or luteinized thecoma with nuclear atypia and mitotic activity may metastasize (1819,3074,3252), although most cases reported as “malignant thecomas” are probably fibrosarcomas or diffuse granulosa cell tumours. Patients with luteinized thecomas associated with sclerosing peritonitis may experience small bowel obstruction, and several have died of complications related to peritoneal lesions, but there has been no recurrence or metastasis of the ovarian lesion (520).

**Fibroma and cellular fibroma**

**Definition**

Fibromas are stromal tumours composed of spindle, oval or round cells producing collagen. In cellular fibromas the cells are closely packed, collagen is scanty, and the mitotic rate is increased.

**Epidemiology**

Fibromas account for 4% of all ovarian tumours. They are most common in middle age (mean 48 years) (709); less than 10% occur before age 30, and they occur only occasionally in children (328).
Clinical features
Fibromas may be found incidentally, but when large, patients may present with non-specific signs and symptoms of a pelvic mass. Between 10-15% of fibromas over 10 cm are associated with ascites [2519], and Meigs syndrome (ascites and pleural effusion with resolution after fibroma removal) occurs in about 1% of cases [1839].

Macroscopy
Fibromas are hard white tumours averaging 6 cm in diameter. Oedematous tumours may be soft, and cyst formation is common. Haemorrhage and necrosis are rare outside the setting of torsion. The majority of tumours are unilateral. Only 8% are bilateral, and less than 10% show focal or diffuse calcification.

Histopathology
Fibromas are composed of spindle-shaped cells with uniform, bland nuclei and scant cytoplasm that may contain small amounts of lipid or occasionally eosinophilic droplets. The cells are arranged in fascicles or in a storiform pattern. Mitoses are absent or rare. Fibromas are generally sparsely to moderately cellular with abundant intercellular collagen, hyalinized plaques and variable degrees of oedema. The cellularity may vary from area to area. About 10% of tumours are uniformly and densely cellular (attaining the cellularity of a diffuse granulosa cell tumour) and are referred to as cellular fibromas [2289]. Cellular fibromas exhibit no more than mild cytological atypia and an average of three or less mitoses per 10 high power fields. Fibromas express vimentin and may be immunoreactive for alpha-inhibin [1816, 2211].

Genetic susceptibility
Ovarian fibromas are common in females with the nevoid basal cell carcinoma syndrome, occurring in about 75% of patients having the syndrome referred to gynaecologists. Syndrome-related tumours are usually bilateral (75%), frequently multinodular, almost always calcified, sometimes massively, and tend to occur at a younger age, usually in children, adolescents, or young adults [1042,1354,2603]. Additional tumours may arise after local excision. The nevoid basal cell carcinoma syndrome has been reported in four generations of a kindred lacking other stigmata of the syndrome [728,1635,2221,2635].

Epidemiology
Fibromas are the most common ovarian sarcoma, occurring at any age but most often in older women.

Macroscopy
Fibromas are large, solid tumours, commonly haemorrhagic and necrotic, and are usually unilateral.

Histopathology
Fibromas are densely cellular, spindle cell neoplasms with moderate to severe cytological atypia, a high mitotic rate (an average of 4 or more mitoses per 10 high power fields) with atypical division figures, haemorrhage and necrosis [90,145,2289].

Somatic genetics
Trisomy 12 as well as trisomy 8 have been reported in an ovarian fibrosarcoma [2963].

Genetic susceptibility
Ovarian fibrosarcomas are rarely associated with Maffucci syndrome [484] and the nevoid basal cell carcinoma syndrome [1517].

Prognosis and predictive factors
The majority of ovarian fibrosarcomas have had a malignant course.

Sex cord-stromal tumours

Fig. 2.69 Fibrosarcoma. Moderate to severe cytological atypia accompanied by numerous mitotic figures characterize this fibrosarcoma.

Fig. 2.70 Stromal tumour with minor sex cord elements. Rarely, fibrothecomas contain a few tubules lined by cells resembling Sertoli cells.
**Stromal tumour with minor sex cord elements**

**Definition**
Stromal tumour with minor sex cord elements is a rare, fibrothecomatous tumour containing scattered sex cord elements (2605,3211). By definition, the sex cord element must account for <10% of the composition of the tumour (2605).

**Clinical features**
This tumour may occur in women of any age. It is usually hormonally inactive, but there have been several cases associated with endometrial hyperplasia or adenocarcinoma.

**Macroscopy**
Macroscopically, the tumour is solid, not distinguishable from thecoma or fibroma, and ranges from 1-10 cm in diameter.

**Histopathology**
Histological examination demonstrates the typical features of thecoma or fibroma in which sex cord structures are intermingled with the fibrothecomatous cells. Sex cord components vary in appearance between fully differentiated granulosa cells and indifferent tubular structures resembling immature Sertoli cells.

**Sclerosing stromal tumour**

**Definition**
A distinctive type of benign stromal tumour characterized by cellular pseudolobules that are composed of fibroblasts and round cells and separated by hypocellular, oedematous or collagenous tissue.

**Epidemiology**
This tumour accounts for 2-6% of ovarian stromal tumours, and more than 80% occur in young women in the second and third decades (433).

**Clinical features**
Presenting symptoms include menstrual abnormalities or abdominal discomfort (433,1280a,1409a,1695a). Hormonal manifestations are rare (433), although a few tumours have been shown to produce estrogens or androgens (614,1222,1778,2315,2964). Virilization may occur in pregnant women (419,738,1308).

**Macroscopy**
The tumour is typically unilateral and sharply demarcated, measuring 3-17 cm in diameter. The sectioned surface is solid, grey-white with occasional yellow foci and usually contains oedematous or cystic areas.

**Histopathology**
Histological examination shows a characteristic pattern with pseudolobulation of the cellular areas separated by hypocellular areas of densely collagenous tissue.
nous or oedematous tissue. The cellular areas contain prominent thin-walled vessels with varying degrees of sclerosis admixed with both spindle and round cells, the latter may resemble luteinized theca cells or show perinuclear vacuolization.

Histochemical studies show the activity of steroidogenesis-related enzymes (1575, 2537) and immunoreactivity for desmin and smooth muscle actin, as well as vimentin (419, 1419, 2512, 2637).

**Prognosis and predictive factors**
The tumour is benign, and there have been no recurrent cases.

**Signet-ring stromal tumour**

**Definition**
A rare stromal tumour composed of signet-ring cells that do not contain mucin, glycogen or lipid (697, 2332, 2605, 2811).

**Clinical findings**
This tumour occurs in adults and is hormonally inactive.

**Macroscopy**
Macroscopically the tumours, may be both solid and cystic or uniformly solid.

**Histopathology**
Histological examination shows a diffuse proliferation of spindle and round cells; the latter show eccentric nuclei with a single large cytoplasmic vacuole and resemble signet-ring cells. The tumour may be composed entirely of signet-ring cells or may occur as a component of an otherwise typical fibroma. With the exception of one case (697), nuclear atypia and mitotic figures are not present. Negative staining for mucin distinguishes this tumour from the Krukenberg tumour. All of the reported cases are benign.

**Sertoli-stromal cell tumours**

**Definition**
Tumours containing in pure form or in various combinations Sertoli cells, cells resembling rete epithelial cells, cells resembling fibroblasts and Leydig cells in variable degrees of differentiation.

**ICD-O codes**
Sertoli-Leydig cell tumour group
- Well differentiated: 8631/0
- Of intermediate differentiation: 8631/1
- With heterologous elements: 8634/1
- Poorly differentiated: 8631/3
- With heterologous elements: 8634/3
- Retiform: 8633/1
- With heterologous elements: 8634/1
- Sertoli cell tumour, NOS: 8640/1

**Sertoli-Leydig cell tumour group**

**Definition**
Tumours composed of variable proportions of Sertoli cells, Leydig cells, and in the case of intermediate and poorly differentiated neoplasms, primitive gonadal stroma and sometimes heterologous elements.

**Synonym**
Androblastoma.

**Epidemiology**
Sertoli-Leydig cell tumours (SLCTs) are rare, accounting for <0.5% of ovarian neoplasms; intermediate and poorly differentiated forms are most common. SLCTs have been reported in females from 2-75 years of age with a mean age of 23-25 years in different studies (2459, 3217, 3243).
Clinical features

Signs and symptoms
One-third of patients are virilized, and others may have estrogenic manifestations. Androgenic manifestations include amenorrhea, hirsutism, breast atrophy, clitoral hypertrophy and hoarseness, whereas estrogenic effects include isosexual pseudoprecocity and menometrorrhagia. One-half of the patients have no endocrine manifestations, and the symptoms are non-specific. Patients with poorly differentiated neoplasms are slightly more likely to present with androgenic manifestations. About 10% of cases have tumour rupture or ovarian surface involvement, and 4% have ascites {3217}.

Imaging
A solid, cystic or solid and cystic mass may be identified on ultrasound, computed tomography or magnetic resonance imaging.

Macroscopy
Over 97% of SLCTs are unilateral. They may be solid, solid and cystic or, rarely, cystic. The size ranges from not detectable to 35 cm (mean 12-14 cm). Poorly differentiated tumours are larger. Solid areas are fleshy and pale yellow, pink or grey. Areas of haemorrhage and necrosis are frequent, and torsion and infarction may be seen.

Tumour spread and staging
About 2-3% of tumours have spread beyond the ovary at presentation {3217}.

Histopathology
In well differentiated SLCTs, Sertoli cells are present in open or closed tubules and lack significant nuclear atypia or mitotic activity {3216}. There is a delicate fibrous stroma in which Leydig cells may be found in small clusters. In tumours of intermediate differentiation, cellular lobules composed of hyperchromatic spindle-shaped gonadal stromal cells with poorly defined cytoplasm are separated by oedematous stroma. These merge with cords and poorly developed tubules of Sertoli cells, some with atypia. With better differentiation of Sertoli cell elements, the distinction between the stromal and Sertoli cell components is more easily made. Leydig cells are found in clusters at the periphery of the cellular lobules or admixed with other elements. They may be vacuolated, contain lipofuscin or rarely have Reinke crystals. Mitotic figures average 5 per 10 high power fields. Mitotic figures are rare among the Leydig cells, which also lack cytological atypia.

In poorly differentiated tumours, a sarcomatoid stroma resembling primitive gonadal stroma is a dominant feature, and the lobulated arrangement of SLCT intermediate differentiation is absent. Occasional tumours contain bizarre nuclei. The mitotic activity in the Sertoli and stromal elements is variable with a mean of over 20 per 10 high power fields.

Immunoprofile
Positivity is seen for vimentin, keratin and alpha-inhibin with differing intensity of expression between sex cord and stromal areas. Rarely, positivity for epithelial membrane antigen may be seen. Positivity for estrogen and progesterone receptors may also be seen in a minority of cases.

Grading
SLCTs are subdivided into well differentiated, intermediate and poorly differentiated forms based on the degree of tubular differentiation of the Sertoli cell component (decreasing with increasing grade) and the quantity of the primitive gonadal stroma (increasing with increasing grade). Leydig cells also decrease with increasing grade. Heterologous elements and/or a retiform pattern may be seen in all but the well differentiated variant.

Somatic genetics
Analysis of six SLCTs has shown limited, if any, loss of heterozygosity with 10 polymorphic DNA markers that have shown high rates of loss of heterozygosity in a variety of tumours. Three of these were assessed for clonality by examining the DNA methylation pattern at a polymorphic site to the androgen receptor gene. The Leydig cells in these three cases were all polyclonal in contrast to the cells from a pure Leydig cell tumour that were monoclonal. These findings suggest that the Leydig cells in SLCTs are reactive cells of ovarian stromal origin and not a neoplastic component of the tumour {1902}. Trisomy 8 was reported as the sole karyotypic abnormality in a SLCT that metastasized {1756}.

Fig. 2.76 Poorly differentiated Sertoli-Leydig cell tumour. A Heterologous elements consisting of mucinous glands are intimately associated with primitive gonadal stroma. B A nodule of primitive gonadal stroma is composed of poorly differentiated spindle-shaped cells with apoptotic bodies.
Genetic susceptibility
A familial occurrence of SLCTs in association with thyroid disease has been reported (1344) with occasional reports of other families since then. The thyroid abnormalities are usually adenomas or nodular goitres. Autosomal dominant inheritance with variable penetrance has been suggested as the method of genetic transmission. SLCT has been reported in association with cervical sarcoma botryoides in three cases (1026).

Prognosis and predictive factors
The mortality from SLCTs as a group is low and is confined to those of intermediate and poor differentiation. Poor differentiation, tumour rupture and heterologous mesenchymal elements were identified as features correlating with the development of metastases (302, 2459). In one large series none of the well differentiated tumours, 11% of those of intermediate differentiation and 59% of those that were poorly differentiated behaved in a clinically malignant fashion (3217). Presentation with stage II or higher disease is also associated with a poor outcome. However, tumours without any apparent poor prognostic factors may behave in an aggressive fashion (1903).

Sertoli-Leydig tumour with heterologous elements
Definition
A SLCT that contains either macroscopic or histological quantities of a tissue not regarded as intrinsic to the sex cord-stromal category. Such elements include epithelial (mostly mucinous) and/or mesenchymal tissues (most commonly chondroid and rhabdomyoblastic) and tumours arising from these elements.

Clinical features
The presence of heterologous elements does not alter the presentation, but 20% of patients have a slightly raised serum alpha-fetoprotein (AFP) due in some cases to hepatocytes as a heterologous element.

Macroscopy
Part or the entire cystic component of a SLCT may be mucinous in type; however, heterologous elements are only occasionally diagnosed macroscopically.

Histopathology
Heterologous elements are seen in approximately 20% of SLCTs. They occur only in those of intermediate or poor differentiation or in retiform tumours but are not identified in well-differentiated tumours. Heterologous mesenchymal elements occur in 5% of SLCTs and usually consist of cartilage, skeletal muscle or rhabdomyosarcoma. They may be admixed with the sex cord areas of the tumour or present as discrete areas. Both cartilage and skeletal...
muscle may appear cellular and of fetal type. The mucinous epithelium is usually bland intestinal or gastric-type epithelium, but sometimes shows borderline or malignant change. Argentaffin cells, goblet cells and carcinoid may be seen. The gonadal stroma may condense around areas of mucinous epithelium, a useful clue to the diagnosis of a SLCT in a tumour that appears to be a mucinous cystadenoma. Hepatocytic differentiation may be recognized by the presence of bile plugs or an acinar arrangement of hepatocytes, but immunohistochemistry is usually necessary to distinguish hepatocytes from Leydig cells (1904).

**Immunoprofile**
Variable positivity is seen in the sex cord elements for vimentin, keratin and alpha-inhibin. The immunoprofile of the heterologous elements is what would be expected from their constituent tissues. The mucinous elements show more extensive staining for cytokeratin 7 than for cytokeratin 20. They are positive for epithelial membrane antigen and may be focally positive for chromogranin. Leydig cells are negative for pan-keratin, CAM 5.2 and AFP but show intense positivity for vimentin and alpha-inhibin. These findings distinguish them from hepatocytes. AFP may be identified in endodermal-like structures in some cases.

**Prognosis and predictive factors**
The small number of cases of this tumour reported make it difficult to determine the significance of individual elements. Heterologous mesenchymal elements (skeletal muscle or cartilage) or neuroblastoma imply a poor outcome with 8 of 10 patients dead of disease (2291). In contrast, gastrointestinal epithelium or carcinoid as the heterologous element does not have prognostic significance (3207). Retiform Sertoli-Leydig cell tumour and variant with retiform elements

**Definition**
Retiform SLCT is composed of anastomosing slit-like spaces that resemble the rete testis and comprise 90% or more of the tumour. Tumours with at least 10% but less than 90% retiform elements are classified as being of intermediate or poor differentiation and qualified "with retiform elements".

**Epidemiology**
Retiform tumours tend to occur in younger patients but may occur at any age (3209). Virilization is less common in tumours with a retiform pattern.

**Macroscopy**
Retiform tumours may contain papillae or polypoid structures.

**Histopathology**
Like heterologous elements, retiform areas occur only in SLCTS of intermediate and poor differentiation (2471,3209). They vary from slit-like spaces to areas comprising a complex microcystic pattern. Dilated spaces may be continuous with sex cord areas of the tumour. The lining cells may be flattened and non-specific or cuboidal and sertoliform. The lumens frequently contain variably inspissated eosinophilic material resembling colloid. Within the SLCT category, retiform tumours shows the highest incidence of heterologous elements (3209).

**Immunoprofile**
Retiform areas stain with keratin and show moderate staining for alpha-inhibin, with a reversed pattern seen in sex cord and stromal areas of the tumour. Vimentin may show subnuclear localization in the retiform areas.

**Differential diagnosis**
Serous tumours, yolk sac tumours and malignant müllerian mixed tumours may resemble a retiform SLCT (3209). The presence of primitive gonadal stroma, heterologous elements, Leydig cells and/or alpha-inhibin positivity assists in making the diagnosis.

**Prognosis and predictive factors**
Approximately 25% of patients with SLCTS that contain retiform elements will have an aggressive course (3209). Many have stage II or higher disease, poor differentiation and/or heterologous elements.

**Sertoli cell tumour**

**Definition**
A neoplasm composed of Sertoli cells arranged in hollow or solid tubular formations with rare, if any, Leydig cells. Simple or complex annular tubules are dominant in those lesions that occur in association with the Peutz-Jeghers syndrome.

**Epidemiology**
Sertoli cell tumours are rare (2882). Patients range in age from 2-79 years.

![Fig. 2.80 Sertoli cell tumour, lipid-rich variant (folliculome lipidique). The Sertoli cells have abundant vacuolated cytoplasm filled with lipid.](image)
Clinical features
The tumours are functional in 40-60% of cases, most often estrogenic, but occasionally androgenic or rarely both. Rarely, the tumour produces progesterone. Clinical manifestations include isosexual pseudoprecocity, menometrorrhagia, amenorrhea, hirsutism, breast atrophy, clitoral hypertrophy and hoarseness. Cases with menstrual disturbances or postmenopausal bleeding may show hyperplasia or adenocarcinoma of the endometrium. A peritoneal decidual reaction may be seen. Patients with Sertoli cell tumour may have elevated levels of serum estrogen, progesterone and lutetizing hormone. Rarely, the tumour may cause hypertension due to renin production.

Macroscopy
These are unilateral neoplasms, and the ovaries are involved with equal frequency. They range in size from 1-28 cm with an average of 7-9 cm. They are well circumscribed, solid neoplasms with a smooth or lobulated external surface, a fleshy consistency and a yellow-tan sectioned surface. Areas of haemorrhage and/or cystic degeneration may be seen in larger tumours. Rare examples are totally cystic or are solid with fibrosis and ossification.

Histopathology
A variety of tubular arrangements characterize Sertoli cell tumours. The tubular pattern is either open or closed (with paired cell arrangements) and simple or complex. Simple tubules are surrounded by a basement membrane and may contain a central hyaline body. Complex tubules form multiple lumens often filled with hyaline bodies and surrounded by a thick basement membrane that may coalesce to form hyalinized areas. Diffuse and pseudopapillary patterns may be seen. In some tumours, cells distended by intracytoplasmic lipid are dominant in a pattern known as "folliculome lipidique". The Sertoli cell tumours that occur in women with the Peutz-Jeghers syndrome may have abundant eosinophilic cytoplasm, termed the oxyphilic variant [852]. The nucleus is typically oval or spherical with a small nucleolus. The cytoplasm is clear or lightly vacuolated, stains for lipid are positive, and glycogen may be demonstrated. Mitotic figures are usually scanty (<1 per 10 high power fields), but >9 mitotic figures per 10 high power fields may be seen in tumours from younger women. The neoplasm may contain rare Leydig cells, but lacks the primitive gonadal stroma characteristic of Sertoli-Leydig cell tumours.

Immunoprofile
Sertoli cell tumours are variably positive for keratins, vimentin and alpha-inhibin. CD99 and calretinin are positive in about 50% of cases. The tumours are negative for epithelial membrane antigen.

Electron microscopy
A diagnostic feature of Sertoli cell tumour is the presence of Charcot-Böttcher (CB) filaments and Spangaro bodies. These bodies represent aggregates of intracytoplasmic microfilaments of varying size and are not present in every cell or every tumour. CB filaments have been found most frequently in the complex tubular variant, the so-called sex cord tumour with annular tubules (SCTAT).

Differential diagnosis
Sertoli cell tumours must be distinguished from struma ovarii, carcinoid and endometrioid carcinoma (see section on endometrioid carcinoma). Phenotypic females with the androgen insensitivity syndrome (AIS) may be incorrectly diagnosed as having a Sertoli cell tumour of the ovary if the syndrome has not been diagnosed preoperatively [2498]. On the other hand, Sertoli cell tumours can occur in the testes of patients with AIS. While most are benign, rare malignant Sertoli cell tumours have been reported in this setting [3165].

Somatic genetics
There is little information on chromosomal abnormalities in these tumours. An extra isochromosome 1q was seen in one tumour [2208].

Genetic susceptibility
A variety of Sertoli cell phenotypes including SCTAT [2599], oxyphilic [852] and lipid rich (folliculome lipidique) variants have been described in patients with the Peutz-Jeghers syndrome (PJS), an autosomal dominant disease with a propensity for breast, intestinal and gynaecological neoplasia.

Prognosis and predictive factors
These tumours are typically benign. In the rare forms that behave clinically in an aggressive fashion, infiltration of the ovarian stroma, extension beyond the ovary and intravascular extension may be seen. Cytological atypia and a high...
mitotic rate may be present in these tumours.

**Stromal-Leydig cell tumour**

**Definition**
An ovarian stromal tumour composed of fibromatous stroma and clusters of Leydig cells containing crystals of Reinke.

**Clinical features**
This tumour is virilizing in approximately one-half of the cases.

**Macroscopy**
These extremely rare neoplasms are usually well circumscribed (302,2165,2842). The sectioned surface has been described as lobulated with a yellow-white appearance. They may be bilateral.

**Histopathology**
Stromal-Leydig cell tumours have two components. Spindle-shaped or ovoid stromal cells identical to those of a fibroma or thecoma are present together with Leydig cells containing Reinke crystals (2789,3252). Typically, in these neoplasms the fibrothecomatous element predominates with the Leydig cell component comprising small nodular aggregates.

Definitive diagnosis requires the presence of Reinke crystals, otherwise the neoplasm would be categorized as luteinized thecoma. Since Reinke crystals may be difficult to identify and since sampling errors may occur, it has been suggested that stromal-Leydig cell tumours are more common than the literature would suggest.

**Prognosis and predictive factors**
The clinical behaviour of stromal-Leydig cell tumours is benign, and neither clinical recurrence nor metastasis has been documented.

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**Sex cord-stromal tumours of mixed or unclassified cell types**

**Definition**
Sex cord-stromal tumours that do not fall in the granulosa-stromal, Sertoli-stromal or steroid cell categories.

**ICD-O codes**
- Sex cord tumour with annular tubules 8623/1
- Variant associated with Peutz-Jeghers syndrome 8623/0
- Gynandroblastoma 8632/1
- Sex cord-stromal tumour, NOS 8590/1

**Sex cord tumour with annular tubules**

**Definition**
A tumour composed of sex cord (Sertoli) cells arranged in simple and complex annular tubules (2599).

**Synonym**
Sertoli cell tumour, annular tubular variant.

**Epidemiology**
Patients with this tumour most commonly present in the third or fourth decades, but the age ranges from 4-76 years. About one-third of cases occur in women with Peutz-Jeghers syndrome (PJS). The average age of patients with PJS is in the mid-twenties and of those unassociated with PJS in the mid-thirties.

**Clinical features**
Nearly all women without PJS present with a palpable mass. Isosexual pseudoprecocity or other features of aberrant estrogen occurs in about 40% of cases, and, occasionally, there are progesterone effects. Those tumours that are associated with PJS are found either incidentally at autopsy or in ovaries removed as part of treatment for other gynaecological disease.

**Macroscopy**
These are unilateral neoplasms except for those occurring in the PJS, which are usually bilateral. PJS-associated lesions are usually macroscopically undetectable; when visible, the tumourlets are multiple and <3 cm in diameter. Bilateral lesions are present in two-thirds of women. Non-PJS cases may be up to 33 cm in diameter. The sectioned surface of the tumours is solid and yellow. Calcification or cystic degeneration may be apparent.

**Histopathology**
Regardless of the clinical setting, the annular tubules show Sertoli cells with pale cytoplasm and nuclei arranged antipodally around a single hyaline body (simple annular tubules) or multiple hyaline bodies (complex annular tubules). Classic tubular Sertoli cell arrangements may be admixed. In PJS lesions the annular tubules are typically widely scattered in the ovarian stroma without forming a distinct mass.
Tumours unassociated with PJS form masses of simple and complex tubules separated by sparse fibrous stroma. Extensive hyalinization may develop. The neoplastic cells may spill over beyond the confines of the tubules and infiltrate the surrounding stroma. Mitotic figures occasionally exceed 4 per 10 high power fields and rarely exceed 10 per 10 high power fields. Areas of well differentiated Sertoli cell tumour characterized by elongated solid tubules and/or microfollicular granulosa cell tumour are often present. Calcification of the hyaline bodies is typically found in over half of the tumours associated with PJS.

Electron microscopy
Ultrastructural assessment has shown Charcot-Böttcher filaments in several cases [2882]. While not required for diagnosis, their presence confirms the identification of the sex cord component as Sertoli cells.

Histogenesis
Although there is ultrastructural evidence supporting differentiation towards Sertoli cells in SCTAT, the histological and clinical features are sufficiently distinctive to merit its classification as a specific form of sex cord-stromal tumour.

Prognosis and predictive factors
All PJS-associated tumourlets have been benign. Up to 25% of SCTATs that occur in the absence of the PJS have been clinically malignant. Tumours with an infiltrative growth pattern and mitotic figures beyond the usual 3-4 per 10 high power fields are more likely to recur or otherwise behave aggressively. It is difficult, however, to predict the behaviour of individual cases. Some tumours produce müllérian inhibiting substance and/or alpha-inhibin, and these tumour markers may be useful in monitoring the course of disease in those cases [1091,2304]. Recurrences are often late and may be multiple. Spread through lymphatics may result in regional and distant lymph node involvement.

Somatic genetics
Germline mutations in a gene encoding serine-threonine kinase have been identified in a SCTAT associated with PJS but not in sporadic cases [548].

Gynandroblastoma

Definition
A tumour composed of an admixture of well differentiated Sertoli cell and granulosa cell components with the second cell population comprising at least 10% of the lesion.

Clinical features
An extremely rare tumour, gynandroblastoma generally occurs in young adults, though it may be encountered in a wide age range (96,432,1820,1996). Nearly all tumours present in stage I and may have either estrogenic or androgenic manifestations. Variable in size, they may be massive (up to 28 cm) with a predominantly solid sectioned surface showing a few cysts.

Histopathology
Well formed hollow tubules lined by Sertoli cells are generally admixed with rounded islands of granulosa cells growing in a microfollicular pattern. Variation from this typical histology with a juvenile granulosa cell pattern or an intermediate or poorly differentiated Sertoli-Leydig cell tumour with or without heterologous elements has been reported [1820]. The tumours are alpha-inhibin positive.

Prognosis and predictive factors
Almost all tumours are stage I at initial presentation and clinically benign. It is important to mention the components of the tumour in the diagnosis, in particular whether the granulosa cell component is of adult or juvenile type and also the subtype of Sertoli-Leydig cell tumour.

Sex cord-stromal tumours 159
 Unclassified sex cord-stromal tumour

Definition
Sex cord-stromal tumours in which there is no clearly predominant pattern of testicular or ovarian differentiation [2605].

Epidemiology
They account for 5-10% of tumours in the sex cord-stromal category.

Clinical features
The tumour may be estrogenic, androgenic or non-functional [2619,2701, 3196].

Histopathology
Histologically, the tumours show patterns and cell types that are intermediate between or common to granulosa-stromal cell tumours and Sertoli-stromal cell tumours.

Prognosis and predictive factors
The prognosis is similar to that of granulosa cell tumours and SLCTs of similar degrees of differentiation [2619].

Steroid cell tumours

Definition
Tumours that are composed entirely or predominantly (greater than 90%) of cells that resemble steroid hormone-secreting cells. This category includes the stromal luteoma, steroid cell tumour, not further classified and the Leydig cell tumours that do not have another component.

ICD-O codes
Steroid cell tumour, NOS 8670/0
Well differentiated 8670/0
Malignant 8670/3
Stromal luteoma 8610/0
Leydig cell tumour 8650/0

Synonym and historical annotation
The designation “lipid cell tumour” is no longer recommended because it is inaccurate as well as nonspecific, since up to 25% of tumours in this category contain little or no lipid [2605]. The term “steroid cell tumour” has been accepted by the World Health Organization (WHO) because it reflects both the morphological features of the neoplastic cells and their propensity to secrete steroid hormones.

Steroid cell tumour, not otherwise specified

Definition
These are steroid cell tumours that cannot be classified into one of the aforementioned groups. It is probable that some of these cases represent Leydig cell tumours in which Reinke crystals cannot be identified. Some may also represent large stromal luteomas where a parenchymal location can no longer be established.

Clinical features
They are usually associated with androgenic manifestations and occasionally with estrogenic effects [1163]. Rare neoplasms have also been associated with progestogenic effects, Cushing syndrome or other paraneoplastic syndromes due to hormone secretion [3218].

Macroscopy
These neoplasms are often large and are usually well circumscribed, often having a lobulated appearance. Occasional neoplasms are bilateral. The sectioned surface ranges from yellow to brown or black. Especially in large tumours, areas of haemorrhage and necrosis may be seen.

Histopathology
These neoplasms are usually composed of solid aggregates of cells with occasional nests or trabeculae. Tumour cells are polygonal with cytoplasm that is usually granular and eosinophilic but which may be vacuolated. Intracytoplasmic fuscinc pigment may be identified. Nuclei may be bland, but in some cases there is considerable nuclear atypia and significant numbers of mitotic figures may be found. Areas of haemorrhage and necrosis can be present. Intracytoplasmic lipid can usually be identified with special stains and rarely may be so abundant as to result in a signet-ring appearance. Occasional tumours contain a considerable amount of fibrous stroma.

Immunoprofile
These neoplasms are usually immunoreactive to alpha-inhibin and variably with anti-cytokeratin antibodies and vimentin.

Differential diagnosis
Luteoma of pregnancy may mimic a lipid-poor or lipid-free steroid cell tumour. The former is usually discovered in patients at caesarean section with a term pregnancy and typically occurs in multiparous Black patients in their third or fourth decade. Also in the differential diagnosis are oxyphilic variants of a number of other ovarian tumours, e.g. struma ovarii, clear cell carcinoma, primary or secondary malignant melanoma and carcinoid.

Prognosis and predictive factors
Approximately one-third of these neoplasms are clinically malignant, and they sometimes have extensive intra-abdominal spread at presentation. Malignant tumours are more likely to be greater than 7 cm diameter, contain areas of haemorrhage and necrosis, exhibit moderate to marked nuclear atypia and have a mitotic count of two or more per 10 high power fields. Occasionally, however, as with other endocrine neoplasms, the behaviour may be unpredictable, and tumours lacking these histological features may behave in a malignant fashion.

Stromal luteoma

Definition
Stromal luteomas are clinically benign steroid cell neoplasms of ovarian stro-
Clinical features
These neoplasms typically occur in postmenopausal women (2171,2472) (average age 58 years) but may occur in young women, pregnant women (2165) or children. They are usually associated with androgenic manifestations, but occasionally produce estrogenic effects and are associated with endometrial carcinoma (1279,2455). In single reports ovarian Leydig cell tumours have been associated with multiple endocrine neoplasia syndrome (2630) and congenital adrenal hyperplasia (1718).

Immunoprofile
Leydig cell tumours of all types are intensely positive for alpha-inhibin and vimentin. There may be focal reactivity for keratins (CAM 5.2, AE1/AE3) with positivity for actin, CD68, desmin, epithelial membrane antigen and S-100 protein reported (2620).

Prognosis and predictive factors
The clinical behaviour of all neoplasms in the pure Leydig cell category is benign, and neither clinical recurrence nor metastasis has been documented.

Hilus cell tumour
Definition
A Leydig cell tumour arising in the ovarian hilus separated from the medullary stroma.

Macroscopy
Hilus cell tumours are usually small, well circumscribed lesions located at the ovarian hilus and typically have a red brown to yellow appearance on sectioning. Rarely, they are bilateral (739,1718). When they are larger, the hilar location may no longer be apparent.

Histopathology
On histological examination the lesion is well circumscribed and comprised of cells with abundant cytoplasm that usually is eosinophilic but which may be clear with abundant intracytoplasmic lipid. Lipofuscin pigment is often seen, and characteristic Reinke crystals were present in 57% of cases in the largest series (2171). These are eosinophilic, rod-shaped inclusions. Occasionally, they are numerous, but they are often identified only after extensive searching.

PTAH histological staining or electron microscopy may facilitate their identification. Often the nuclei in Leydig cell tumours cluster with nuclear-rich areas separated by nuclear-free zones. The nuclear features are usually bland, but occasionally focal nuclear atypia may be found, an observation of no clinical significance. Mitotic figures are rare. Often, there is a background of hyperplasia of the adjacent non-neoplastic hilar cells in association with non-myelinated nerve fibres.

Although the definitive diagnosis of a hilar cell tumour requires the identification of Reinke crystals, a presumptive diagnosis can be made without crystals if the typical histological features are present in a neoplasm with a hilar location, especially if it is associated with hilus cell hyperplasia or nerve fibres (2171).

Leydig cell tumour, non-hilar type
Definition
A Leydig cell tumour that originates from the ovarian stroma and containing crystals of Reinke.

Epidemiology
Leydig cell tumours of non-hilar type have been reported much less often than hilus cell tumours, but their true relative frequency is unknown.

Macroscopy
These tumours are macroscopically well circumscribed and centered in the medullary region (2472).

Histopathology
They are histologically composed of steroid cells without discernible lipid and surrounded by ovarian stroma that often shows stromal hyperthecosis. Leydig cells containing demonstrable crystals of Reinke must be identified histologically in order to make the diagnosis, and lipofuscin pigment is often present.

Histogenesis
These tumours originate from the ovarian stroma, an origin supported by the rare non-neoplastic transformation of ovarian stromal cells to Leydig cells (2789).
Germ cell tumours

Definition
A heterogeneous group of tumours reflecting the capacity for multiple lines of differentiation of the main stem cell system. The great majority of these neoplasms originate at different stages of development from germ cells that colonize the ovary.

Epidemiology
Germ cell tumours account for approximately 30% of primary ovarian tumours, 95% of which are mature cystic teratomas [1409,1502]. The remaining germ cell tumours are malignant and represent approximately 3% of all ovarian cancers in Western countries but have been reported to represent up to 20% of ovarian tumours in Japanese women [1970]. The median age at presentation is 18 years [883]. Malignant germ cell tumours are the most common ovarian cancer among children and adolescent females. Approximately 60% of ovarian tumours occurring in women under the age of 21 are of germ cell type, and up to one-third of them may be malignant [1555].

Aetiology
The aetiology of ovarian germ cell malignancies is unknown.

Clinical features
Signs and symptoms
Pain and a mass are the common presentations in young women [2586, 2587,2903]. Teenagers who present with abdominal masses and who have never menstruated should be evaluated for the possibility of a gonadoblastoma that has undergone malignant progression. Preoperative karyotyping of such individuals can be helpful to identify underlying chromosomal abnormalities in cases of gonadoblastoma.

Imaging
The ultrasonographic appearance of dermoid cyst ranges from a predominantly solid-appearing mass due to the echogenic aspect of sebaceous material intermixed with hair to a predominantly cystic mass [2132]. Computed tomography can accurately diagnose a teratoma because of fat attenuation within the cyst, and its complex appearance with dividing septa, hypodensity, calcified structures, and the identification of the Rokitansky protuberance [1080,2132]. Radiographic studies of fetiform teratoma demonstrate portions of skull, vertebra and limb bones within the tumour [19]. There are no diagnostic findings for other germ tumours; they often have solid and cystic components.

Histopathology
Morphologically, the different tumour types present in this group replicate in a distorted, grotesque form various stages of embryonal development from early, transient structures to mature adult tissues that in their turn may also be capable of undergoing malignant change [2248].

Histogenesis
As for histogenesis, they are believed to be from the primordial germ cells that migrate into the gonadal ridge at 6 weeks of embryonic life [2848]. A small proportion may also arise from non-germ stem cells present in the adult female genital tract [2039].

Primitive germ cell tumours
Definition
Tumours that contain malignant germ cell elements other than teratoma.

ICD-O codes
Dysgerminoma 9060/3
Yolk sac tumour 9071/3
Embryonal carcinoma 9070/3
Polyembryoma 9072/3
Non-gestational choriocarcinoma 9100/3
Mixed germ cell tumour 9085/3

Dysgerminoma
Definition
A tumour composed of a monotonous proliferation of primitive germ cells associated with connective tissue septa containing varying amount of lymphocytes and macrophages. Occasionally, syncytiotrophoblastic differentiation or somatic cysts occur. This tumour is identical to testicular seminoma.

Macroscopy
The usually well encapsulated tumour masses are apparently unilaterial in 90% of cases. Macroscopic involvement of the contralateral ovary is apparent in 10% of cases, and in another 10% occult foci of dysgerminoma can be detected by biopsy [1920]. Tumours average 15 cm in maximal dimension and on section are solid, uniform or lobular and creamy white or light tan. Irregular areas of coag-

Fig. 2.87 Dysgerminoma in a 28 year old nulligravida woman. A Magnetic resonance image sagital view shows a 10 x 15 cm predominantly solid tumour with some central cystic changes. B Sectioned surface of the tumour shows a predominantly solid, multilobulated appearance with some cystic degeneration and foci of necrosis.
ulative necrosis may be present and may be associated with cystic change or macroscopic calcification. However, the presence of minute, sandy calcifications should point towards the presence of a concomitant gonadoblastoma. Focal haemorrhagic areas may be indicative of the presence of other germ cell components, possibly containing trophoblastic tissue.

**Histopathology**

The proliferating germ cells have a monotonous appearance with a polygonal shape, abundant pale cytoplasm and fairly uniform nuclei. They aggregate in cords and clumps, although sometimes the lack of cohesion between cells may lead to the formation of pseudoglandular spaces. Although the stroma is usually reduced to thin perivascular sheaths, occasionally it can be abundant. It always contains variable amounts of chronic inflammatory infiltrate, mainly composed of T lymphocytes (700) and macrophages. In fact, epithelioid granulomas are a prominent feature in a quarter of cases. Inflammation can also be present in the metastases. The mitotic rate is variable, and some tumours show anisokaryosis. Differentiation in the form of syncytiotrophoblastic cells is found in 5% of cases (3246). In these cases, beta-human chorionic gonadotropin (β-hCG)-secreting syncytiotrophoblast originates directly from dysgerminoma cells without intervening cytotrophoblast.

**Immunoprofile**

Most dysgerminomas show positivity for vimentin and placental-like alkaline phosphatase (PLAP) (1660,2011), the latter is usually found in a membranous location. An inconstant and heterogeneous cytoplasmic positivity can be found to cytokeratins (rarely), desmin, glial fibrillary acidic protein, as well as to S-100 protein and carcinoembryonic antigen (CEA). C-kit gene product (CD117) is present in dysgerminoma as it is in seminoma (2965), further supporting the similarity to its testicular counterpart.

**Precursor lesions**

There is no known precursor lesion for the vast majority of dysgerminomas, except for those arising from gonadoblastoma.

**Histogenesis**

Some dysgerminomas may subsequently be the precursors of other primitive germ cells neoplasms such as yolk sac tumour (2185).

**Prognosis and predictive factors**

Dysgerminomas respond to chemotherapy or radiotherapy. The clinical stage of the tumour is probably the only significant prognostic factor (2605). The presence of a high mitotic index and, in some
cases, anisokaryosis has no prognostic implication. The behaviour of dysgerminoma with trophoblastic differentiation is identical to the usual type, but with the advantage of having β-hCG as a serum marker.

**Yolk sac tumour**

**Definition**

Yolk sac tumours are morphologically heterogeneous, primitive teratoid neoplasms differentiating into multiple endodermal structures, ranging from the primitive gut to its derivatives of extraembryonal (secondary yolk sac vesicle) and embryonal somatic type, e.g. intestine, liver (2035). These neoplasms have many epithelial patterns and are typically immunoreactive for alpha-fetoprotein.

**Synonym and historical annotation**

Since the secondary yolk sac component represents only one of its many lines of differentiation, the current nomenclature is clearly restrictive. Perhaps the term “endodermal primitive tumours” would be more accurate in defining all the possible lines of differentiation, both epithelial and mesenchymal, that occur in these neoplasms.

The term “endodermal sinus tumour”, although still in use, is misleading, since the endodermal sinus is neither a structure present in human embryogenesis (1463) nor is it a constant feature of these neoplasms, as it only occurs in a minority of cases (1537).

**Macroscopy**

These tumours are usually well encapsulated with an average diameter of 15 cm (1537). The sectioned tumour surface is soft and grey-yellow with frequent areas of necrosis, haemorrhage and liquefaction. Cysts can be found in the periphery forming a honeycomb appearance (2043); rarely, they can be unicystic (522). A relatively frequent finding is the presence of a benign cystic teratoma in the contralateral ovary (3033).

**Histopathology**

Although a marked histological heterogeneity due to numerous patterns of differentiation coexisting in the same neoplasm may occur, almost invariably characteristic areas are present that allow for the correct diagnosis.

The characteristic reticular pattern formed by a loose, basophilic, myxoid stroma harbouring a meshwork of microcystic, labyrinthine spaces lined by clear or flattened epithelial cells with various degrees of atypia and cytoplasmic PAS-positive, diastase-resistant hyaline globules permits tumour identification. Irregular but constant amounts of hyaline, amorphous basement membrane material are found in relation to the epithelial cells. Both hyaline globules and the coarse aggregates of basement membrane material (2032,2979) are good histological indicators for tumour identity. Less frequently, in 13-20% of cases, papillary fibrovascular projections lined by epithelium (Schiller-Duval bodies) are found that bear a resemblance to the structures of the choriovitelline placenta of the rat, a fact that permitted the establishment of the teratoid, endodermal identity of these tumours (2896).

**Histological variants**

Less common histological variants include the polyvesicular vitelline tumour, solid yolk sac tumour, parietal yolk sac tumour, glandular types of yolk sac tumour and hepatoid yolk sac tumour. In the polyvesicular vitelline tumour cystic, organoid change of the epithelial spaces occurs that consists of multiple dilatations lined by mesothelial-like cells that coexist with a columnar, PAS-positive epithelium (2043).

The solid yolk sac tumour shows areas of solid epithelial sheets of cells with a characteristic abundant clear cytoplasm and numerous hyaline globules. These areas may resemble anaplastic changes of dysgerminoma or even clear cell tumours (1537) but have the distinctive immunophenotype of a yolk sac tumour. Although exceptionally rare, parietal-type yolk sac tumours that are AFP-negative have been described (596,620). They are analogous to the experimental murine tumour of the same name and can be identified by the massive deposition of amorphous extracellular basement membrane, a material similar to the Reichert membrane of the murine parietal yolk sac.

Differentiation into organized somatic endodermal derivatives such as endodermal type gland-like structures resembling early lung and intestine as well as liver tissue can occur in a focal fashion in as many as a third of tumours (1968, 2515,2979). In rare instances these differentiated tissues may become the predominant elements in the tumour. Extensive differentiation of endodermal type glands characterizes the glandular variants of yolk sac tumours, which may adopt different morphological subtypes.

**Table 2.05**

<table>
<thead>
<tr>
<th>Site differentiated</th>
<th>Tissue differentiated</th>
<th>Histological pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraembryonal endoderm</td>
<td>Primitive endoderm and secondary yolk sac</td>
<td>Reticular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endodermal sinus</td>
</tr>
<tr>
<td>Allantois</td>
<td>Polyvesicular</td>
<td></td>
</tr>
<tr>
<td>Murine-type (?) parietal yolk sac</td>
<td>Parietal</td>
<td></td>
</tr>
<tr>
<td>Somatic endoderm</td>
<td>Primitive intestine and lung (?)</td>
<td>Glandular</td>
</tr>
<tr>
<td></td>
<td>Early liver</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

Fig. 2.89 Yolk sac tumour. Sectioned surface is predominantly solid and fleshy with areas of haemorrhage, necrosis and cyst formation.
narr epithelium and surrounded by an oedematous, mesoblastic-type stroma that exhibits the characteristic appearance of early endoderm in both early differentiated intestine and the pseudoglandular phase of the embryonal lung (2038). Indeed, similar tumours are reported in the lung itself (1968). This gland-like aspect coupled with the presence of subnuclear vacuolization in the columnar lining mimics early secretory endometrium and endometrioid carcinoma of the ovary and, thus, was named the "endometrioid" variant (522).

Some endometroid yolk sac tumours are highly differentiated and difficult to distinguish from grade 1 endometrioid carcinoma. Another type of glandular yolk sac tumour is composed of typical small cribiform glands resembling early intestinal differentiation. This type has been termed the intestinal-type of yolk sac tumour (533). Extensive differentiation into hepatic tissue is another form of somatic differentiation (2515). In some yolk sac tumours extensive solid nodular areas of liver tissue can be found (2284) and can be so well formed that they reproduce their laminar structure complete with sinusoids and even haematopoiesis. Finally, since any immature teratoid tissue is considered to be capable of undergoing fully accomplished differentiation, it is possible that pure endodermal immature teratoma composed solely of AFP-secreting endodermal glands and mesenchyme may be closely related to yolk sac tumours (2042).

Predominance of mesenchymal, rather than epithelial, elements with differentiation into other components such as cartilage, bone or muscle may occur as a postchemotherapeutic conversion and be responsible for the occurrence of associated sarcomas in some cases (1854). The haematopoietic capacity of the normal secondary yolk sac may have its neoplastic counterpart in yolk sac tumours, where isolated cases of haematological disorders have been reported associated with ovarian yolk sac tumours (1782) in a similar way to those occurring in extragonadal germ cell tumours.

**Immunoprofile**

AFP is the characteristic marker of the epithelial component of yolk sac tumours, although it is not exclusive to them, as it can also be found in some ovarian tumours that are not of germ cell type. AFP is found as a dense granular cytoplasmic deposit and is absent in hyaline globules, which are rarely immunoreactive. A host of other substances can be found in yolk sac tumours recapitulating the complex functions of early endoderm, including those involved in haematopoiesis (1158, 2011). The usual positivity for cytokeratins may differentiate solid yolk sac tumour from dysgerminoma. CD30 is usually positive in embryonal carcinoma (736) but is only focally positive in yolk sac tumour. Leu M1, which is positive in clear cell carcinoma, is negative in yolk sac tumour. The absence of estrogen and progesterone receptors in yolk sac tumour differentiates areas of yolk sac epithelium from associated areas of true endometrioid tumour (533).

**Prognosis and predictive factors**

Because numerous patterns of differenti-
ation may coexist in the same neoplasm, their behaviour, with some exceptions (1500), is not conditioned by specific tumour morphology but shows a generally favourable response to chemotherapy. Although the histological appearance bears little prognostic implications, mature or well differentiated glandular forms may have an indolent course even when treated by surgery alone (1500, 2284).

**Embryonal carcinoma and polyembryoma**

**Definition**

Embryonal carcinoma is a tumour composed of epithelial cells resembling those of the embryonic disc and growing in one or more of several patterns, glandular, tubular, papillary and solid. Polyembryoma is a rare tumour composed predominantly of embryoid bodies resembling early embryos.

**Epidemiology**

These rare tumours are the ovarian counterparts of their more frequent testicular homologues. Many are reported as a component of mixed germ cell tumours that originate from gonadoblastoma (see section on mixed germ cell-sex cord stromal tumours), arising in Y-chromosome containing dysgenetic gonads (and thus are technically “testicular” tumours) or even in 46 XX gonads (3253). They are multipotent stem cell tumours reproducing the primitive stages of embryonal differentiation.

**Clinical features**

Clinically, β-hCG stimulation may determine various hormonal manifestations such as precocious pseudopuberty in premenarchal girls and vaginal bleeding in adult women (1536).

**Histopathology**

Histologically, embryonal carcinoma reveals disorganized sheets of large primitive AFP and CD30-positive cells (736,1536), forming papillae or crevices which coexist with β-hCG positive syncytiotrophoblasts as well as early teratoid differentiation such as squamous, columnar, mucinous or ciliated epithelia. Its even more infrequent organoid variant is called polyembryoma due to a structural organization into blastocyst-like formations that resemble early presomatic embryos. These so-called embryoid bodies show embryonic disks with corresponding amniotic or primary yolk sac cavities and are surrounded by a mesoblast-like loose connective tissue. The surrounding tissues can differentiate into endodermal structures such as intestine or liver (2287) and trophoblast. However close the resemblance to normal early structures, the sequences of early embryonal development are not reproduced (1969).

**Non-gestational choriocarcinoma**

**Definition**

A rare germ cell tumour composed of cytotrophoblast, syncytiotrophoblast and extravillous trophoblast.
Clinical features
Clinically, hormonal manifestations such as precocious pseudopuberty and vaginal bleeding are present in children and young adults.

Macroscopy
Macroscopically, tumours are large and haemorrhagic, and large luteinized nodules or cysts due to \( \beta \)-hCG stimulation may appear in the uninvolved ovarian tissue.

Histopathology
Morphologically identical to gestational choriocarcinoma, primary non-gestational choriocarcinoma is rare in pure form, differentiates as an admixture of cytotrophoblast, syncytiotrophoblast and extravillous trophoblast and is usually found associated with other germ cell components [2704]. Histologically, there are fenestrated or plexiform sheets or pseudopapillae of cytotrophoblast and extravillous trophoblast admixed with numerous syncytiotrophoblasts. Tumour can be found in blood-filled spaces and sinusoids. Vascular invasion is frequent. The immunophenotype is characteristic for each type of proliferating trophoblastic cell [1759] and includes cytokeratins, human placental lactogen and, above all, \( \beta \)-hCG.

Differential diagnosis
When found in a pure form in childbearing age, gestational choriocarcinoma, either primary in the ovary [3024] or metastatic [718] must be excluded. This may be accomplished by identifying paternal sequences by DNA analysis [1698,2655].

Prognosis and predictive factors
The distinction from gestational choriocarcinoma is important since non-gestational choriocarcinoma has a less favourable prognosis and requires more aggressive chemotherapeutic treatment regimens.

Mixed germ cell tumours
Definition
Mixed germ cell tumours are composed of at least two different germ cell elements of which at least one is primitive.

Clinical features
The value of tumour markers such as \( \beta \)-hCG and AFP in the diagnosis and follow-up of patients with mixed germ cell tumours containing elements of choriocarcinoma or yolk sac tumour has been proven over the years [2850]. Elevated serum levels of these markers should prompt a search for different components with extensive sampling of the tumour.

Histopathology
Histologically, the most common combination of neoplastic germ cell elements found in ovarian mixed germ cell tumours is dysgerminoma and yolk sac tumour [2850]. Additional neoplastic germ cell elements, including immature or mature teratoma, embryonal carcinoma, polyembryoma and/or choriocarcinoma, may also be present. All components of a mixed germ cell tumour and their approximate proportions should be mentioned in the diagnosis.

Most ovarian embryonal carcinomas are really malignant mixed germ cell tumours, usually admixed with yolk sac tumour and showing a large or predominant component of embryonal carcinoma [2850]. Although polyembryoma may have been the predominant malignant germ cell element within the tumour, a careful review of all the published cases of ovarian polyembryoma shows that other germ cell elements were also present [2850]. Also, ovarian choriocarcinoma of germ cell origin is in the majority of cases combined with other neoplastic germ cell elements. Immunohistochemical demonstration of \( \beta \)-hCG and AFP is a useful diagnostic modality in this group of tumours, as is the demonstration of PLAP in a component of dysgerminoma.

Prognosis and predictive factors
All elements in a malignant mixed germ cell tumour are capable of widespread metastatic dissemination. The metastases may be composed of a single neoplastic germ cell element or of various elements. Although these tumours are highly responsive to platinum-based chemotherapy, the therapeutic regimens should be based primarily on the most malignant elements of the tumour [2850].

Biphasic or triphasic teratomas
Definition
Tumours composed of derivatives of two or three primary germ layers (ectoderm, mesoderm, endoderm).
### ICD-O codes
- Immature teratoma: 9080/3
- Mature teratoma: 9080/0
- Cystic teratoma: 9080/0
- Dermoid cyst: 9084/0

### Immature teratoma

#### Definition
A teratoma containing a variable amount of immature, embryonal-type (generally immature neuroectodermal) tissue.

#### Epidemiology
Immature teratoma represents 3% of teratomas, 1% of all ovarian cancers and 20% of malignant ovarian germ cell tumours and is found either in pure form or as a component of a mixed germ cell tumour (989). It occurs essentially during the two first decade of life (from 1-46 years; average 18) (989,1174,2060).

### Macroscopy
Immature teratoma is typically unilateral, large, variegated (6-35 cm; average, 18.5), predominantly solid, fleshy, and grey-tan and may be cystic with haemorrhage and necrosis (989,2060).

### Histopathology
Immature teratoma is composed of variable amounts of immature embryonal-type tissues, mostly in the form of neuroectodermal rosettes and tubules, admixed with mature tissue. Neuroepithelial rosettes are lined by crowded basophilic cells with numerous mitoses (2060) and may be pigmented. Immature mesenchyme in the form of loose, myxoid stroma with focal differentiation into immature cartilage, fat, osteoid and rhabdomyoblasts is often present as well (2060). Immature endodermal structures including hepatic tissue, intestinal-type epithelium with basal vacuolization and embryonic renal tissue resembling Wilms tumour are encountered less frequently. Immature vascular structures may occur and are sometimes prominent.

### Grading
Based on the quantity of the immature neuroepithelial component, primary and metastatic ovarian immature teratomas (including peritoneal implants and lymph nodes metastases) are separately graded from 1 to 3 (2060). More recently the possibility of using a two-tiered (low grade and high grade) grading system was suggested (2072). Adequate sampling of the primary tumour (one block per 1 or 2 cm of tumour) and of all resected implants is crucial, as the tumour grade may vary in different implants.

#### Somatic genetics
Immature teratomas grades 1-2 are

### Table 2.06
Grading of ovarian immature teratomas.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Tumours with rare foci of immature neuroepithelial tissue that occupy less than one low power field (40x) in any slide.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Tumours with similar elements, occupying 1 to 3 low power fields (40x) in any slide.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Tumours with large amount of immature neuroepithelial tissue occupying more than 3 low power fields (40x) in any slide.</td>
</tr>
</tbody>
</table>

### Table 2.07
Management of immature teratomas according to grade of primary tumours and/or implants.

<table>
<thead>
<tr>
<th>Grade of Tumour and/or Implants</th>
<th>Three-tiered grading (2060)</th>
<th>Two-tiered grading (2072)</th>
<th>Stage</th>
<th>Combination chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 ovarian tumour</td>
<td>Low grade</td>
<td>Ia</td>
<td>Not required</td>
<td></td>
</tr>
<tr>
<td>Grade 2 or 3 ovarian tumour</td>
<td>High grade</td>
<td>Ia</td>
<td>Required</td>
<td></td>
</tr>
<tr>
<td>Grade 2 or 3 implants</td>
<td>High grade</td>
<td>≥ II</td>
<td>Required</td>
<td></td>
</tr>
<tr>
<td>Grade 0 implants* regardless of ovarian tumour grade</td>
<td>≥ II</td>
<td>Not required</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Those extraovarian implants that are composed of mature tissue, essentially glia.

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Fig. 2.98 A Immature teratoma, high grade. Neuroectodermal rosettes lie in a background of glial tissue. B Mitotic figures are evident within the immature neuroectodermal tissue.
diploid in 90% of cases, whereas most (66%) of grade 3 tumours are aneuploid \((165,2684)\). Similarly, karyotypic abnormalities are most often seen in grade 3 tumours \((165)\). Immature teratomas show fewer DNA copy number changes detected by comparative genomic hybridization than other ovarian germ cell tumours and do not usually exhibit a gain of 12p or i(12p) \((1518,2378)\).

Prognosis and predictive factors

The stage and grade of the primary tumour and the grade of its metastases are important predictive factors. Prior to the chemotherapy era, the overall survival rate of patients with grade 1, 2 and 3 neoplasms was 82%, 63% and 30%, respectively \((2060)\).

The use of cisplatin-based combination chemotherapy has dramatically improved the survival rate of patients; 90-100% of those receiving this regimen remain disease-free \((989)\).

Mature teratoma

Definition

A cystic or, more rarely, a solid tumour composed exclusively of mature, adult-type tissues. A cyst lined by mature tissue resembling the epidermis with its appendages is clinically designated as “dermoid cyst”. Homunculus or fetiform teratoma is a rare type of mature, solid teratoma containing highly organized structures resembling a malformed fetus (“homunculus” = little man).

Epidemiology

Age

Although most mature cystic teratomas occur during the reproductive years, they have a wide age distribution, from 2-80 years (mean, 32), and 5% occur in postmenopausal women \((564)\). Mature solid teratoma occurs mainly in the first two decades of life \((199,2922)\).

Incidence

Mature cystic teratoma accounts for 27-44% of all ovarian tumours and up to 58% of the benign tumours \((1502)\). In addition to their pure form, dermoid cysts are found macroscopically within 25% of immature teratomas and in the ovary contralateral to a malignant primitive germ cell tumour in 10-15% of the cases.

Clinical features

Signs and symptoms

Most mature cystic teratomas present with a mass, but at least 25% (up to 60% in some series) are discovered incidentally \((546)\). Symptoms such as a pelvic mass or pain are more common when the mature teratoma is solid \((199,2922)\).

The following complications have been described:

1. Torsion of the pedicle occurs in 10-16% of the cases, is responsible for acute abdominal pain and may be complicated by infarction, perforation or intra-abdominal haemorrhage.

2. Tumour rupture occurs in 1% of cases and can be spontaneous or traumatic. The spillage of the cyst contents into the peritoneum produces chemical peritonitis with granulomatous nodules mimicking tuberculosis or carcinomatosis. Rupture of mature teratoma containing neuroglial elements is thought to be responsible for gliomatosis peritonei characterized by peritoneal “implants” composed of mature glial tissue and does not affect the prognosis \((2389)\). However, a recent molecular study has demonstrated that these glial implants were heterozygous, whereas the associated mature ovarian teratomas were homozygous at the same microsatellite loci. This finding suggests that glial implants may arise from metaplasia of pluripotent müllerian stem cells rather than from implantation of the associated ovarian teratomas \((845)\). Similarly, peritoneal melanosis characterized by pigmentation of the peritoneum has been reported in cases of dermoid cysts.

3. Infection of the tumour occurs in 1% of cases.
Haemolytic anaemia has been reported in rare cases \(^{(1020)}\).

**Macroscopy**

Dermoid cyst is an ovoid, occasionally bilateral (8-15% of cases), cystic mass of 0.5-40 cm (average 15 cm) with a smooth external surface and is filled with sebaceous material and hair. A nodule composed of fat tissue with teeth or bone protrudes into the cyst and is termed a Rokitansky protuberance. Mature solid teratoma is a large, solid mass with multiple cysts of varying size, a soft, cerebroid appearance and small foci of haemorrhage.

**Histopathology**

Mature teratomas are composed of adult-type tissue derived from two or three embryonic layers. Benign tumours such as struma ovarii, carcinoid, corticotroph cell adenoma, prolactinoma, naevus and glomus tumour may arise within a typical dermoid cyst \(^{(143, 1389, 2162, 2682)}\).

**Histogenesis**

The presence of Barr bodies (nuclear sex chromatin) and a 46 XX karyotype is consistent with origin through parthenogenetic development. Selective tissue microdissection and genetic analysis of mature ovarian teratomas demonstrated a genotypic difference between homozygous teratomatous tissues and heterozygous host tissue in support of their origin from a post-meiotic germ cell \(^{(1667, 3032)}\). Lymphoid aggregates associated with squamous or glandular epithelium within teratomas are heterozygous and derived from host tissue, whereas well differentiated thymic tissue is homozygous, suggesting capability for lymphoid differentiation \(^{(3032)}\).

**Prognosis and predictive factors**

Dermoid cysts with histological foci (up to 21 mm\(^2\)) of immature neuroepithelial tissue have an excellent prognosis \(^{(3174)}\). Recurrence in the form of a dermoid cyst (3% of cases) or immature teratoma (2-2.6% of cases) in the residual ipsilateral ovary is most frequent when the initial cysts are bilateral or multiple and have ruptured \(^{(104, 3174)}\). Monodermal teratomas and somatic-type tumours associated with dermoid cysts

**Struma ovarii**

**Definition**

A mature teratoma composed either exclusively or predominantly of thyroid tissue. Struma ovarii may harbour changes histologically identical to thyroid adenoma, carcinoma (malignant struma ovarii) or both. Those admixed with a carcinoid (strumal carcinoid) are classified separately.

**Epidemiology**

Struma ovarii, the most common type of monodermal teratoma, accounts for 2.7% of all ovarian teratomas \(^{(3146)}\) with...
malignant struma ovarii representing 0.01% of all ovarian tumours and 5-10% of all struma ovarii. Most patients are in their fifth decade [3146].

Clinical features
Signs and symptoms
Patients present with a palpable abdominal mass or unusual symptoms including Meigs syndrome [983], cervical thyroid hypertrophy and thyrotoxicosis (5% of cases) with high pelvic iodine uptake [2697]. An elevated serum level of thyroglobulin occurs in malignant struma ovarii [2412].

Macroscopy
The tumour is unilateral and varies from 0.5-10 cm in diameter. It has a brown solid and gelatinous sectioned surface and sometimes appears as a nodule within a dermoid cyst. Entirely cystic strumas containing green gelatinous material also occur [2831].

Histopathology
Struma ovarii is composed of normal or hyperplastic thyroid-type tissue with patterns seen in thyroid adenoma such as microfollicular, macrofollicular, trabecular and solid. Oxyphil or clear cells may be found [2832]. Cystic struma is composed of thin fibrous septa lined by flat, cuboidal cells with sparse typical thyroid follicles in the cyst wall [2831]. Immunoreactivity for thyroglobulin may be helpful in problematic cases such as cystic struma, oxyphilic or clear cell variants and a trabecular architecture that might be indistinguishable from Sertoli-Leydig cell tumours. Criteria used for malignant changes within struma ovarii are the same as those used for a diagnosis of malignancy in the thyroid gland [677,2387]. Papillary carcinomas (85% of cases) display the characteristic ground glass nuclei. However, follicular carcinomas are difficult to diagnose since struma ovarii generally lacks a capsule and has irregular margins. The thyroid tissue of struma may be uniformly malignant in some cases, undoubtedly arising in such cases from histological foci of normal-appearing thyroid tissue, which are not extensive enough in itself to qualify for the diagnosis of struma ovarii.

Prognosis and predictive factors
Tumours with the morphology of papillary or follicular thyroid cancer and extraovarian spread at presentation are probably the only lesions that deserve a designation of malignant struma, whilst the so-called "benign strumatosis", peritoneal implants composed of benign thyroid-type tissue, does not alter the prognosis. Factors increasing the likelihood of recurrences include the size, the presence of ascites or adhesions and solid architecture, whereas the mitotic rate and vascular invasion (identified in 15% of malignant strumas) are not prognostically helpful features [2387].

Carcinoids
Definition
These tumours contain extensive components of well differentiated neuroendocrine cells and most subtypes resemble carcinoids of the gastrointestinal tract. They may occur in pure form or within a dermoid cyst, a mucinous cystic tumour or a Brenner tumour. It should be distinguished from isolated neuroendocrine cells found within some mucinous and Sertoli-Leydig cell tumours.

Epidemiology
Ovarian carcinoids account for 0.5-1.7% of all carcinoids [2743], and the age range is 14-79 years (mean 53) [166, 2388,2390,2392].

Clinical features
Signs and symptoms
Carcinoid syndrome is a clinical sign of insular carcinoids in 30% of patients and is rare in trabecular (13%) and strumal (3.2%) carcinoids [631,2743]. Peptide YY production by the tumour cells causes severe constipation and pain with defecation in 25% of trabecular carcinoids [2656]. Strumal carcinoids may cause symptoms of functioning thyroid tissue in 8% of cases [2390].
Diagnostic procedures
Elevated urine 5-hydroxyindoleacetic acid (5-HIAA) and serum serotonin levels are found in patients with carcinoid syndrome [631,2388].

Macroscopy
Primary ovarian carcinoids are unilateral and present as a firm tan nodule (less than 5 cm) protruding into a typical dermoid cyst (32-60% of tumours) or are predominantly solid with small cysts. The sectioned surface is firm, homogeneous and tan to yellow.

Histopathology
Insular carcinoid accounts for 26-53% of cases [631,2743]) and resembles midgut derivative carcinoids. It is composed of nests of round cells with uniform nuclei and abundant eosinophilic cytoplasm enclosing small red argentaffin granules at the periphery of the nests. Acinus formation and a cribriform pattern with luminal eosinophilic secretion are present [2388].

Trabecular carcinoid accounts for 23-29% of cases [631,2743] and resembles hindgut or foregut derivative carcinoids. It exhibits wavy and anastomosing ribbons composed of columnar cells with the long axes of the cells parallel to one another and oblong nuclei with prominent nucleoli. The abundant cytoplasm is finely granular with red-orange argentophilic granules at both poles of the nucleus [2392].

Mucinous carcinoid accounts for only 1.5% of cases [2743] and resembles goblet cell carcinoids arising in the appendix. The well differentiated mucinous carcinoid is composed of numerous small glands lined by columnar or cuboidal cells, some of which contain intracytoplasmic mucin or have a goblet cell appearance, whilst others disclose orange-red neuroendocrine granules. Individual tumour cells may contain both mucin and neuroendocrine granules. Glands may be floating within pools of mucin that also dissect the surrounding fibrous stroma with isolated signet-ring cells infiltrating the stroma. Atypical mucinous carcinoid demonstrates crowded glands or a cribriform pattern. Carcinoma arising in mucinous carcinoid exhibits large islands of tumour cells or closely packed glands with high grade nuclei, numerous mitoses and necrosis [166].

Strumal carcinoid accounts for 26-44% of cases [631,2743] and is composed of a variable proportion of thyroid tissue and carcinoid, the latter mostly having a trabecular architecture. The neuroendocrine cells invade progressively the strumal component, replacing the follicular lining cells. Glands or cysts lined by columnar epithelium with goblet cells may be found [2390].

Carcinoids with mixed patterns (essentially insular and trabecular), are classified according to the pattern that predominates [2388].

Immunoprofile
Carcinoids are immunoreactive to at least one of the neuroendocrine markers (chromogranin, synaptophysin, Leu-7) and various peptide hormones such as pancreatic polypeptide, gastrin, vasoactive intestinal peptides and glucagon [166].

Differential diagnosis
Metastatic gastrointestinal carcinoid to the ovary should be ruled out specifically when extraovarian disease is detected. Bilateral and multinodular ovarian involvement, the absence of other teratomatous components and the persistence of the carcinoid syndrome after oophorectomy favour the diagnosis of metastasis [166,2391].

Prognosis and predictive features
Almost all primary trabecular and strumal carcinoids occur in women with stage I disease and have an excellent outcome. The overall survival of patients with insular carcinoid is 95% at 5 years and 88% at 10 years [2388].

Primary ovarian mucinous carcinoid, like those in the appendix, has a more aggressive behaviour with extraovarian spread and lymph node metastases. The presence of frank carcinoma within the tumour is an important prognostic factor [166].

Neuroectodermal tumours
Definition
Tumours composed almost exclusively of neuroectodermal tissue, closely resem-
blining neoplasms of the nervous system with a similar spectrum of differentiation.

**Epidemiology**

Less than 40 cases are reported in patients 6-69 years old (average 28), \(1077,1418,1476\).

**Clinical features**

The tumours usually present as a pelvic mass.

**Macroscopy**

Tumours are unilateral and 4-20 cm in diameter, averaging 14 cm \(1476\). The sectioned surface varies from solid with friable, gray-pink tissue to cystic with papillary excrescences in their inner or outer surface \(1077\).

**Tumour spread and staging**

The majority of patients have stage II or III disease at laparotomy usually in the form of peritoneal implants \(1476\).

**Histopathology**

These tumours are morphologically identical to their nervous system counterparts. They may be divided into three categories as follows:

1. Well differentiated forms such as ependymoma.
2. Poorly differentiated tumours such as primitive neuroectodermal tumour (PNET), and medulloepithelioma.
3. Anaplastic forms such as glioblastoma multiforme.

Whilst ependymomas are not found in association with teratoma, other neuroectodermal tumours in the ovary may be associated with elements of mature or immature teratoma \(2605\). Cases previously reported as neuroblastoma or medulloblastoma would now most likely be classified as PNETs since the morphology of all three tumours is similar with the term medulloblastoma being reserved for cerebellar and neuroblastoma for adrenal neoplasms \(1474\). Medulloepithelioma, on the other hand, has a distinctive appearance characterized by papillary, tubular or trabecular arrangements of neoplastic neuroepithelium mimicking the embryonic neural tube \(1474\). Ependymomas and anaplastic tumours are immunoreactive for glial fibrillary acidic protein. The characteristic immunoprofile of PNETs, vimentin and MIC2 protein (CD99) positive and GFAP, cytokeratin, desmin, chromogranin, and inhibin negative, help to distinguish these tumours from small cell carcinoma and juvenile granulosa cell tumour.

**Somatic genetics**

Reverse transcription-polymerase chain reaction in a case of ovarian PNET led to the detection of \(EWS/FLI1\) chimeric transcript, originating from the characteristic t(11;22)(q24;q12) translocation of the PNET/Ewing tumour family \(1418\).

**Prognosis and predictive factors**

Most patients with ovarian ependymomas survive despite multiple recurrences, whereas patients with PNET and anaplastic tumours have a poor outcome \(1476\).

**Carcinomas**

**Definition**

A dermoid cyst in which a secondary carcinoma develops.

**Epidemiology**

Malignancy arising within a mature cystic teratoma is a rare complication (1-2% of cases), mostly reported in postmenopausal women (mean 51-62 years) \(1214,1429,2164\).

**Clinical features**

The tumour may present as a dermoid cyst or as an advanced ovarian cancer depending on tumour stage \(2605\). The tumour may show adherence to surrounding pelvic structures \(1214,1429,2164\).

**Macroscopy**

On macroscopic examination cauliflower exophytic growth, infiltrative grey-white plaques or thickenings of the cyst wall with necrosis and haemorrhage may be seen \(1214,1429,2164\).

**Histopathology**

The malignancy may be detectable only after histological examination, thus dermoid cysts in postmenopausal women must be adequately sampled. Any component of a mature teratoma may undergo malignant transformation. Carcinomas are the most common malignancy, with squamous cell carcinomas accounting for 80% of cases and 51% of all primary ovarian squamous cell carcinomas \(1214,2255\). Adenocarcinoma is the second most common malignancy arising in dermoid cysts \(1456\). Adenocarcinoma of intestinal type \(2970\), Paget disease, adenosquamous carcinoma, transitional cell carcinoma \(1456\), undifferentiated carcinoma, small cell carcinoma, basal cell carcinoma and carcinosarcoma \(123\) have been described \(2605\). The malignant component invades other parts of the dermoid cyst and its wall.

**Somatic genetics**

Selective tissue microdissection and genetic analyses of malignant tumours
associated with mature teratomas showed an identical homozygous genotype for the malignant component and the mature teratomatous tissues, thus demonstrating a direct pathogenetic relationship \(683\).

**Prognosis and predictive features**

The prognosis of squamous cell carcinoma is poor with a 15-52% overall 5-year survival and disease related death usually within 9 months. Vascular invasion is associated with a high mortality rate \(1214\). Although relatively few cases have been reported, the prognosis of adenocarcinoma appears to be similar to that of squamous cell carcinoma \(2970\).

**Sarcomas**

Sarcomas account for 8% of cases of malignancies in dermoid cysts and are more often seen in younger patients than those with squamous cell carcinoma. Cases of leiomyosarcoma, angiosarcoma \(2021\), osteosarcoma \(2006\), chondrosarcoma, fibrosarcoma, rhabdomyosarcoma and malignant fibrous histiocytoma have been reported \(2605\).

**Melanocytic tumours**

Melanomas are rare, occurring much less commonly than metastatic melanoma \(630\). Overall, one-half of the patients with stage I dermoid-associated melanoma are alive at 2 years \(404\). Melanocytic naevi of various types may arise within a typical dermoid cyst \(1544\).

**Sebaceous tumours**

Sebaceous tumours are specialized neoplasms arising within an ovarian dermoid cyst that resemble various forms of cutaneous sebaceous gland tumours (sebaceous adenoma, basal cell carcinoma with sebaceous differentiation, sebaceous carcinoma). The hallmark of these lesions is the presence of large numbers of mature, foamy or bubbly sebaceous cells that stain positively with oil red O in a tumour arising within a dermoid cyst \(491\).

**Pituitary-type tumours**

Corticotroph cell adenoma and prolactinoma, respectively responsible for Cushing syndrome and hyperprolactinemia with amenorrhea, may arise within a typical dermoid cyst and have a benign clinical course \(143,1389,2162\).

**Retinal anlage tumours**

Pigmented progonoma and malignant tumours derived from retinal anlage within ovarian teratomas have macroscopically pigmented areas that correspond to solid nests, tubules and papillae composed of atypical cells with melanin-containing cytoplasm \(1112,1466,2712\).

**Other monodermal teratomas and related tumours**

Neural cyst of the ovary lined by a single layer of ependymal cells with white matter, astrocytes and reactive glia in the underlying wall corresponds to a monodermal teratoma with unidirectional neurogenic differentiation \(894\). Similarly, endodermal variants of mature teratoma lined exclusively by respiratory epithelium \(508\) and ovarian epidermoid cysts \(823\) may fall into the category of monodermal teratoma. Mucinous cystadenomas arising within mature teratomas have a homozygous teratomatous genotype, supporting their germ cell origin \(1731\). Mesodermal derived tumours such as lipoma composed of mature adipocytes with scattered benign sweat glands may occur \(961\). Glomus tumour may rarely arise within a typical dermoid cyst \(2682\).
Mixed germ cell-sex cord-stromal tumours

This group of neoplasms is composed of a mixture of germ cell and sex cord-stromal elements. They have mainly benign clinical behaviour except in cases with a malignant germ cell component.

Gonadoblastoma

Definition
A neoplasm composed of tumour cells closely resembling dysgerminoma or seminoma, intimately admixed with sex cord derivatives resembling immature Sertoli or granulosa cells and in some cases containing stromal derivatives mimicking luteinized stromal or Leydig cells devoid of Reinke crystals.

ICD-O code
Gonadoblastoma 9073/1

Epidemiology
Gonadoblastomas typically are identified in children or young adults with one-third of the tumours being detected before the age of 15 (2598).

Aetiology
Gonadoblastomas are frequently associated with abnormalities in the secondary sex organs (2598,2847). In over 90% of the cases of gonadoblastoma a Y chromosome was detected (2598,2605,2849,2850).

Localization
Gonadoblastoma is found more often in the right gonad than in the left and is bilateral in 38% of cases (2598). Recent reports suggest an even higher frequency of bilateral involvement (2850).

Clinical features
Signs and symptoms
The usual patient with a gonadoblastoma is a phenotypic female who is frequently virilized (2605). A minority may present as phenotypic males with varying degrees of feminization.

The clinical presentation of a patient with a gonadoblastoma can vary considerably depending upon whether or not a tumour mass is present, on the nature of the underlying abnormal gonads, on the development of secondary sex organs and the occasional secretion of steroid hormones (2598). A patient with pure gonadal dysgenesis may present with a failure to develop secondary sex organs and characteristics at puberty but has a normal height, and other congenital anomalies are absent. Those with Turner syndrome have sexual immaturity, a height of less than 150 cm and one or more congenital anomalies including neonatal lymphedema, web neck, prognathism, shield-shaped chest, widely spaced nipples, cubitus valgus, congenital nevi, coarctation of the aorta, renal anomalies, short fifth metacarpal bones and others (2598). If a germ cell malignancy develops in the dysgenetic gonad, the patient may present with lower abdominal or pelvic pain.

Macroscopy
Pure gonadoblastoma varies from a histological lesion to 8 cm, and most tumours are small, measuring only a few cm (2598,2849,2850). When a gonadoblastoma is overgrown by dysgerminoma or other neoplastic germ cell elements, much larger tumours are encountered. The macroscopic appearance of gonadoblastoma varies depending on the presence of hyalinization and calcification and on the overgrowth by other malignant germ cell elements.

Histopathology
Histologically, gonadoblastoma is a tumour composed of two main cell types, germ cells which are similar to those present in dysgerminoma or seminoma and sex cord derivatives resembling immature Sertoli or granulosa cells. The stroma in addition may contain collections of luteinized or Leydig-like cells devoid of Reinke crystals. The tumour is arranged in collections of cellular nests surrounded by connective tissue stroma. The nests are solid, usually small, oval or round, but occasionally may be larger or elongated. The cellular nests are composed of germ cells and sex cord deriv-
Mixed germ cell-sex cord-stromal tumours

or oval and contain dark, oval or slightly elongated carrot-shaped nuclei. They do not show mitotic activity [2598,2849,2850]. The sex cord derivatives are arranged within the cell nests in three typical patterns as follows:

1. Forming a coronal pattern along the periphery of the nests.
2. Surrounding individual or collections of germ cells.
3. Surrounding small round spaces containing amorphous, hyaline, eosinophilic, PAS-positive material resembling Call-Exner bodies.

The connective tissue stroma surrounding the cellular nests may be scant or abundant and cellular, resembling ovarian stroma, or dense and hyalized. It may contain luteinized or Leydig-like cells devoid of Reinke crystals [2598,2849,2850].

Three processes, hyalinization, calcification and overgrowth by a malignant germ cell element, usually dysgerminoma, may alter the basic histological appearance of gonadoblastoma. The hyalinization occurs by coalescence of the hyaline bodies and bands of hyaline material around the nests with replacement of the cellular contents. Calcification originates in the hyaline Call-Exner-like bodies and is seen histologically in more than 80% of cases [2598]. It tends to replace the hyalinized nests forming rounded, calcified concretions. Coalescence of such concretions may lead to the calcification of the whole lesion, and the presence of smooth, rounded, calcified bodies may be the only evidence that gonadoblastoma has been present. The term “burned-out gonadoblastoma” has been applied to such lesions [2598,2849,2850].

Gonadoblastoma is overgrown by dysgerminoma in approximately 50% of cases, and in an additional 10% another malignant germ cell element is present [2598,2846,2849,2850]. Gonadoblastoma has never been observed in metastatic lesions or outside the gonads [2598,2849,2850]. In most cases the gonad of origin is indeterminate because it is overgrown by the tumour. When the nature of the gonad can be identified, it is usually a streak or a testis. The contralateral gonad, when identifiable, may be either a streak or a testis, and the latter is more likely to harbour a gonadoblastoma [2598,2849,2850]. Occasionally, gonadoblastoma may be found in otherwise normal ovaries [2077,2598,2849,2850].

**Tumour spread and staging**

At the time of operation gonadoblastomas typically are bilateral, although at times they may be not macroscopically detectable in the gonad. Those that are overgrown by dysgerminoma or other malignant germ cell tumour may be much larger. If a malignant germ cell tumour develops, the potential for metastatic disease exists. Dysgerminomas typically spread by the lymphatic route, less frequently by peritoneal dissemination. Therefore, it is extremely important not only to remove both gonads but to perform surgical staging if at the time of operative consultation a malignant germ cell tumour is identified. The typical staging for a dysgerminoma or other malignant germ cell tumour includes pelvic and para-aortic lymph node sampling as well as peritoneal washings if no ascites is present (2586).

The operation should include omentectomy, and multiple peritoneal samplings are required. For patients with spread of a malignant germ cell tumour other than dysgerminoma, aggressive cytoreductive surgery is appropriate (2586).

**Precursor lesions**

Gonadoblastoma is almost invariably associated with an underlying gonadal disorder. When the disorder is identifiable, it is usually pure or mixed gonadal dysgenesis with a Y chromosome being detected in over 90% of the cases [2598,2605].

**Prognosis and predictive factors**

**Clinical criteria**

Patients having gonadoblastoma without dysgerminoma or other germ cell tumour are treated by surgical excision of the gonads without additional therapy. However, if dysgerminoma and/or another malignant germ cell element is present, surgical staging and postoperative combination chemotherapy, the most popular current regimen being bleomycin, etoposide and cisplatin (BEP), are required. Other regimens include etoposide and carboplatin [2586]. Dysgerminoma is exquisitely sensitive to chemotherapy, as it was previously shown to be exquisitely responsive to radiation therapy.
Histopathological criteria
Pure gonadoblastoma may show extensive involvement of the gonad but does not behave as a malignant lesion (2598, 2849,2850). More frequently, its germ cell component gives rise to a malignant germ cell neoplasm capable of invasion and metastases. Gonadoblastoma may sometimes undergo ablation by a process of marked hyalinization and calcification. In such cases the lesion becomes innocuous, but great care must be taken to exclude the presence of viable elements, especially of germ cell lineage. Dysgerminoma arising within gonadoblastoma tends to metastasize less frequently and at a later stage than dysgerminoma arising de novo (2598, 2849,2850). There is no satisfactory explanation for this phenomenon. The patients can be treated similarly to patients with pure dysgerminoma with a very high likelihood of complete cure.

Mixed germ cell-sex cord-stromal tumour

Definition
A neoplasm composed of intimately admixed germ cells and sex cord derivatives that has a different histological appearance from gonadoblastoma. Mixed germ cell-sex cord-stromal tumour also differs from gonadoblastoma by its occurrence in anatomically, phenotypically and genetically normal females (2844,2845,2847).

Epidemiology
Mixed germ cell-sex cord-stromal tumours usually occur in infants or children under the age of 10, but have been occasionally reported in postmenarchal women (1556,2844,2852).

Aetiology
Patients with mixed germ cell-sex cord-stromal tumour have normal gonadal development and a normal XX karyotype. The tumour is not associated with gonadal dysgenesis, and its aetiology is unknown (1556,2844,2852,3270).

Clinical features
Patients with a mixed germ cell-sex cord-stromal tumour generally present with lower abdominal pain. In almost a fourth of the cases patients have isosexual precocity and may have vaginal bleeding and bilateral breast development (1556,2852,3270). Physical examination routinely reveals a large mass in the adnexal area or in the lower abdomen.

Macroscopy
This tumour, unlike gonadoblastoma, tends to be relatively large, measuring 7.5-18 cm and weighing 100-1,050 grams. Except for two reported cases, mixed germ cell-sex cord-stromal tumour is unilateral (1321,2849,2850). The tumour is usually round or oval and is surrounded by a smooth, grey or grey-yellow capsule. In most cases it is solid, but in some cases it may be partly cystic. The sectioned surface is grey-pink or yellow to pale brown. There is no evidence of calcification. In all cases the fallopian tube, the uterus and the external genitalia are normal.

Tumour spread and staging
Since mixed germ cell-sex cord-stromal tumours are less aggressive than gonadoblastoma and uncommonly bilateral, the routine evaluation of patients with a mixed germ cell-sex cord-stromal tumour can be less extensive. Although the tumours are often of considerable size, metastases have occurred in only two cases (124,1556). If intraoperative consultation is inconclusive, it is appropriate to limit the operation to removal of the involved gonad and to await the final pathology results before performing any definitive surgery that might impair future fertility.

Histopathology
Mixed germ cell-sex cord-stromal tumour is composed of germ cells and sex cord derivatives resembling immature Sertoli or granulosal cells intimately admixed with each other. The tumour cells form four distinctive histological patterns as follows:

1. A cord-like or trabecular pattern composed of long, narrow, ramifying cords or trabeculae that in places expand to form wider columns and larger round cellular aggregates surrounded by connective tissue stroma that varies from dense and hyalinized to loose and oedematous.

2. A tubular pattern composed of solid tubules surrounded by fine connective tissue septa and containing peripherally located smaller epithelial-like sex cord derivatives surrounding large, round germ cells with clear or slightly granular cytoplasm and large vesicular nuclei containing prominent nucleoli.

3. A haphazard pattern consisting of scattered collections of germ cells surrounded by sex cord derivatives, which may be very abundant.

4. A mixed pattern showing an admixture of the above mentioned patterns without any predominance. The germ cells show mitotic activity and a close similarity to those of dysgerminoma, but in some cases they are better differentiated showing smaller nuclei and less marked mitotic activity. Unlike the
Mixed germ cell-sex cord-stromal tumours

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Finding in gonadoblastoma, the sex cord derivatives also show mitotic activity (2847, 2849, 2850).

The composition of a mixed germ cell-sex cord-stromal tumour varies, and in some areas the sex cord elements may predominate, whereas in others there is a predominance of germ cells. The cystic spaces seen in some tumours resemble the cystic spaces seen in cystic and retiform Sertoli cell tumours and should not be confused with cysts and papillae seen in ovarian serous tumours, which they may resemble superficially (2849, 2850).

Although originally mixed germ cell-sex cord-stromal tumours were found to occur in pure form, it was later noted that approximately 10% of cases are associated with dysgerminoma or other malignant germ cell elements. This finding is by far less common than in gonadoblastoma.

The tumour is always found in normal ovaries, and whenever the unaffected contralateral gonad is examined, it is a normal ovary.

Genetic susceptibility

Familial clustering of these rare tumours has not been reported.

Prognosis and predictive factors

In the majority of cases the mixed germ cell-sex cord-stromal tumour occurs in pure form. Mixed germ cell-sex cord-stromal tumours are generally benign and are treated by unilateral oophorectomy. Preservation of fertility should be a priority in those patients that appear to have a unilateral mixed germ cell-sex cord-stromal tumour.

The association with other neoplastic germ cell elements is more common in postmenarchal subjects, but it may be seen in children in the first decade (2849, 2850). One case of mixed germ cell-sex cord-stromal tumour was associated with para-aortic lymph node and abdominal metastases (1556). Another patient developed intra-abdominal metastatic disease two years following the excision of a large ovarian tumour (124). Both patients are well and disease free following surgery and chemotherapy. It is of interest that the tumour associated with the intra-abdominal recurrence showed an unusual histological pattern of sex cord tumour with annular tubules, but differed from the latter by the presence of numerous germ cells (124).

In those cases with metastatic disease, aggressive surgical cytoreduction is performed, and the BEP regimen is routinely used postoperatively.

Fig. 2.113 Mixed germ cell-sex cord-stromal tumour associated with dysgerminoma. The former is composed of clusters of germ cells and small sex-cord type cells in a dense fibrous stroma. Note the dysgerminoma in the right upper portion of the field.
Tumours and related lesions of the rete ovarii

Definition
A varied group of benign and malignant tumours and related lesions that originate from the rete ovarii, a vestigial structure present in the ovarian hilus and histologically identical to its testicular homologue.

ICD-O codes
- Rete ovarii adenocarcinoma 9110/3
- Rete ovarii adenoma 9110/0

Clinical features
Most lesions are incidental findings in postmenopausal patients. Sizeable cysts and tumours manifest as pelvic masses. Some cases may present with hormonal symptoms due to concomitant hilus cell hyperplasia or stromal luteinization in adenomas.

Histopathology
The rete is an unusual site for any type of pathology. In order to diagnose a lesion as originating in the rete, it must be located in the ovarian hilus and be composed of cuboidal or columnar non-ciliated cells arranged in retiform spaces. Areas of normal rete and hilus cells should be found in the vicinity of the tumour or show a transition (2495). Dilated areas and cysts are the most frequent histological finding, but a few solid proliferative lesions have been reported. The rete ovarii appears to be functionally related to folliculogenesis (385). Although its embryology is not fully understood, it is likely to be mesonephric in origin. Recently, attention has been focused on its morphology and immunophenotype in order to find histogenetic relationships with neoplasms of uncertain origin such as tumours of probable wolffian origin (682) and retiform Sertoli-Leydig cell tumours (1904), as well as to differentiate it from endometriosis (2494) and to identify new mesonephric identity markers (2110). These studies show constant coexpression of vimentin and cytokeratin and positivity for CD10 (2110), frequent positivity for calretinin, inhibin and CA125 and isolated positivity to A103 (melan-A) and epithelial membrane antigen (605,1450, 2495,2792).

Immunoprofile
Immunohistochemically, adenomas and adenocarcinomas are positive for CAM 5.2, cytokeratin 19, CA125, CD10 and occasionally for epithelial membrane antigen and estrogen and progesterone receptors.

Adenocarcinoma
Adenocarcinoma of the rete ovarii is

Fig. 2.114 Carcinoma of the rete ovarii. The epithelial cells lining the papillae show marked atypia.

Fig. 2.115 Adenoma of the rete ovarii. Note the tubulopapillary architecture.
exceptional. A bilateral tumour with a retiform tubulopapillary histology admixed with transitional-like areas has been reported (2495). The patient initially had stage II disease, and the tumour recurred with elevated serum levels of CA125.

Adenoma
Adenoma of the rete ovarii typically occurs as an incidental finding in middle-aged or elderly women, is located in the hilus and is well circumscribed (2495). It is composed of closely packed elongated tubules, some of which are dilated and contain simple papillae, and may show stromal luteinization or concomitant hilus cell hyperplasia. All reported adenomas have behaved in a benign fashion.

Cystadenoma and cystadenofibroma
One cystadenofibroma and two cystadenomas of the rete ovarii, one of which was bilateral, have been reported (2040). In both instances they originated from the rete, involved only the ovarian medulla and were tubulopapillary cystic proliferations of clear columnar cells. The stroma was densely populated by luteinized cells, which caused irregular bleeding in both postmenopausal patients. The bilateral case had on one side a non-invasive adenoma but with marked cellular atypia and pleomorphism.

Adenomatous hyperplasia
Among the proliferative lesions, adenomatous hyperplasia of the rete ovarii is similar to the same lesion in the testis (1169). It is differentiated from adenoma only by its poorly defined margins.

Cysts
Most cysts are unilocular with an average diameter of 8.7cm (2495) and a smooth inner surface. Histologically, they show serrated contours with crevice formation. Their lining consists of a single layer of cuboidal to columnar non-ciliated cells. Their walls contain tracts of smooth muscle and foci of hilus cells, which are sometimes hyperplastic and may be responsible for some hormonal manifestations (2496).
Miscellaneous tumours and tumour-like conditions of the ovary

Table 2.08
Comparison of small cell carcinoma of the hypercalcaemic type with juvenile granulosa cell tumour.

<table>
<thead>
<tr>
<th>Small cell carcinoma, hypercalcaemic type</th>
<th>Juvenile granulosa cell tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I in 50% of cases</td>
<td>Stage I in greater than 97% of cases</td>
</tr>
<tr>
<td>Highly malignant</td>
<td>Usually non-aggressive</td>
</tr>
<tr>
<td>Hypercalcaemia in two-thirds of cases</td>
<td>Hypercalcaemia absent</td>
</tr>
<tr>
<td>Never estrogenic</td>
<td>Usually estrogenic</td>
</tr>
<tr>
<td>Scant or non-specific stroma</td>
<td>Fibrothecomatous stroma common</td>
</tr>
<tr>
<td>Follicles often contain mucicarminophilic basophilic secretion</td>
<td>Follicles rarely contain mucicarminophilic basophilic secretion</td>
</tr>
<tr>
<td>Prominent nuclei</td>
<td>Rounded euchromatic nuclei,</td>
</tr>
<tr>
<td>Mitoses frequent</td>
<td>Indistinct nuclei</td>
</tr>
<tr>
<td>Usually epithelial membrane antigen positive</td>
<td>Epithelial membrane antigen negative</td>
</tr>
<tr>
<td>Alpha-inhibin negative</td>
<td>Alpha-inhibin positive</td>
</tr>
</tbody>
</table>

L.M. Roth
A. Tsubura
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Definition
A group of benign and malignant ovarian tumours of diverse or uncertain origin.

ICD-O codes
- Small cell carcinoma, hypercalcaemic type 8041/3
- Small cell carcinoma, pulmonary type 8041/3
- Large cell neuroendocrine carcinoma 8013/3
- Adenoid cystic carcinoma 8200/3
- Basal cell tumour 8090/1
- Hepatoid carcinoma 8576/3
- Malignant mesothelioma 9050/3
- Gestational choriocarcinoma 9100/3
- Hydatidiform mole 9100/0
- Ovarian wolffian tumour 9110/1
- Wilms tumour 8960/3
- Paraganglioma 8693/1
- Myxoma 8840/0

Small cell carcinoma, hypercalcaemic type

Definition
An undifferentiated carcinoma that is usually associated with paraendocrine hypercalcaemia and is composed primarily of small cells.

Clinical features
This neoplasm typically occurs in young women and is associated with paraendocrine hypercalcaemia in approximately two-thirds of patients (3204). Most of the patients presented with abdominal swelling or pain related to their tumour; however, one patient had a neck exploration for presumed parathyroid disease with negative results before the ovarian tumour was discovered (3204).

Macroscopy
The tumours are usually large and predominantly solid, pale white to gray masses. Necrosis, haemorrhage and cystic degeneration are common.

Tumour spread and staging
In approximately 50% of the patients the tumour has spread beyond the ovary at the time of initial laparotomy.

Histopathology
On histological examination the tumours typically grow diffusely, but they may form small islands, trabeculae or cords. They frequently form follicle-like spaces that almost always contain eosinophilic fluid, and nuclei show easily discernible nucleoli. Foci of either benign or malignant mucinous epithelium are present in 10-15% of the cases. Typically, the cells of the tumour contain scant cytoplasm, but in approximately one-half of cases a component of large cells with abundant eosinophilic cytoplasm and nuclei containing prominent nucleoli is present.

Immunoprofile
Small cell carcinomas generally stain for epithelial membrane antigen but not for inhibin (2376). Variable staining of the neoplastic cells for vimentin, cytokeratin and epithelial membrane antigen is observed (46).

Cytometric studies
Flow cytometric studies of paraffin-embedded tissue has demonstrated that the neoplastic cells are diploid (755).

Electron microscopy
Electron microscopic examination has shown an epithelial appearance to the neoplasm consisting of small desmosomes and, in some cases, tight junctions (695). Dilated granular endoplasmic reticulum containing amorphous material is characteristically present within the cytoplasm (695,696). Few or no neurosecretory granules have been identified.

Differential diagnosis
Because of the young age of the patients and the presence of follicle-like spaces in the neoplasm, the differential diagnosis includes juvenile granulosa cell tumour.

Small cell carcinoma, hypercalcaemic type

Stage I in 50% of cases
Highly malignant
Hypercalcaemia in two-thirds of cases
Never estrogenic
Scant or non-specific stroma
Follicles often contain mucicarminophilic basophilic secretion
Nuclei hyperchromatic
Mitoses frequent
Usually epithelial membrane antigen positive
Alpha-inhibin negative

Usual stages of tumour
Stage I in greater than 97% of cases
Usually non-aggressive
Hypercalcaemia absent
Usually estrogenic
Fibrothecomatous stroma common
Follicles rarely contain mucicarminophilic basophilic secretion
Rounded euchromatic nuclei,
Indistinct nuclei
Mitoses variable
Epithelial membrane antigen negative
Alpha-inhibin positive
This tumour may also be confused with adult type granulosa cell tumours, malignant lymphoma and other small cell malignant neoplasms that involve the ovary [695]. The absence of membrane immunoreactivity for MIC2 protein (CD99) serves to distinguish small cell carcinoma from primitive neuroectodermal tumour (see section on germ cell tumours).

**Histogenesis**

The histogenesis of small cell carcinoma has not been definitively established [755]. It has been proposed that this tumour may be a variant of a surface epithelial-stromal tumour [2376]. A study utilized a mouse xenograft model in which tumour fragments of small cell carcinoma were cultured in six subsequent generations of nude mice. The transplanted tumour morphology remained the same as that of primary tumour from the patient, and serum calcium levels were significantly higher in tumour-bearing mice compared to controls. By comparative genomic hybridization and electron microscopy the tumour appeared to be a distinct tumour entity, not related to either a germ cell tumour or epithelial ovarian cancer [3050].

**Genetic susceptibility**

The neoplasm has been familial in several instances. The tumour has occurred in three sisters, in two cousins and in a mother and daughter [3204]. The familial tumours were all bilateral in contrast to the rarity of bilateral tumours in general.

**Prognosis and predictive factors**

In the largest series of patients approximately one-third of patients with stage IA disease were alive and free of tumour at last follow up [3204]. Almost all the patients with a stage higher than IA died of disease.

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**Small cell carcinoma, pulmonary type**

**Definition**

A small cell carcinoma resembling pulmonary small cell carcinomas of neuroendocrine type.

**Synonym**

Small cell carcinoma of neuroendocrine type.

**Clinical features**

Patients typically are postmenopausal and present with pelvic or abdominal masses.

**Macroscopy**

The tumours are typically large and solid with a cystic component.

**Histopathology**

The pulmonary type resembles small cell carcinoma of the lung and is associated with a surface epithelial-stromal tumour, most often endometrioid carcinoma [761]. The neoplastic cells have nuclei with finely stippled chromatin, lack nucleoli and show molding. The cytoplasm is scant. Mitoses are numerous. The appearance varies somewhat depending on cellular preservation.

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Fig. 2.117 Small cell carcinoma, hypercalcaemic type. The ovary is involved by a solid, knobby tumour that has extended through the capsule to the right.

Fig. 2.118 Small cell carcinoma, hypercalcaemic type. A Note the follicle-like space. B There is a diffuse proliferation of mitotically active small cells with enlarged nuclei that contain small nucleoli.
Immunoprofile
Immunohistochemical markers for neuron specific enolase are typically positive, and a minority of cases were positive for chromogranin [761].

Cytometric studies
The majority of neoplasms are aneuploid by flow cytometry [761].

Prognosis and predictive factors
The neoplasm is highly malignant, and the behaviour has been aggressive regardless of stage [761].

Large cell neuroendocrine carcinoma
Definition
A malignant tumour composed of large cells that show neuroendocrine differentiation.

Synonym
Undifferentiated carcinoma of non-small cell neuroendocrine type.

Clinical features
Two series of ovarian neuroendocrine carcinomas of non-small cell type have been reported [455,756]. The patients were in the reproductive age group or beyond (mean 56 years) and presented with symptoms related to a pelvic mass in the majority of cases [756].

Histopathology
These tumours have in all the reported cases been associated with a tumour of surface epithelial-stromal type, either benign or malignant [455,542,756]. The neuroendocrine component consisted of medium to large cells. Nuclei contained prominent nucleoli, and mitoses were frequent. The solid component stained for chromogranin, and neuropeptides were demonstrated in some cases.

Prognosis and predictive factors
This type of tumour appears to be highly aggressive; only the neuroendocrine carcinoma component was present in the metastatic sites [455].

Hepatoid carcinoma
Definition
A primary ovarian neoplasm that histologically resembles hepatocellular carcinoma and is positive for alpha-fetoprotein.

Epidemiology
Hepatoid carcinoma of the ovary is a rare tumour; only 12 cases have been reported [1798,2629,2951]. It mainly occurs in postmenopausal women with a mean age of 59.6 years (range, 35-78 years).

Clinical features
The symptoms are not specific and are related to an ovarian mass [2629]. Elevation of serum alpha-fetoprotein (AFP) is characteristic, and CA125 is elevated in most cases.

Macroscopy
Tumours vary from 4-20 cm in maximum dimension with no distinctive macroscopic features [1798,2629,2951]. In some cases, formalin fixation reveals green-coloured areas suggestive of bile production [2629].

Fig. 2.119 Hepatoid carcinoma. A Note the trabecular pattern with thick cords of hepatoid cells. B Positive staining for alpha-fetoprotein is observed.

Histopathology
The tumour cells are arranged in sheets, cords and trabeculae with moderate to abundant amounts of eosinophilic cytoplasm and distinctive cell borders resembling hepatocellular carcinoma. Mitoses are generally conspicuous. PAS-positive, diastase-resistant hyaline globules and Hall stain-positive bile pigment can be seen. The presence of immunoreactive AFP and protein induced by vitamin K absence or antagonist II (PIVKA-II) shows functional differentiation toward hepatocytes [1307,2629]. CA125 is positive in one-half of the tumours [2629].

Differential diagnosis
Metastatic hepatocellular carcinoma and hepatoid yolk sac tumour must be ruled out [3197].

Histogenesis
Tumours admixed with serous carcinoma and tumour cells positive for CA125 suggest an ovarian surface epithelial origin [1307,2610,2629].

Prognosis and predictive factors
Clinical outcome is poor. Seven out of 12 patients died between 4 months and 5 years (mean, 19 months) after initial diagnosis, and 2 patients had a tumour recurrence after 6-7 months [1798,2629,2951].

Tumours resembling adenoid cystic carcinoma and basal cell tumour
Definition
A group of primary ovarian tumours that histologically resemble certain tumours of the salivary glands or cutaneous basal cell carcinoma.
Clinical features
Adenoid cystic-like carcinoma presents typically as a pelvic mass or abdominal distension in postmenopausal women [758]. On the other hand, the two cases of adenoid cystic carcinoma occurred in the reproductive age group [837,3248]. Cases of basal cell carcinoma of the ovary also typically present as a pelvic mass but occur over a wide age range [758].

Histopathology
These neoplasms histologically resemble adenoid cystic carcinoma, basal cell tumours of salivary gland or cutaneous basal cell carcinoma and occur in several forms. The adenoid cystic-like carcinomas resemble adenoid cystic carcinoma of salivary gland but lack a myoepithelial component [758]. On the other hand a myoepithelial component has been demonstrated in the cases of adenoid cystic carcinoma [837,3248]. Cribriform patterns composed of uniform small cells surrounding round lumens and cysts were typical, and luminal mucin and hyaline cylinders were common to both forms. A surface epithelial-stromal component was present in the great majority of cases of adenoid cystic-like carcinoma [758] but was absent in the cases of adenoid cystic carcinoma [837,3248]. The cases of basal cell tumour consisted of aggregates of basaloïd cells with peripheral palissading [758]. Several tumours of this type had foci of squamous differentiation or gland formation, and some showed an ameloblastoma-like pattern. A case of a monomorphic adenoma of salivary gland type described as a cribriform variant of basal cell adenoma has been reported [2492]. In none of the reported cases in this group was there evidence of a teratoma or other germ cell tumour.

Immunoprofile
Actin and S-100 protein stains were both positive in the two cases of adenoid cystic carcinoma [837,3248]; however, these stains were negative in the cases of adenoid cystic-like carcinoma [758].

Prognosis and predictive factors
The prognosis of adenoid cystic-like carcinoma is generally unfavourable and appears to depend on the degree of malignancy of the surface epithelial-stromal component. On the other hand, cases of basal cell tumour and adenoid cystic carcinoma have an excellent prognosis with relatively limited follow up.

Ovarian malignant mesothelioma

Definition
Ovarian malignant mesotheliomas (OMMs) are mesothelial tumours confined mostly or entirely to the ovarian surface and/or the ovarian hilus.

Aetiology
In the largest series there was no history of asbestos exposure [526].

Clinical features
The clinical presentation was usually abdominal or pelvic pain or abdominal swelling and an adnexal mass on pelvic examination [526].

Macroscopy
The tumours were typically solid and varied from 3-15 cm in maximum dimension. Most were bilateral.

Histopathology
The tumours usually involved both the serosa and the parenchyma of the ovary. The histological and immunohistochemical characteristics of the OMM are analogous to those observed in peritoneal mesotheliomas. The proliferating mesothelial tumour cells may invade and partly replace ovarian tissue and/or the hilar soft tissue.

Differential diagnosis
Just like diffuse peritoneal malignant mesotheliomas, OMMs can extensively involve one or both ovaries in a macroscopically and histologically carcinomatous growth pattern and may thus be confused with ovarian epithelial neoplasms. In this context immunohistochemical detection of thrombomodulin, calretinin, Ber-EP4 and cytokeratin 5/6 provide the most useful markers [2113].

Prognosis and predictive factors
In the absence of sufficient follow-up data for this rare neoplasm, OMM can be assumed to have a prognosis similar to its disseminated peritoneal analogue.
**Gestational choriocarcinoma**

**Definition**
A rare tumour composed of both cytotrophoblast and syncytiotrophoblast that arises as a result of an ectopic ovarian pregnancy. No germ cell or common epithelial component is present.

**Clinical features**
Patients with choriocarcinoma have symptoms related to a large haemorrhagic mass that may rupture causing haematoperitoneum.

**Macrosopy**
Choriocarcinoma consists typically of a haemorrhagic mass.

**Histopathology**
The typical appearance is an admixture of syncytiotrophoblast and cytotrophoblast often arranged in a plexiform pattern (142,1317). The specimens must be sampled extensively to rule out a germ cell, or in the older age group, a surface epithelial component. They must be distinguished from rarely reported ovarian hydatidiform moles, which have hydropic chorionic villi with cistern formation and trophoblastic proliferation.

**Prognosis and predictive factors**
The prognosis of gestational choriocarcinoma is more favourable than that of the nongestational type. Single agent chemotherapy with methotrexate or actinomycin D is highly effective.

**Hydatidiform mole**

**Definition**
Hydatidiform mole is an ectopic ovarian molar pregnancy. Ovarian hydatidiform moles have hydropic chorionic villi with cistern formation and trophoblastic proliferation.

**Clinical features**
Patients with hydatidiform mole have symptoms related to large haemorrhagic masses that may rupture causing haematoperitoneum.

**Macrosopy**
Hydatidiform mole typically consists of a haemorrhagic mass; chorionic vesicles may be identified.

**Histopathology**
Hydatidiform moles show characteristic hydropic chorionic villi with cistern formation and trophoblastic proliferation (2821,3212).

**Ovarian wolffian tumour**

**Definition**
A tumour of presumptive wolffian origin characterized by a variety of epithelial patterns.

**Synonyms**
Ovarian tumour of probable wolffian origin, retiform wolffian tumour.

**Localization**
Although more common in the broad ligament, this tumour also occurs in the ovary [1262,3212].

**Clinical features**
Patients are in the reproductive age group or beyond and present with abdominal swelling or a mass [3212]. Preoperative serum oestriadiol levels may be elevated and return to normal postmenopausal levels after operation [1289].
Histopathology
This epithelial tumour may show diffuse, solid tubular, hollow tubular and sieve-like patterns, and combinations of the various patterns may occur. Cases have been reported associated with endometrial hyperplasia [1262, 1289].

Immunoprofile
The neoplasms are positive for CAM5.2, cytokeratins 7 and 19 and vimentin but are negative for cytokeratin 20, 34betaE12, B72.3, carcinoembryonic antigen, and epithelial membrane antigen [2321, 2878, 2926]. The neoplastic cells often express CD10 [2110] and often are weakly positive for alpha-inhibin [1499].

Histogenesis
Cases have been reported arising within the rete ovarii [662, 2878]. An immunohistochemical study based on a comparison with mesonephric remnants and paramesonephric structures supported but did not prove a mesonephric origin of these neoplasms [2926].

Prognosis and predictive factors
These tumours typically are not aggressive; however, a significant minority of patients have had an aggressive course [3212]. The malignant cases sometimes, but not always, show nuclear atypia and increased mitotic activity.

Wilms tumour
Definition
A primary ovarian neoplasm that has the typical features of a Wilms tumour of the kidney.

Epidemiology
Several cases of pure Wilms tumour of the ovary have been reported [1303, 2506].

Clinical features
The tumour occurs in patients in the reproductive age group and beyond and presents as a rapidly growing adnexal mass.

Histopathology
They have the typical appearance of a Wilms tumour including small tubules, glomeruloid structures and blastema. No teratomatous elements were identified.

Prognosis and predictive factors
Two of the patients were living and well 10 months and 7 years postoperatively.

Paraganglioma
Definition
A unique neuroendocrine neoplasm, usually encapsulated and benign, arising in specialized neural crest cells associated with autonomic ganglia (paraganglia).

Synonym
Phaeochromocytoma.

Clinical features
A single case of a paraganglioma of the ovary in a fifteen year old girl with hypertension has been reported [832]. In addition, two unpublished cases have been described [2805].

Histopathology
The tumours consist of polygonal epithelioid cells arranged in nests separated by a fibrovascular stroma.

Immunoprofile
The tumour is positive for chromogranin. In addition, stains for S-100 protein can identify sustentacular cells [2605].

Biochemistry
Epinephrine and norepinephrine were extracted from the tumour [832].

Myxoma
Definition
A benign mesenchymal tumour composed of cells with bland nuclear features producing abundant basophilic intercellular ground substance.

Clinical features
Patients with ovarian myxomas present in the reproductive age group typically with an asymptomatic unilateral adnexal mass [757].

Macroscopy
The tumours are large, averaging 11 cm in diameter. The sectioned surface is soft, often with cystic degeneration.

Histopathology
Myxoma is a sharply demarcated tumour composed of spindle and stellate-shaped cells within an abundant, well vascularized myxoid background. Small foci of non-myxoid fibrous tissue or smooth muscle may be present. Lipoblasts are not identified. Mitoses are rare. The intercellular material stains with alcian blue and colloidal iron. Staining is prevented by pretreatment with hyaluronidase indicating that the material is hyaluronic acid.

Immunoprofile
Immunohistochemical stains show that the tumours are positive for vimentin and smooth muscle actin but negative for most other common immunohistochemical markers [567].

Electron microscopy
Ultrastructural features of thin filaments condensed into dense bodies also support the presence of myofibroblasts [567].

Histogenesis
Based on an immunohistochemical comparison with myxoid areas of ovarian stromal tumours, myxomas were considered to be a variant of the thecoma-fibroma group [3254].

Prognosis and predictive factors
The tumour is practically always benign although one case diagnosed originally as myxoma had a late recurrence after 19 years [2901]. In that case the original tumour showed occasional mitotic figures (less than 1 per ten high power fields), slight atypia and occasional vacuolated cells. The recurrent neoplasm, but not the original, was aneuploid by DNA-flow cytometry [2901].

Malignant soft tissue tumours not specific to the ovary
Pure soft tissue sarcomas of somatic type rarely occur as primary tumours of the ovary. They typically present as a rapidly enlarging adnexal mass. Their histological appearance is similar to soft tissue tumours in other locations. Among the reported cases of pure sarcomas are...
fibrosarcoma [1517,1867], leiomyosarcoma [917,1416,1895,1983,2037], malignant peripheral nerve sheath tumour [2797], lymphangiosarcoma, angiosarcoma [2021,2064], rhabdomyosarcoma [2018], osteosarcoma [1215] and chondrosarcoma [2851]. These tumours should be classified according to the WHO Histological Typing of Soft Tissue Tumours [3086]. Similarly, tumours may also arise as a component of a complex ovarian tumour such as malignant müllerian mixed tumour, adenosarcoma, immature teratoma or dermoid cyst or from heterologous elements in a Sertoli-Leydig cell tumour. Rare sarcomas of various types may be associated with surface epithelial stromal tumours, particularly serous, mucinous and clear cell adenocarcinoma. These tumours must be distinguished from metastatic sarcoma to the ovary [3222].

Benign soft tissue tumours not specific to the ovary

Of the remaining soft tissue tumours, leiomyomas and haemangiomas are most common. Occasional benign neural tumours, lipomas, lymphangiomas, chondromas, osteomas and ganglioneuromas have been reported. Their appearance is similar to soft tissue tumours in other locations. These tumours should be classified according to the World Health Organization Histological Typing of Soft Tissue Tumours [3086].

Tumour-like conditions

Definition
Non-neoplastic conditions that can mimic an ovarian neoplasm clinically, macroscopically and/or histologically.

Luteoma of pregnancy

Definition
Single or multiple nodules composed of lutein cells with abundant eosinophilic cytoplasm that are detected at the end of a term pregnancy.

Synonym
Nodular theca-lutein hyperplasia of pregnancy.

Epidemiology
Patients with luteoma of pregnancy are typically in their third or fourth decade and multiparous, and 80% are Black [2056,2364,2788].

Clinical features
Most patients are asymptomatic, and the tumour is usually found incidentally at term during caesarean section or postpartum tubal ligation [2788]. Exceptionally, a pelvic mass is palpable or obstructs the birth canal. Approximately 25% of patients are hirsute or show signs of virilization. Elevated levels of plasma testosterone and other androgens may be observed.

Macroscopy
The tumours vary from not being macroscopically detectable to over 20 cm. In one series the medium diameter of the tumour was between 6-7 cm [2056]. The sectioned surface is circumscribed, solid, fleshy and red to brown. In approximately one-half of cases the lesions are multiple and at least one-third are bilateral.

Histopathology
There is a diffuse proliferation of polygonal, eosinophilic cells that contain little or no lipid [2364]. The nuclei are round and contain prominent nucleoli. follicle-like spaces may be present. Mitotic figures may be frequent. The tumour cells were found to be positive for alpha-inhibin, CD99, cytokeratin and vimentin [2242].

Differential diagnosis
The differential diagnosis includes lipid-poor steroid cell tumours, metastatic melanoma and corpus luteum of pregnancy. Steroid cell tumours occurring during pregnancy may present a difficult differential diagnosis; however, the typical clinical setting of luteoma of pregnancy would be an unusual presentation for a steroid cell tumour. The presence of follicle-like spaces or multiple nodules favours the diagnosis of luteoma of pregnancy. In contrast to luteoma of pregnancy, steroid cell tumours that have a high mitotic rate are likely to exhibit significant nuclear atypia. Metastatic melanoma may be multinodular and contain follicle-like spaces; however, the presence of melanin pigment in some cases and positive stains for S-100 protein and often HMB-45 and Melan A and negative stains for alpha-inhibin would confirm the diagno-
sis. Corpus luteum of pregnancy has a central cavity and a convoluted border. It is composed of granulosa-lutein and theca-lutein layers and contains hyaline or calcified bodies. Multinodularity of the tumour or bilaterality favour luteoma of pregnancy.

**Histogenesis**
Luteoma of pregnancy appears dependent on beta-human chorionic gonadotropin for its growth based on its clinical presentation at term and regression following the conclusion of the pregnancy.

**Prognosis and predictive factors**
The tumours regress after the conclusion of the pregnancy.

**Uncommon tumour-like conditions associated with pregnancy**
Many tumour-like conditions occur during or subsequent to a pregnancy including ovarian pregnancy, hyperreactio luteinalis, large solitary luteinized follicle cyst of pregnancy and puerperium (513), granulosa cell proliferations of pregnancy (524), hilus cell proliferation of pregnancy and ectopic decidua (505).  

**Stromal hyperthecosis**

**Definition**
Stromal hyperthecosis consists of hyperplastic ovarian stroma containing clusters of luteinized stromal cells.

**Epidemiology**
The lesion typically occurs in women in the late reproductive years and beyond.

**Clinical features**
The patients may present with endocrine manifestations including virilization, obesity, hypertension and decreased glucose tolerance and may have elevated levels of plasma testosterone. Bilateral ovarian enlargement is typically encountered at laparotomy.

**Macroscopy**
The ovaries are typically enlarged and may measure up to 7 cm in greatest dimension (2605). With rare exceptions, the lesion is bilateral. The sectioned surface is predominately solid and white to yellow. Multiple superficial cysts may be present in premenopausal women.

**Histopathology**
On histological examination hyperplastic stroma is present containing clusters of luteinized stromal cells. In premenopausal women the outer cortex may be thickened and fibrotic with luteinized follicle cysts as is observed in the polycystic ovary syndrome.

**Differential diagnosis**
The lesion is distinguished from the closely related condition of stromal hyperplasia by the absence of luteinized stromal cells in the latter. Polycystic ovarian disease typically occurs in younger women and is less distinctly virilizing. The ovaries are more cystic than is typically seen in stromal hyperthecosis.

**Somatic genetics**
Patients with acanthosis nigricans and masculinization (HAIR-AN syndrome) all had the histologic findings of premenopausal hyperthecosis in their ovaries (729).

**Prognosis and predictive factors**
The lesion is usually treated by oophorectomy, and the postoperative course is uneventful.

**Stromal hyperplasia**

**Definition**
A tumour-like proliferation of ovarian stromal cells without the presence of luteinized stromal cells.

**Clinical features**
Patients are typically menopausal or early postmenopausal. It is much less estrogenic or androgenic than stromal hyperthecosis, and patients may occasionally have obesity, hypertension or abnormal glucose metabolism (2605).

**Macroscopy**
Ill defined white or pale yellow nodules that sometimes coalesce are present in the cortical or medullary regions of the ovary or both. In extensive cases the ovaries may be enlarged, and the architecture replaced.

**Histopathology**
The medullary and to a lesser extent the cortical regions are replaced by a nodular or diffuse densely cellular proliferation of small stromal cells with scanty amounts of collagen. In advanced cases the ovarian architecture is completely replaced and follicle derivatives are not observed.

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**Fig. 2.125** Stromal hyperthecosis. **A** The ovaries are enlarged and solid with a smooth external surface and have a multilobulated sectioned surface with a few follicle cysts. **B** Note the clusters of luteinized stromal cells within hyperplastic ovarian stroma.
Differential diagnosis
Stromal hyperplasia is distinguished from stromal hyperthecosis by the absence of luteinized stromal cells. It is distinguished from low grade endometrial stromal sarcoma by the presence of spindle shaped rather than round or oval stromal cells and the absence of mitotic figures or spiral arterioles.

Fibromatosis

Definition
Fibromatosis is a tumour-like enlargement of one or both ovaries due to a non-neoplastic proliferation of collagen-producing ovarian stroma.

Clinical features
The patients range from 13-39 years with an average of 25. The typical presentation is menstrual irregularities, amenorrhea or, rarely, virilization [3214].

Macroscopy
The ovaries range from 8-14 cm and have smooth or lobulated external surfaces. The sectioned surface is typically firm and grey or white, and small cysts may be apparent. About 80% of cases are bilateral.

Histopathology
There is a proliferation of spindle-shaped fibroblasts with a variable but usually large amount of collagen. Foci of luteinized stromal cells as well as oedema may be present. Ovarian architecture is maintained, and the fibrous proliferation surrounds follicle derivatives. Nests of sex cord type cells are present in some cases [384]. Most cases show diffuse involvement of the ovaries, but occasional cases are localized.

Differential diagnosis
The lesion is distinguished from fibroma in that the latter is usually unilateral and does not incorporate follicular derivatives. However, it differs from ovarian oedema in that oedema in the latter is massive and fibrous proliferation is not observed. It differs from stromal hyperplasia in that the latter does not produce abundant collagen and is usually unilateral. The sex cord type nests may superficially resemble a Brenner tumour, but the latter shows transitional cell features and replaces the ovarian architecture.

Prognosis and predictive factors
The lesion does not spread beyond the ovaries.

Massive ovarian oedema

Definition
Formation of a tumour-like enlargement of one or both ovaries by oedema fluid.

Epidemiology
The age range is 6-33 with an average of 21 years [3214].

Clinical features
Most patients present with abdominal pain, which may be acute, and a pelvic mass. [3214]. Others may present with abnormal uterine bleeding, hirsutism or virilization. Elevated levels of plasma testosterone and other androgens may be observed. At laparotomy ovarian enlargement, which is usually unilateral, is encountered, and torsion is observed in approximately one-half of the patients.

Macroscopy
The external surface is usually white and opaque. The ovaries range from 5-35 cm in size with an average diameter of 11 cm [3214]. The sectioned surface typically exudes watery fluid.

Histopathology
On histological examination oedematous, hypocellular ovarian stroma is present, and the ovarian architecture is preserved. The outer cortex is thickened and fibrotic. Clusters of luteinized stromal cells are present in the oedematous stroma in a minority of cases, especially those that have endocrine symptoms.

Differential diagnosis
The differential diagnosis includes an oedematous fibroma and Krukenberg tumour. The diffuse nature of the process and the preservation of ovarian architecture are unlike an oedematous fibroma, which is likely to be a circumscribed mass. The distinction from Krukenberg tumour is based on the absence of signet-ring cells and the typically unilateral mass, whereas Krukenberg tumours are bilateral in the vast majority of cases. It is important for the pathologist to recognize this lesion at the time of intraoperative consultation so that fertility may be maintained in these young patients.

Histogenesis
In many cases the oedema is due to partial torsion of the ovary insufficient to cause necrosis [1390,2463].

Prognosis and predictive factors
The lesion is usually treated by oophorectomy, and the postoperative course is uneventful.

Other tumour-like conditions
A wide variety of other conditions can, on occasion, mimic an ovarian neoplasm. Those not associated with pregnancy include follicle cyst, corpus luteum cyst, ovarian remnant syndrome, polycystic ovarian disease, hilus cell hyperplasia, simple cyst, idiopathic calcification, uterus-like adnexal mass [48], spenic-gonadal fusion, endometriosis and a variety of infections.

Fig. 2.126 massive ovarian oedema. The sectioned surface of the ovary was moist and exuded watery fluid.

Fig. 2.127 massive ovarian oedema. A portion of the ovarian cortex remains around an oedematous ovary.
Lymphomas and leukaemias

Malignant lymphoma

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

Epidemiology
Although unusual, ovarian involvement is more frequent than that of other sites in the female genital tract [1588]. The peak incidence of ovarian involvement by lymphoma is in the fourth and fifth decades, although it may occur at any age. Ovarian involvement by lymphoma may either be primary or secondary; however, the latter is much more common.

Clinical features
Lymphoma rarely presents clinically as an ovarian mass, and in most cases it is only one component of an intra-abdominal or generalized lymphoma [483]. An exception is Burkitt lymphoma, which may account for about one-half of the cases of malignant ovarian neoplasms in childhood in endemic areas [2605]. In such cases involvement of one or both ovaries is second in frequency only to jaw involvement.

Macroscopy
Lymphoma is bilateral in approximately one-half of the cases. The tumours are large and typically have an intact capsule. The sectioned surfaces are typically white, tan or grey-pink and occasionally contain foci of haemorrhage or necrosis.

Tumour spread and staging
Ovarian involvement by lymphoma is rare and is associated with simultaneous involvement of the ipsilateral tube in 25% of the cases [2119].

Histopathology
The histological appearance of ovarian lymphomas is similar to that observed at other sites; however, the neoplastic cells tend to proliferate in cords, islands and trabeculae with occasional follicle-like spaces or alveoli and often have a sclerotic stroma [2605]. In some cases ovarian follicular structures may be spared, but in others the entire ovarian architecture is obliterated. Almost any type of lymphoma may occur in the ovary; however, the most common are diffuse large B-cell, Burkitt and follicular lymphomas [1900,2119].

Differential diagnosis
Dysgerminoma is the most important and perhaps the most difficult differential diagnosis of ovarian lymphoma, particularly of the large B-cell type, which it may mimic both macroscopically and histologically [2605,3226]. Careful attention to the appearance of the cell nuclei and immunohistochemical stains for lymphoid markers and placental-like alkaline phosphatase are important in reaching the correct diagnosis. Other tumours that may be confused with lymphoma include granulocytic sarcoma, undifferentiated carcinoma, small carcinoma of the hypercalcaemic type and metastatic breast carcinoma [2605,3226].

Prognosis and predictive factors
Almost one-half (47%) of the patients with lymphoma who presented with ovarian involvement were alive at their last follow up with a median survival of 5 years [1900].

Leukaemia

Definition
A malignant haematopoetic neoplasm that may be primary or secondary.

Epidemiology
Ovarian involvement by leukaemia may either be primary or secondary; however, the latter is much more common [428]. A series of primary granulocytic sarcomas of the female genital tract including 7 cases of the ovary was reported [2099].

Fig. 2.128 Diffuse large B-cell lymphoma of ovary. A Intermediate-power magnification shows a diffuse growth pattern. Nuclei are medium-sized to large and polymorphic. B Immunohistochemical stain is positive for CD20.
Clinical features
Rarely, a patient presents with an ovarian granulocytic sarcoma with or without haematological evidence of acute myeloid leukaemia [2099]. Cases of acute lymphoblastic leukaemia, mostly in children and teenagers, are known to recur in the ovaries during hematological remission.

Macroscopy
The ovarian tumours are usually large and may be either unilateral or bilateral. They are typically solid, soft, and white, yellow or red-brown; occasionally, they may be green, and such tumours have been designated as a “chloroma” [2605].

Histopathology
Granulocytic sarcomas have a predominantly diffuse growth pattern, but sometimes a cord-like or pseudoacinar arrangement of the tumour cells is present locally [2099]. They are usually composed of cells with finely dispersed nuclear chromatin and abundant cytoplasm that may be deeply eosinophilic. The identification of eosinophilic myelocytes is helpful in establishing the diagnosis; however, they are not always present.

Differential diagnosis
The most important differential diagnosis is malignant lymphoma. Histochemical stains for chloracetate esterase or immunohistochemical stains for myeloperoxidase, CD68 and CD43 will establish the diagnosis in almost all cases [2099].

Plasmacytoma
Definition
A clonal proliferation of plasma cells that is cytologically and immunophenotypically identical to plasma cell myeloma but manifests a localized growth pattern.

Clinical findings
Ovarian plasmacytoma is a rare tumour that may present clinically with a unilateral adnexal mass. The 7 reported patients were 12-63 years old [782].

Macroscopy
The tumours were large, and the sectioned surface was white, pale yellow or grey.

Prognosis and predictive factors
One patient developed multiple myeloma 2 years after removal of the tumour.
Secondary tumours of the ovary

Definition
Malignant tumours that metastasize to the ovary from extraovarian primary neoplasms. Tumours that extend to the ovary directly from adjacent organs or tissues are also included in this category. However, most ovarian carcinomas associated with uterine cancers of similar histological type are independent primary neoplasms. General features of ovarian metastasis include: bilaterality, small multinodular surface tumours, extensive extraovarian spread, unusual patterns of dissemination, unusual histological features, blood vessel and lymphatic invasion and a desmoplastic reaction.

Synonym
Metastatic tumours.
The term Krukenberg tumour refers to a metastatic mucinous/signet-ring cell adenocarcinoma of the ovaries which typically originates from primary tumours of the G.I. tract, most often colon and stomach.

Epidemiology
Metastatic tumours to the ovary are common and occur in approximately 30% of women dying of cancer. Approximately 6-7% of all adnexal masses found during physical examination are actually metastatic ovarian tumours, frequently unsuspected by gynaecologists (1587,2605,2980). The metastasis often masquerades as a primary ovarian tumour and may even be the initial manifestation of the patient’s cancer. Pathologists also tend to mistake metastatic tumours for primary ovarian neoplasms even after histological examination. Carcinomas of the colon, stomach, breast and endometrium as well as lymphomas and leukaemias account for the vast majority of cases (3226). Ovarian metastases are associated with breast cancer in 32-38% of cases, with colorectal cancer in 28-35% of cases and with tumours of the genital tract (endometrium, uterine cervix, vagina, vulva) in 16% of cases. In recent years attention has been drawn to mucinous tumours of the appendix, pancreas and biliary tract that often spread to the ovary and closely simulate ovarian mucinous borderline tumours or carcinomas (590,1848,2406,3199,3200).

Aetiology
The routes of tumour spread to the ovary are variable. Lymphatic and haematogenous metastasis to the ovaries is the most common form of dissemination (1587,2605,2980). Direct extension is also a common manner of spread from adjacent tumours of the fallopian tube, uterus and colorectum (3226). Transtubal spread provides an explanation for some surface ovarian implants from uterine cancers. Neoplasms may also reach the ovary by the transperitoneal route from abdominal organs, such as the appendix (3199). Embolic spread often produces multiple nodules within the substance of the ovary and commonly is accompanied by prominent intravascular nests of tumour in the ovarian hilum, mesovarium and mesosalpinx.

Clinical features
Signs and symptoms
Ovarian metastases can be discovered in patients during follow-up after treatment of a primary tumour, serendipitously diagnosed during a surgical procedure for treatment of an abdominal tumour or fortuitously found at autopsy. The circumstances leading to the discovery of these metastatic lesions depends on the site of the primary tumour (951,1802). Ovarian metastasis was detected before the breast cancer in only 1.5% of cases.

Table 2.09
Metastatic tumours to the ovary.

<table>
<thead>
<tr>
<th>Clues to the diagnosis</th>
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<tbody>
<tr>
<td>1 - Bilaterality (mucinous and endometrioid-like)</td>
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<tr>
<td>2 - Small, superficial, multinodular tumours</td>
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<td>3 - Vascular invasion</td>
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<td>4 - Desmoplastic reaction</td>
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<td>5 - Extensive, unusual extraovarian spread</td>
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<tr>
<td>6 - Unusual clinical history</td>
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Fig. 2.130 Metastatic colonic adenocarcinoma of the ovaries. A The ovaries are replaced by bilateral, multinodular metastases. Note the additional leiomyomas of the corpus uteri (centre). B This tumour shows a garland-like glandular pattern with focal segmental necrosis of glands and luminal necrotic debris. C Immunohistochemical stain for carcinoembryonic antigen is strongly positive.
In patients with a gastrointestinal cancer, the ovarian malignant growth was discovered before, or more frequently, at the same time as the gastrointestinal primary (2232). In 35% of patients with a Krukenberg tumour, the diagnosis of the digestive primary preceded the diagnosis of the ovarian metastasis (1933,2545). When a patient presents with abdominopelvic symptoms leading to suspicion of an ovarian tumour, the symptoms are non-specific and similar to those of ovarian cancer, i.e. pelvic masses, ascites or bleeding (1598,2545). Eighty percent of patients with a Krukenberg tumour had bilateral ovarian metastases, and 73% of patients with ovarian metastases from breast carcinoma had extraovarian metastases (951,2545).

**Imaging**

Several studies have evaluated radiological findings in patients with a Krukenberg tumour (1094,1460). When imaging features were compared, patients with a Krukenberg tumour more frequently had a solid mass with an intratumour cyst, whereas primary ovarian growths were predominantly cystic (1460). Magnetic resonance (MR) imaging seems to be more specific than computed tomography scan. Identification of hypointense solid components in an ovarian mass on T2-weighted MR images seems to be characteristic of a Krukenberg lesion, but this aspect is not specific (1094).

**Macroscopy**

Ovarian metastases are bilateral tumours in approximately 70% of cases (2605).

They grow as superficial or parenchymatous solid nodules or, not uncommonly, as cysts. The size of ovarian metastases is variable even from one side to the other. The ovaries may be only slightly enlarged or measure 10 cm or more.

**Site of origin**

The frequencies of various sites of origin of secondary ovarian tumours differ among different countries according to the incidence of various cancers therein. Colonic adenocarcinoma probably accounts for most metastatic ovarian tumours that cause errors in diagnosis (1587,2605,3226). Frequently, the ovarian metastases and the primary tumour are discovered synchronously, or the intestinal tumour has been resected months or years previously.
Occasionally, the colonic adenocarcinoma is found several months to years after resection of the ovarian metastases. Rectal or sigmoid colon cancer accounts for 75% of the metastatic colon tumours to the ovary [1587,2605,3226]. The primary tumour can also be located in the pancreas, biliary tract or the appendix [590,1848,2406,3199,3200]. The Krukenberg tumour is almost always secondary to a gastric carcinoma but may occasionally originate in the intestine, appendix, breast or other sites [367,2605,3226]. Rarely, breast cancer metastatic to the ovary presents clinically as an ovarian mass. A much higher percentage of cases of lobular carcinoma of the breast, including those of signet-ring cell type, metastasizes to the ovary than does ductal carcinoma [1142]. A wide variety of other tumours may metastasize to the ovary.

**Histopathology**

The identification of surface implants, multinodularity and intravascular tumour emboli are extremely helpful histological clues in the recognition of secondary ovarian tumours that spread through the abdominal cavity and tubal lumen. The histological appearance of the metastases is variable, depending on the nature of the primary tumour.

**Differential diagnosis**

Sometimes, metastases resemble primary ovarian tumours [2605,2980,3226]. Metastatic colonic adenocarcinoma to the ovary may be confused with primary endometroid or mucinous carcinoma depending on whether the colonic carcinoma is predominantly mucinous or non-mucinous. Features that help to distinguish colon cancer from endometroid carcinoma include luminal necrotic debris, focal segmental necrosis of the glands, occasional presence of goblet cells and the absence of müllerian features (squamous differentiation, an adenofibromatous component or association with endometriosis). Also the nuclei lining the glands of metastatic colon carcinoma exhibit a higher degree of atypia than those of endometroid carcinoma. Metastatic tumours may also closely resemble primary mucinous ovarian tumours. The former may be moderately differentiated or so well differentiated that they can be mistaken for mucinous borderline or less often benign ovarian tumours. Metastatic mucinous tumours to the ovary can originate in the large intestine, pancreas, biliary tract or the appendix. Features supportive of the diagnosis of a metastasis include bilaterality, histological surface involvement by epithelial cells (surface implants), irregular infiltrative growth with desmoplasia, single cell invasion, signet-ring cells, vascular invasion, coexistence of benign-appearing mucinous areas with foci showing a high mitotic rate and nuclear hyperchromasia and histological surface mucin [1614]. Immunostains for cytokeratin 7 and 20 should be used with caution and along with thorough consideration of all clinical information keeping in mind that no tumour shows absolute consistency in its staining with these markers [2183]. Krukenberg tumours must be distinguished from primary and other metastatic ovarian tumours including clear cell adenocarcinoma, mucinous (goblet cell) carcinoid and a variety of ovarian tumours that contain signet-ring-like cells filled with non-mucinous material. Ovarian clear cell adenocarcinoma may have a signet-ring-like component that simulates a Krukenberg tumour; however, the identification of a characteristic tubulocystic pattern, hobnail cells, stromal hyalinization and eosinophilic secretion are helpful in establishing the diagnosis. Mucinous carcinoid, either primary or metastatic, may contain large areas of signet-ring cells; however, teratomatous elements other than carcinoid are usually present in the former. The tubular variant of Krukenberg tumour, sometimes associated with stromal hyalinization...

**Fig. 2.134** Metastatic lobular carcinoma of the breast. Sectioned surface shows a solid, multinodular tumour.

**Fig. 2.135** Metastatic malignant melanoma. The ovary is replaced by a multinodular nodular black tumour.

**Fig. 2.136** Metastatic renal cell carcinoma to the ovary. Note the tubules lined by cells with abundant clear cytoplasm.
mal luteinization, can be confused with a Sertoli-Leydig cell tumour. Positive mucicarmine and PAS-stains with diastase digestion are of great value in establishing the diagnosis of a Krukenberg tumour. Occasional Krukenberg tumours may closely resemble fibromas on macroscopic examination and may contain relatively few signet-ring cells. Bilaterality and positive mucin stains facilitate the differential diagnosis. Distinction between a transitional cell carcinoma of the urinary tract metastatic to the ovary and a primary transitional cell carcinoma may be difficult (2100,3220). Clinical information may be necessary to resolve the issue. Renal cell carcinoma rarely metastasizes to the ovaries; however, when it does, it must be distinguished from a primary clear cell carcinoma. The metastatic tumour usually shows a sinusoidal vascular pattern, a homogenous clear cell pattern without hobnail cells, the absence of hyalinized papillae and the absence of mucin (3226). A metastatic carcinoma can be confused with a primary carcinoma, granulosa cell tumour, Sertoli-Leydig cell tumour, Brenner tumour, adenofibroma or endometrioid carcinoma (2605,3226). Bilaterality and extraovarian extension are important features of metastatic carcinoma.

In the ovary, metastatic malignant melanoma may be confused with primary malignant melanoma; the latter is unilateral and usually associated with a dermoid cyst. When a melanoma is composed predominantly of large cells, it may resemble steroid cell lesions such as steroid cell tumour or luteoma of pregnancy; when it is composed predominantly of small cells it may be confused with a variety of other tumours characterized by small cells (3223). Positive stains for melanin, S-100 protein, melan A, and/or HMB-45 should establish the diagnosis of melanoma. Sarcomas may metastasize to the ovary from the uterus or extragenital sites and may occasionally be discovered before the primary tumour (3222). Metastatic low grade endometrial stromal sarcoma (ESS) may simulate a primary ovarian sex cord-stromal tumour. Features helpful in their distinction include the presence of extraovarian disease, bilaterality and the characteristic content of spiral arterioles in metastatic low grade ESS. Metastatic epithelioid leiomyosarcoma may have an appearance that simulates the solid tubular pattern of a Sertoli cell tumour. Although lymphoma and leukaemia can involve the ovaries simulating various primary tumours, they rarely present clinically as an ovarian mass. In countries where Burkitt lymphoma is endemic, however, it accounts for approximately half the cases of malignant ovarian tumours in childhood. Dysgerminoma is one of the most common and difficult differential diagnoses. The appearance of the cell nuclei is very important. Immunohistochemistry for lymphoid markers and placental alkaline phosphatase are helpful. Carcinoïd, granulosa cell tumour or small cell carcinoma can also resemble lymphoma. In patients with acute myeloid leukaemia, ovarian involvement in the form of granulocytic sarcoma (‘chloroma’) may rarely constitute the initial clinical presentation of the disease. Histological examination reveals a diffuse growth pattern with a prominent ‘single file’ arrangement of the tumour cells. Myeloid differentiation can be demonstrated by the chloroacetate esterase stain. Immunoperoxidase stains for lysozyme, CD68, and LCA are also helpful.

Recognition of the secondary nature of an ovarian tumour depends on a complete clinical history, a careful operative search for a primary extraovarian tumour, and accurate evaluation of the macroscopic and histological features of the ovarian tumour. In rare cases the primary tumour is not found until several years after resection of the ovarian metastases (2605,3226).

**Prognosis and predictive factors**

Ovarian metastases often represent a late disseminated stage of the disease in which other haematogenous metastases are also found. The prognosis is, therefore, poor.
Peritoneal tumours

Definition
Rare neoplasms with primary manifestation in the abdominal cavity in the absence of a visceral site of origin. Both malignant and benign tumours may occur.

ICD-O code
- Peritoneal mesothelioma: 9050/3
- Multicystic mesothelioma: 9055/1
- Adenomatoid tumour: 9054/0
- Desmoplastic small round cell tumour: 8806/3
- Primary peritoneal carcinoma: 8461/3
- Primary peritoneal borderline tumour: 8463/1

Clinical features
Signs and symptoms
Patients with malignant peritoneal tumours typically present with non-specific manifestations including abdominal discomfort and distension, digestive disturbances and ascites. Less frequently, a palpable mass or pelvic pain may be evident. Benign peritoneal tumours are usually asymptomatic.

Tumour spread and staging
Malignant peritoneal tumours spread primarily by exfoliation of cancer cells from the primary site of origin. Lymphatic and haematogenous dissemination also commonly occurs. However, some tumours have been shown to arise from separate intra-abdominal sites and are believed to have a multifocal origin [2576]. The staging involves a combination of radiological and operative findings, but these tumours do not have individual staging systems given their relative infrequency. Most malignant tumours are confined to the abdominal cavity at initial presentation. Benign peritoneal tumours do not metastasize and present as an isolated lesion, often detected at the time of operation for another indication.

Mesothelial tumours
Definition
Benign or malignant mesothelial tumours that arise within the peritoneum.

Peritoneal malignant mesothelioma
Definition
Malignant mesothelial tumours that arise within the peritoneum. Epithelial mesotheliomas may be divided into diffuse, well differentiated papillary and deciduoid types. A less common variant is the sarcomatous mesothelioma, which includes the desmoplastic type.

Epidemiology
Age and sex distribution
Patients with diffuse mesotheliomas are on average 50 years old [1443], and those with well differentiated papillary tumours are 58 [383].

Incidence and mortality
Primary neoplasms of the peritoneum are rare compared to the wide variety of benign and malignant peritoneal müllerian proliferations that women develop. Two clinically benign to low grade proliferations, multicystic mesothelioma and well differentiated papillary mesothelioma, are more common than diffuse malignant mesothelioma, and the latter is vastly less common than primary or secondary extraovarian serous carcinoma.

Aetiology
Well differentiated papillary, diffuse epithelial and deciduoid mesotheliomas appear clinically related to asbestos exposure in some cases [383,2633].

Clinical features
The most common presenting features are ascites and abdominal pain [1443].

Macroscopy
The tumour typically consists of multiple nodules measuring <1.5 cm in greatest

Fig. 2.138 Well differentiated papillary mesothelioma of the peritoneum. A Note the distinct papillary architecture of this peritoneal tumour. B Papillae with fibrous connective tissue cores are lined by a single layer of uniform mesothelial cells.
dimension (1443). The serosal surfaces have an appearance indistinguishable from the more common peritoneal carcinomatosis or extraovarian carcinoma.

**Histopathology**

Well differentiated papillary and diffuse malignant mesotheliomas are the most common types. Diffuse and well differentiated papillary mesotheliomas typically are composed of characteristic uniform cells with abundant eosinophilic cytoplasm. Another variant of epithelial mesothelioma is the deciduoid type that simulates an exuberant ectopic decidual reaction (2633). Sarcomatous mesotheliomas, including the desmoplastic type, also occur but are relatively less common than in the pleura (493). All well differentiated papillary mesotheliomas have, at least focally, a conspicuous well developed papillary architecture or a tubulopapillary pattern. A single layer of uniform, cuboidal or flattened mesothelial cells with bland nuclear features lines the papillae and tubules. Mitoses are rare. Occasionally, mild cytological atypia is present. Extensive fibrosis associated with irregularity of the glandular elements is common, and such areas may be confused with invasive foci of malignant mesothelioma or adenocarcinoma. Pseudomembranous bodies are present in some cases.

**Differential diagnosis**

The most reliable indicator of malignancy in these tumours is invasion of fat or of organ walls; however, in small biopsies invasion may be difficult to assess (493). In the peritoneal cavity entrapment of benign cells in organizing granulation tissue or between fat lobules is frequent and confusing (493). Diffuse peritoneal malignant mesotheliomas may macroscopically and histologically show a carcinomatous growth pattern and thus may be confused with primary peritoneal serous papillary neoplasms. In this context immunohistochemical detection of calretinin in the nuclei and Ber-EP4 were the most useful markers, whereas other mesothelial markers had too low a sensitivity for practical use (2113). Well differentiated papillary mesothelioma lacks the stratification, complex papillae and the mixed cell population of low grade serous neoplasms and lacks the stratification, cytological atypia and mitotic figures of serous carcinoma. Similarly, it lacks the cytological atypia of diffuse malignant mesothelioma and in some instances is localized within the peritoneum. The absence of a history of a prior operation or reactive changes elsewhere and the formation of convincing papillae distinguish well differentiated papillary mesothelioma from mesothelial hyperplasia.

**Prognosis and predictive factors**

The diffuse epithelial mesotheliomas are typically highly aggressive; however, unlike pleural mesotheliomas, a sizeable number of tumours are relatively indolent (1443). No morphological features were found to separate the favourable and unfavourable group of these tumours. The well differentiated papillary type is often localized and has a relatively favourable outcome (383,1027) compared to the diffuse peritoneal type.

**Multicystic mesothelioma**

**Definition**

A multiloculated cystic mesothelial tumour that typically has an indolent course. In a few instances multiple recurrences occur, and the disease may progress to diffuse malignant mesothelioma (1039).

**Synonym**

Multilocular peritoneal inclusion cyst.

**Epidemiology**

The tumour most frequently occurs in young to middle aged women.

**Clinical findings**

Patients typically present with an abdominal or pelvic mass associated with chronic pain. Occasional tumours are found incidentally at laparotomy.

**Aetiology**

An association with asbestos exposure has not been reported.

**Macroscopy**

Typically, the lesion is a large multicystic mass that may be solitary but is more commonly either diffuse or multifocal and consists of multiple, translucent, grape-like clusters of fluid filled cysts delimited by fibrous bands. The individual cysts are usually less than 1.0 cm in diameter but may be up to 20 cm.

**Tumour spread and staging**

The tumour affects chiefly the pelvic peritoneum, particularly the cul-de-sac, uterus and rectum, and there may be an
abdominal or retroperitoneal component. It grows along the serosa as multiple translucent, fluid-filled cysts. Occasionally, the cysts are solitary or form a free floating mass.

**Histopathology**

The tumour is made up of multiple cysts lined by one to several layers of flattened or cuboidal mesothelial cells embedded in a delicate fibrovascular stroma [3087]. The lesions typically do not have atypia or significant mitotic activity; however, the occasional presence of cytological atypia may lead to a misdiagnosis of malignancy. Hobnail-shaped cells, foci of mesothelial hyperplasia and, less frequently, squamous metaplasia may be seen. Fibrous septa are usually prominent and may occasionally produce foci with the appearance of an adenomatoid tumour. The stroma may show marked inflammatory change that make it difficult to recognize the nature of the lesion.

**Differential diagnosis**

The chief differential diagnostic consideration is malignant mesothelioma. Attention to the macroscopic appearance, i.e. multiple cysts rather than solid plaque-like necrotic masses and the usual absence of cytological atypia are sufficient to avoid the error in most cases. Cystic lymphangioma may mimic a multicystic peritoneal mesothelioma, but the cells lining the former do not express keratin.

**Histogenesis**

The majority of investigators consider this entity to be an unusual type of mesothelial neoplasm that has a tendency to recur locally and may rarely transform into a conventional mesothelioma [1039,3087]. Some investigators, however, consider the lesion to be a non-neoplastic reactive mesothelial proliferation [2456]. A case termed cystic adenomatoid mesothelioma showed a transition from a uterine adenomatoid tumour and is illustrated above.

**Prognosis and predictive factors**

These tumours have an indolent course, but approximately one-half of cases recur at intervals ranging from 1-27 years [1410,2456]. There are rare instances of multiple recurrences and of transformation into a conventional malignant mesothelioma [1039,3087]. In the largest series 8% of patients with adequate follow up died of tumour [3087].

**Adenomatoid tumour**

**Definition**

A benign tumour of the peritoneum originating from mesothelium and forming gland-like structures.

**Synonym**

Benign mesothelioma.

**Epidemiology**

Peritoneal origin of this neoplasm is very rare [571].

**Macroscopy**

Lesions are usually solitary, less than 2 cm in diameter and have a white-grey appearance.

**Histopathology**

Histologically, multiple, small, slit-like or ovoid spaces are lined by a single layer of low cuboidal or flattened epithelial-like cells. Although adenomatoid tumours can be confused with carcinomas, nuclear atypia is absent or minimal, and mitotic figures are infrequent. Notably, adenomatoid tumours have no significant intracellular mucin, as might be found in neoplasms of müllerian origin. Clinically, they are asymptomatic, and
rarely, if ever, do they recur after adequate excision [506].

**Smooth muscle tumour**

**Leiomyomatosis peritonealis disseminata**

**Definition**
A benign entity in which numerous small nodules composed of smooth muscle are present in the peritoneal cavity.

**Synonym**
Diffuse peritoneal leiomyomatosis.

**Epidemiology**
This condition is rare and occurs in women predominantly in their late reproductive years.

**Clinical findings**
With few exceptions the patients are asymptomatic. The tumours are found incidentally at the time of laparotomy for a leiomyomatous uterus or during caesarean section. At the time of operation the surgeon is likely to be alarmed since this entity may be macroscopically indistinguishable from diffuse carcinomatosis of the peritoneum. Intraoperative consultation is required to establish the diagnosis.

**Macroscopy**
The tumour typically consists of numerous small, grey-white nodules.

**Histopathology**
The tumours consist of multiple nodules of well differentiated smooth muscle arranged in an intersecting pattern. Cases may occur in conjunction with endometriosis or multicystic mesothelioma, and a single case was associated with both conditions [3268].

**Prognosis and predictive factors**
The tumours may regress spontaneously, and conservative management is appropriate.

**Tumour of uncertain origin**

**Desmoplastic small round cell tumour**

**Definition**
A malignant peritoneal tumour of uncertain origin that shows divergent differentiation and is typically composed of nodules of small cells surrounded by a prominent desmoplastic stroma.

**ICD-O code**
8806/3

**Epidemiology**
Desmoplastic small cell tumour (DSRCT) is an extremely rare malignancy that has a strong male predilection and occurs most commonly in adolescents and young adults (mean age 19 years) [984].

**Histopathology**
Histologically, DSRCT consists of sharply circumscribed aggregates of small epithelioid cells separated by fibrous stroma. The tumour cells typically are uniform with scanty cytoplasm, have indistinct cell borders, and small to medium-sized, round, oval or spindle-shaped hyperchromatic nuclei. Mitotic figures are numerous. Immunohistochemistry indicates simultaneous divergent expression within the tumour including reactivity for epithelial (keratin, epithelial membrane antigen), neural (neuron-specific enolase) and muscle/mesenchymal (desmin) markers [984].

**Histogenesis**
These tumours are malignant neoplasms of uncertain histogenesis. Their location primarily in the peritoneum suggests a possible histogenetic relationship with mesothelium. The distinctive immunophenotype suggests multilineage [984,1038].

**Somatic genetics**
DSRCT has a characteristic reciprocal chromosome translocation t(11;22)(p13;q12) which results in the fusion of the Ewing tumour (EWS) gene and the Wilms tumour (WT1) gene [900,903]. The resultant chimeric EWS-WT1 transcript produces a tumour-specific fusion protein that turns the WT1 tumour suppressor gene into a dominant oncogene [2340]. As a result, cytogenetic analysis can be helpful in excluding the diagnosis of other round cell tumours.

**Genetic susceptibility**
No familial clustering has been described.

**Prognosis and predictive factors**

**Clinical criteria**
Multimodality therapy with induction chemotherapy, aggressive surgical debulking and external beam radiotherapy is advocated for the initial treatment of DSRCT. However, the prognosis is over-
whelingly poor (1038, 1547, 2310).

Histopathological criteria
Although the detection rate of micrometastases in bone marrow and body fluids has recently been shown to be higher with reverse transcriptase polymerase chain reaction of the EWS-WT1 fusion transcript, the clinical significance of molecularly-detectable micrometastases of DSRCT remains unknown (128).

Primary epithelial tumours of müllerian type

Definition
Primary epithelial tumours of the peritoneum that resemble malignant ovarian surface epithelial-stromal tumours.

Primary peritoneal carcinoma

Definition
A variety of extraovarian neoplasms that histologically resemble surface-epithelial-stromal tumours of ovarian origin.

Epidemiology
Primary peritoneal carcinoma (PPC) occurs almost exclusively in women with a median age of 62 years. The lifetime risk is estimated to be 1 case per 500 women, since approximately 15% of "typical" epithelial ovarian cancers are actually PPCs (2575, 2576).

Histopathology
Histological and immunohistochemical examination of PPC is virtually indistinguishable from epithelial ovarian carcinoma. The most common histological variant is serous adenocarcinoma, but clear cell, mucinous, transitional cell and squamous cell carcinomas have all been reported to originate from the peritoneum. Rare cases of primary psammosarcoma of the peritoneum have been described (1001). The following are required to meet the criteria for PPC:

1. Both ovaries must be normal in size or enlarged by a benign process.
2. The involvement in the extraovarian sites must be greater than the involvement on the surface of either ovary.
3. The ovarian tumour involvement must be either non-existent, confined to ovarian surface epithelium without stromal invasion, or involving the cortical stroma with...
Histogenesis
PPC is believed to develop de novo from the peritoneal lining of the pelvis and abdomen [2575]. It may develop in a woman years after having bilateral oophorectomy [2262]. Some cases have been shown to originate from multiple peritoneal sites, supporting the hypothesis that cells derived from the coelomic epithelium may independently undergo malignant transformation [1954,2575,2576].

Somatic genetics
PPC exhibits a distinct pattern of chromosomal allelic loss compared to epithelial ovarian cancer [176,421,1259]. Overexpression of the TP53, EGFR, ERBB2, ERBB3, and ERBB4 genes has been reported, in addition to loss of normal WT1 expression [2574,2575]. TP53 gene mutations commonly occur in PPC, but KRAS mutations are very infrequent [965,2575]. PPC BRCA1 mutation carriers have a higher incidence of TP53 mutations, are less likely to exhibit ERBB2 overexpression, and are more likely to have a multifocal disease origin [2575]. This unique molecular pathogenesis of BRCA-related PPC is believed to affect the ability of current methods to reliably prevent or detect this disease prior to metastasis [1402].

Genetic susceptibility
Germline BRCA1 mutations occur in PPC with a frequency comparable to the BRCA1 mutation rate in ovarian cancer. Although the penetrance is unknown, PPC should be considered a possible phenotype of the familial breast and ovarian cancer syndrome [175]. The multifocal disease origin is thought to explain why PPC has been a common cause of detection failures in familial ovarian cancer screening programs. Screening strategies for these women cannot rely on ultrasonography and CA125 testing to detect early disease [1402].

Prognosis and predictive factors
The staging, treatment and prognosis of PPC are similar to those of epithelial ovarian cancer. Optimal surgical cytoreduction for histological grade 1 and 2 lesions are associated with longer median survival [2575]. Carboplatin or cisplatin in conjunction with paclitaxel is the current first-line recommended chemotherapy [1436]. The clinical behaviour of psammocarcinoma more closely resembles that of serous borderline tumours than that of serous carcinomas of the usual type. Patients with psammocarcinoma follow a protracted course and have a relatively favourable prognosis [1001].

Primary peritoneal borderline tumours
Definition
A variety of extraovarian neoplasms that histologically resemble borderline surface epithelial-stromal tumours of ovarian origin. By definition minimal or no ovarian surface involvement is present.

Epidemiology
The age in the two largest series has ranged from 16-67 years with a mean of 32 years.

Clinical features
Infertility and abdominal pain are the most common presenting complaints [204]. Occasional patients present with an abdominal mass. At operation the peritoneal lesions may be focal or diffuse. They commonly appear as mililiary granules and may be mistaken for peritoneal carcinomatosis.

Histopathology
The vast majority of cases are serous in type. The histological appearance is similar to that of non-invasive peritoneal implants of epithelial or desmoplastic type [278]. Psammoma bodies are a prominent feature.

Prognosis and predictive factors
The usual treatment is hysterectomy, bilateral salpingo-oophorectomy and omentectomy. Younger patients who desire to maintain fertility may be treated conservatively [278]. The prognosis is excellent. Occasional tumour recurrences with bowel obstruction have been described. Rarely, the patient may develop an invasive low grade serous carcinoma of the peritoneum. Rare deaths due to tumour have been reported.