Pathology of cancers of the female genital tract including molecular pathology

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Abstract
To better understand pathology reports, gynecologic oncologists must be familiar with the terminology used in gynecologic pathology. This chapter of the FIGO Cancer Report 2018 summarizes the clinical and pathological features of the most common cancers of the female genital tract, as well as their main molecular genetic alterations. In selected cases, an approach for processing surgical specimens is also included.

KEYWORDS
Cervical cancer; Endometrial cancer; FIGO Cancer Report; Ovarian and fallopian tube cancer; Vulvar cancer

1 | INTRODUCTION
Pathology reports include not only histopathologic diagnoses, but also specific information relating to prognosis and treatment. Thus, pathologists must have sufficient familiarity with the staging classification and management of gynecologic cancers to assure that their reports communicate clinically relevant information. Likewise, full comprehension of the pathology report by the gynecologic oncologist requires familiarity with the terminology used in gynecologic pathology. This chapter summarizes the pathological features of the most common gynecologic malignancies, as well as an approach for processing selected gynecologic surgical specimens.

2 | VULVA
2.1 | Malignant tumors and premalignant conditions
2.1.1 | Squamous cell carcinoma
Carcinoma of the vulva accounts for 4% of all female genital cancers and occurs mainly in women aged over 60 years. Squamous cell carcinoma is the most common type (86%). These tumors are divided into two groups: keratinizing squamous cell carcinomas unrelated to HPV (>70% of cases), and warty and basaloid carcinomas, which are strongly associated with high-risk HPV (<25% of cases), mainly HPV16,1,2

2.1.1.1 | Etiologic factors and precursor lesions
Keratinizing squamous carcinomas frequently develop in older women (mean age, 76 years), sometimes in the context of long-standing lichen sclerosus. The precursor lesion is referred to as differentiated vulvar intraepithelial neoplasia (dVIN) or VIN simplex (Fig. 1A), which carries a high risk of cancer development. In contrast, the HPV-associated warty and basaloid carcinomas develop from a precursor lesion called squamous intraepithelial lesion (SIL) VIN comprising a spectrum of alterations ranging from low-grade SIL VIN (VIN1) to high-grade SIL VIN (VIN 2–3) (Fig. 1B). Recent proposals from both the International Society for the Study of Vulvovaginal Disease (ISVVD) and the College of American Pathologists (CAP)/American Society for Colposcopy and Cervical Pathology (ASCCP) have recommended replacement of the older three-tiered system (VIN 1–3) used to describe these lesions with a two-tiered system\textsuperscript{3} (see Table 1 in Rogers and Cuello\textsuperscript{6}—this Supplement). HPV-associated SIL VIN lesions have a low risk of progression to invasive carcinomas (approximately 6%), except in older or immunosuppressed women.1,2 These tumors tend to develop in younger women.
2.1.1.2 | Pathology

Squamous intraepithelial lesion VIN may be single or multiple, and macular, papular, or plaque-like. Histologic grades are labeled low-grade SIL (VIN 1) corresponding to mild dysplasia, and high-grade SIL (VIN 2–3) corresponding to moderate, and severe dysplasia, respectively. However, high-grade SIL (VIN 3)—which includes squamous cell carcinoma in situ [CIS]—is by far the most common. This lesion is treated with wide excision.

Most tumors are exophytic, but some may be ulcerative. Microscopically, the tumor is composed of invasive nests of malignant squamous epithelium with central keratin pearls (Fig. 2). The tumors generally grow slowly, extending to contiguous skin, vagina, and rectum. Typically, they initially metastasize to superficial inguinal lymph nodes, and then to deep inguinal, femoral, and pelvic lymph nodes.¹²

2.1.1.3 | Clinical features

The International Federation of Gynecology and Obstetrics (FIGO) staging of vulvar cancer defines tumors of any size limited to the vulva as Stage I carcinomas; tumors extending to adjacent perineal structures (lower one-third of the urethra, lower one-third of the vagina, or anus) as Stage II; tumors with positive inguinofemoral lymph nodes as Stage III; and tumors invading the upper two-thirds of the urethra, upper two-thirds of the vagina, distal structures, or distant metastasis as Stage IV. Tumor grade and number, size, and location of lymph node metastases determine survival. Well-differentiated tumors have a better mean survival, approaching 90% if nodes are negative. Two-thirds of women with inguinal node metastases survive 5 years, but only one-fourth of those with pelvic node metastases live that long.⁵

Prognosis correlates with stage of disease and lymph node status. The number of inguinal lymph nodes with metastases is the most important single factor. The prognosis of patients with vulvar cancer is good because presentation in modern times is generally early, with an overall 5-year survival of 70%.⁵

2.1.2 | Verrucous carcinoma

Vulvar verrucous carcinoma is a distinct variety of squamous cell carcinoma that manifests as a large fungating mass resembling a giant condyloma acuminatum. HPV, usually type 6 or 11, is commonly identified. The tumor invades with broad tongues. Verrucous carcinomas rarely metastasize. Wide local surgical excision is the treatment of choice.

2.1.3 | Basal cell carcinoma

Basal cell carcinomas of the vulva are identical to their counterparts in the skin. They are not associated with HPV, rarely metastasize, and are usually cured by surgical excision.

2.1.4 | Malignant melanoma

Although uncommon, malignant melanoma is the second most frequent cancer of the vulva (5%). It occurs in the sixth and seventh
decades, but occasionally is found in younger women. It is highly aggressive, and the prognosis is poor. Management should be according to guidelines for melanoma treatment elsewhere.

2.1.5 Extramammary Paget disease

This disorder usually occurs on the labia majora in older women. The lesion is large, red, moist, and apparently sharply demarcated. The origin of the diagnostic cells (Paget cells) is controversial; they may arise in the epidermis or epidermally derived adnexal structures.

Intraepidermal Paget disease may have been present for many years and is often far more extensive throughout the epidermis than preoperative biopsies indicate. Unlike Paget disease of the breast, which is almost always associated with underlying duct carcinoma, extramammary Paget disease is less commonly associated with carcinoma of the skin adnexa (20%–30% of the time). Metastases rarely occur, so treatment requires wide local excision or simple vulvectomy.1,2

3 VAGINA

3.1 Malignant tumors of the vagina

Primary malignant tumors of the vagina are uncommon, constituting about 2% of all genital tract tumors. Most (80%) vaginal malignancies represent metastatic spread. Tumors confined to the vagina are usually treated by radical hysterectomy and vaginectomy or with radiation. Squamous cell carcinomas account for over 90% of primary vaginal malignancies. Prognosis is related to the extent of spread of the tumor at the time of its discovery. The 5-year survival rate for tumors confined to the vagina (Stage I) is 80%, whereas it is only 20% for those with extensive spread (Stages III/IV).1

3.1.1 Embryonal rhabdomyosarcoma (sarcoma botryoides)

Embryonal rhabdomyosarcoma occurs almost exclusively in girls under 4 years of age. It arises in the lamina propria of the vagina and consists of primitive spindle rhabdomyoblasts, some of which show cross-striations. Tumors less than 3 cm in greatest dimension tend to be localized and may be cured by wide excision and chemotherapy. Larger tumors have often spread to adjacent structures, regional lymph nodes, or distant sites. Even in advanced cases, half of patients survive with radical surgery and chemotherapy.1,2

4 CERVIX

4.1 Squamous cell neoplasia

Cytological screening in high-resource countries has decreased cervical carcinoma by 50% to 85%; however, worldwide cervical cancer remains the fourth most common cancer in women.6

4.2 Cervical squamous intraepithelial neoplasia (SIL)

Cervical squamous intraepithelial neoplasia SIL (CIN) is a spectrum of intraepithelial changes that begins with minimal atypia and progresses through stages of greater intraepithelial abnormalities to invasive squamous cell carcinoma. The terms CIN, dysplasia, CIS, and squamous intraepithelial lesion (SIL) are commonly used interchangeably1,2 (Fig. 3).

4.2.1 Epidemiology and molecular pathogenesis

HPV infection with persistent expression leads to CIN and cervical cancer (Fig. 4). Low-grade SIL (CIN1) is a permissive infection (i.e. HPV is episomal, freely replicates, and thereby causes cell death). Huge numbers of virus must accumulate in the cytoplasm before being visible as a koilocyte (Fig. 3). In most cases of higher-grade SIL (CIN2-3), viral DNA integrates into the cell genome. Proteins encoded by E6 and E7 genes of HPV 16 respectively bind and inactivate p53 and Rb proteins, thereby invalidating their tumor suppressor functions. After HPV integrates into host DNA, copies of the whole virus do not accumulate and koilocytes are absent in many cases of high-grade dysplasia and all invasive cancers. Cells in high-grade CIN usually contain HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Globally, HPV types 16 and 18 are found in 70% of invasive cancers with some variation from region to region; the other high-risk types account for another 25%.7

4.2.2 Pathology

SIL CIN is nearly always a disease of metaplastic squamous epithelium in the transformation zone. The normal process by which cervical squamous epithelium matures is disturbed in CIN, as evidenced morphologically by changes in cellularity, differentiation, polarity, nuclear features, and mitotic activity. High-grade SIL (CIN3) is synonymous with severe dysplasia and CIS. The sequence of histologic changes from low-grade SIL (CIN1) to high-grade SIL (CIN2-3) is shown in Figure 3.1,2

4.2.3 Clinical features

The mean age at which women develop SIL (CIN) is 24–27 years for CIN1 and CIN2, and 35–42 years for CIN3. Based on morphologic criteria, half of cases of low-grade SIL (CIN1) regress, 10% progress to high-grade SIL (CIN3), and less than 2% become invasive cancer. The average time for all grades of dysplasia to progress to high-grade SIL (CIN3) is about 10 years. At least 20% of cases of high-grade SIL (CIN3) progress to invasive carcinoma in that time.1

When SIL (CIN) is discovered, colposcopy delineates the extent of the lesion and indicates areas to be biopsied. Diagnostic endocervical curettage also helps to determine if there is endocervical involvement. Women with low-grade SIL (CIN1) are often followed conservatively (i.e. repeat Pap smears plus close follow-up). High-grade lesions are
treated with excision LEEP (loop electrosurgical excision procedure), cervical conization (removal of a cone of tissue around the external os), ablation such as laser, cryosurgery, thermal coagulation, or rarely, hysterectomy may be done.  

4.3 | Microinvasive (superficially invasive) squamous cell carcinoma

This is the earliest stage (IA) of invasive cervical cancer. In this setting, stromal invasion usually arises from overlying SIL (CIN) (Fig. 5). Presently, staging of microinvasive disease is based on width and depth of invasion, defined as follows:

1. Invasion less than 3 mm (Stage IA1) or 5 mm (stage IA2) below the basement membrane.
2. 7-mm maximum lateral extension.

The earliest invasive changes ("early stromal invasion" or ESI) appear as tiny irregular epithelial buds emanating from the base of CIN3 lesions. These small (<1 mm) tongues of neoplastic epithelial cells do not affect the prognosis of CIN3 lesions. In the 2009 FIGO classification, ESI was excluded from Stage IA1. Some gynecologic oncologists further limit microinvasive carcinoma to tumors lacking lymphovascular space invasion (LVSI). Stage IA2 tumors are associated with lymph node metastases in about 8% of cases whereas those that invade less than or equal to 3 mm (Stage IA1) have less than a 1%–2% risk of lymph node metastases. Conization or simple hysterectomy generally cures microinvasive cancers less than 3 mm deep.  

The role of LVSI as a prognostic indicator is more controversial than that of the depth of invasion and lateral extent of tumor. The stroma in which foci of invasion lie can retract during preparation of the tissue sections for microscopic examination. A clear space can easily be mistaken for LVSI. Whereas some studies concluded that the presence of tumor in lymphatic spaces was of no value by itself in predicting which patients are likely to have lymph node metastases, other studies have reported that the presence of LVSI is an important prognostic indicator.

4.4 | Invasive squamous cell carcinoma

4.4.1 | Pathology

Early stages of cervical cancer are often poorly defined lesions or nodular and exophytic masses. If the tumor is within the endocervical canal, it can be an endophytic mass, which can infiltrate the stroma and cause diffuse cervical enlargement. Most tumors are nonkeratinizing, with solid nests of large malignant squamous cells and no more than individual cell keratinization. Most remaining cancers show nests of keratinized cells in concentric whorls, so-called keratin pearls. 

Cervical cancer spreads: (1) by direct extension; (2) by contiguity; (3) through lymphatic vessels; and (4) only rarely by the hematogenous
4.4.2 | Clinical features

HPV testing is the most reliable screening test for detecting cervical cancer, and is supplanting cytology in some screening algorithms in women aged over 25 years. Co-testing with HPV testing and cytology is also recommended in women aged over 30 years. Where HPV testing is not available, the Pap smear remains the most commonly used screening test, but quality assurance is a vital component of such screening programs.

The clinical stage of cervical cancer is the best predictor of survival. Overall 5-year survival is 60%, and by each stage it is: I, 90%; II, 75%; III, 35%; and IV, 10%. About 15% of patients develop recurrences on the vaginal vault, bladder, pelvis, or rectum within 2 years of therapy. Radical hysterectomy is favored for localized tumor, especially in younger women; radiation therapy, chemotherapy, or combinations of the two are used for more advanced tumors.1,5 (See Bhatla et al.8 in this Supplement).

4.5 | Endocervical adenocarcinoma

This tumor makes up 20% of cervical cancers. The incidence of cervical adenocarcinoma has increased recently, with a mean age of 56 years at presentation. Most tumors (70%) are HPV-associated adenocarcinomas of endocervical cell (usual) type that may exhibit foci of adenocarcinoma in situ.1,2 HPV-unrelated types (gastric-type and clear cell carcinoma) are less common and behave more aggressively than HPV-associated tumors.

Adenocarcinoma in situ (AIS) generally arises at the squamocolumnar junction and extends into the endocervical canal. This lesion may not always be contiguous and can be multifocal. Invasive adenocarcinoma typically presents as a polypoid or papillary mass. It is often not visible and presents somewhat later than its squamous counterpart. Adenocarcinoma of the endocervix spreads by local invasion and lymphatic metastases, and overall survival is somewhat worse than for squamous carcinoma.

4.6 | Cervical cone biopsy/excision and trachelectomy

Cone biopsy is the standard procedure performed for women with high-grade CIN and glandular lesions (Fig. 6). The conventional cone biopsy is obtained using a scalpel (“cold knife”), but today it is more often used for glandular lesions. Ectocervical lesions are best
5.1.1 | Hyperplasia without atypia
This is an exaggerated proliferation of glands of irregular size and shape with increase in the gland-to-stroma ratio compared with proliferative endometrium, but without significant nuclear atypia. Risk factors include obesity, polycystic ovarian disease, and diabetes. Hyperplasia without atypia is the result of unopposed estrogenic stimulation. Patients have a 3–4-fold increased endometrial carcinoma risk, rising to 10-fold after 10 years. Progression to endometrial carcinoma occurs in 1%–3% of women with hyperplasia without atypia.

5.1.2 | Atypical hyperplasia/endometrial intraepithelial neoplasia (EIN)
This lesion shows marked glandular crowding, often as back-to-back glands, with little intervening stroma and cytologic atypia. Epithelial cell nuclei are large and hyperchromatic with prominent nucleoli. One-quarter to one-third of these women will be diagnosed with endometrioid carcinoma at immediate hysterectomy or during the first year of follow-up. Trimble et al., on behalf of the Society of Gynecologic Oncology Clinical Practice Committee, demonstrated up to a 42.6% (123/289) risk of associated cancers in this group.

EIN refers to a monoclonal neoplastic growth of genetically altered cells with greatly increased risk of becoming the endometrioid type of endometrial carcinoma. The main diagnostic criterion of EIN is that gland area exceeds that of stroma (volume percentage stroma <55%). Atypical hyperplasia/EIN contains many of the genetic changes seen in endometrioid endometrial carcinoma, i.e., microsatellite instability, and PTEN, KRAS, and CTNNB1 (beta-catenin) mutation.1,2

5.2 | Endometrial carcinoma
Endometrial carcinoma is the sixth most frequent cancer diagnosed in women globally, with an age standardized incidence rate of 8.2 per 100 000. It is the fourth most common cancer in women in industrialized countries and the most common gynecologic cancer. Three-quarters of women with endometrial cancer are postmenopausal. The median age at diagnosis is 63 years.1,2

Endometrial carcinoma is classified into two different types (Fig. 7 and Table 1). Type I tumors (Fig. 7A) (about 80%), endometrioid carcinomas, are often preceded by endometrial hyperplasia or EIN and are associated with estrogenic stimulation. They occur mainly in pre- or perimenopausal women and are associated with obesity, hyperlipidemia, anovulation, infertility, and late menopause. Typically, most endometrioid carcinomas are confined to the uterus and follow a favorable course. In contrast, type II tumors (Fig. 7B) (about 10%) are nonendometrioid, largely serous carcinomas, arising occasionally in endometrial polyps or from precancerous lesions in atrophic endometria (endometrial “intraepithelial”...
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Endometrial cancer is the most common extracolonic cancer in women with hereditary nonpolyposis colon cancer syndrome (also known as Lynch syndrome)—a defect in DNA mismatch repair that is also associated with ovarian, urethelial, and breast cancers.\(^\text{10}\)

5.2.1 | Molecular pathogenesis

A dualistic model of endometrial carcinogenesis has been proposed. According to this model, normal endometrial cells transform into endometrioid carcinoma through replication errors, so-called “microsatellite instability,” and subsequent accumulation of mutations in oncogenes and tumor suppressor genes. For nonendometrioid carcinomas, alterations of p53 and loss of heterozygosity on several chromosomes drive malignant transformation.\(^\text{10}\)

Six main molecular alterations have been described in type I endometrioid carcinomas: microsatellite instability (25%–30% of the cases); PTEN mutations (30%–60%); PIK3CA mutations (26%–39%); ARID1A (20%); K-RAS mutations (10%–30%); and CTNNB1 (\(\beta\)-catenin) mutations with nuclear protein accumulation (25%–38%). In contrast, most type II nonendometrioid carcinomas have p53 mutations, Her-2/neu amplification, and loss of heterozygosity on several chromosomes. Nonendometrioid carcinomas may also derive from endometrioid carcinoma with microsatellite instability through tumor progression and subsequent p53 mutations.\(^\text{10}\)

The Cancer Genome Atlas (TCGA) has conducted the most comprehensive genomic analysis of endometrial carcinomas reported to date.\(^\text{11}\) TCGA has expanded the dualistic classification of endometrial carcinoma (types I and II) to four distinct molecular subgroups: (1) an ultramutated POLE subgroup; (2) a hypermutated microsatellite unstable subgroup; (3) a copy-number low/microsatellite stable subgroup; and (4) a copy-number high/serous-like subgroup. Even if overlapping of the molecular genetics findings makes it still difficult to separate significant prognostic categories, POLE mutations predict favorable prognosis, particularly in high-grade tumors. On the other hand, patients with endometrioid tumors that are serous-like at the molecular level might benefit from treatments that are typically used for serous carcinomas.\(^\text{11}\)

Molecular classification of grade 3 endometrial endometrioid carcinomas reveals that these tumors are a mixture of molecular subtypes of endometrial carcinoma, rather than a homogeneous group. Molecular markers identify prognostic subgroups, with therapeutic implications.

5.2.2 | Pathology

5.2.2.1 | Endometrioid carcinoma of the endometrium

This type of endometrial cancer is composed entirely of glandular cells and is the most common histologic variant (80%–85%). The FIGO system divides this tumor into three grades on the basis of the ratio of glandular to solid elements, the latter signifying poorer differentiation. Less common histologic variants include endometrioid adenocarcinoma with squamous differentiation and the mucinous and secretory types, both associated with good prognosis.\(^\text{1–5}\)

5.2.2.2 | Nonendometrioid endometrial carcinomas

These are aggressive as a group, and histologic grading is not clinically useful, all cases being considered high grade.

1. Serous carcinoma histologically resembles, and behaves like, high-grade serous carcinoma of the ovary (Fig. 7B). It often shows transstubal spread to peritoneal surfaces. An intraepithelial form has been termed “serous endometrial intraepithelial carcinoma” (serous EIC), not to be confused with EIN, described earlier. Patients with this type of tumor need to be staged and treated as if they had ovarian cancer.

2. Clear cell carcinoma is a tumor of older women. It contains large cells with abundant cytoplasmic glycogen (“clear cells”) or cells with bulbous nuclei that line glandular lumina (“hobnail cells”). Clear cell carcinomas have poor prognosis.

| TABLE 1 | Clinicopathologic features of endometrial carcinoma. |
|----------|-------------------------------------------------------|
|          | Type I: Endometrioid carcinoma | Type II: Serous carcinoma |
| Age      | Pre- and perimenopausal | Postmenopausal |
| Unopposed estrogen | Present | Absent |
| Hyperplasia precursor | Present | Absent |
| Grade    | Low | High |
| Myometrial invasion | Superficial | Deep |
| Growth behavior | Stable | Progressive |
| Genetic alterations | Microsatellite instability, PTEN, PIK3CA, CTNNB1 (\(\beta\)-catenin) | TP53 mutations, loss of heterozygosity |
3. Carcinosarcoma (malignant mixed mesodermal tumor): In this highly malignant tumor, pleomorphic epithelial cells intermingle with areas showing mesenchymal differentiation. These mixed neoplasms are derived from a common clone thought to be of epithelial origin. Overall 5-year survival is 25%.

5.2.3 | Clinical features

Unlike cervical cancer, endometrial cancer may spread directly to para-aortic lymph nodes, thereby skipping pelvic nodes. Patients with advanced cancers may also develop pulmonary metastases (40% of cases with metastases).

Women with well-differentiated cancers confined to the endometrium are usually treated by simple hysterectomy and frequently bilateral salpingo-oophorectomy. Postoperative radiation is considered if: (1) the tumor is poorly differentiated or nonendometrioid in type; (2) myometrium is deeply invaded (more than 50% of the myometrium); (3) the cervix is involved; or (4) lymph nodes contain metastases.

Survival in endometrial carcinoma is related to multiple factors: (1) stage, histologic type, and, for endometrioid tumors, grade; (2) age; and (3) other risk factors, such as progesterone receptor activity, depth of myometrial invasion (Fig. 8), and extent of lymphovascular invasion. Actuarial survival of all patients with endometrial cancer following treatment is 80% after 2 years, decreasing to 65% after 10 years. Serous carcinomas have an overall survival of less than 50% and account for more than half of the mortality from this disease.

5.3 | Endometrial sarcomas

Currently, endometrial sarcomas are classified into three categories: (1) low-grade endometrial stromal sarcoma (LG-ESS); (2) high-grade endometrial stromal sarcoma (HG-ESS); and (3) undifferentiated endometrial sarcoma (UES). LG-ESSs represent less than 2% of uterine cancers. They may be polypoid or may diffusely invade the myometrium. The tumor cells resemble endometrial stromal cells in the proliferative phase. Nuclear atypia may be minimal to severe and mitotic activity may be restrained. Expression of CD-10 and estrogen and progesterone receptors helps confirm the diagnosis. The most common cytogenetic abnormality of LG-ESS is a recurrent translocation involving chromosomes 7 and 17 [t(7;17)(p15;q21)], which results in a fusion between JAZF1 and SUZ12 (formerly designated as JJAZ1).

This generally portends a better prognosis.

The recently re-established HG-ESS has features intermediate between LG-ESS and undifferentiated sarcomas. It may appear as an intracavitary polypoid or a mural mass. Microscopically, it consists predominantly of high-grade round-cells that are sometimes associated with a low-grade spindle cell component usually fibromyxoid. Mitotic activity is very striking and typically more than 10 per 10 high-power fields (HPFs). Necrosis is usually present. HG-ESS typically harbors the YWHAE-FAM22 genetic fusion as a result of t(10;17)(q22;p13).

Higher-grade poorly differentiated sarcomas originating in the endometrium are designated as undifferentiated endometrial sarcoma.

5.3.1 | Clinical features

Many years may elapse before LG-ESSs recur clinically, and metastases may occur even if the original tumor was confined to the uterus at initial surgery. Recurrences usually involve the pelvis first, followed by lung metastases. Prolonged survival and even cure are feasible, despite metastases. By contrast, UES recur early, generally with widespread metastases. Compared with patients with LG-ESSs, those with HG-ESSs and undifferentiated endometrial sarcoma have earlier and more frequent recurrences (often <1 year) and are more likely to die of disease. LG-ESSs can be successfully treated with surgery followed by progestin therapy, with an expectation of 90% survival 10 years after diagnosis.

5.4 | Uterine adenosarcoma

Uterine (müllerian) adenosarcoma is a distinctive low-grade tumor with benign glandular epithelium and malignant stroma. It should be distinguished from carcinosarcoma, which is highly aggressive in which both epithelial and stromal elements are malignant. One-fourth
of patients with adenosarcoma, particularly cases with myometrial invasion and sarcomatous overgrowth, eventually succumb to local recurrence or metastatic spread.1,2

5.5 | Leiomyosarcoma

Leiomyosarcoma is a malignancy of smooth muscle origin whose incidence is only 1/1000 that of leiomyoma. It accounts for 2% of uterine malignancies. Its pathogenesis is uncertain. Women with leiomyosarcomas are on average more than a decade older (age above 50 years) than those with leiomyomas, and the malignant tumors are larger (10–15 cm vs 3–5 cm).1,2

5.5.1 | Pathology

Leiomyosarcoma should be suspected if an apparent leiomyoma is soft, shows areas of necrosis on gross examination, or has irregular borders (invasion of adjacent myometrium). Mitotic activity (10 or more mitoses per 10 HPFs), nuclear atypia, and geographical necrosis are the best diagnostic criteria (Fig. 9A,B). Myxoid and epithelioid leiomyosarcomas may contain only five mitoses per 10 HPFs. Size is important as tumors less than 5 cm in diameter almost never recur.

Most leiomyosarcomas are large and are advanced when detected. They are usually fatal despite combinations of surgery, radiation therapy, and chemotherapy. Five-year survival is about 25%.1,2 Almost all leiomyosarcomas are high-grade tumors and, usually, their diagnosis is straightforward; however, a small fraction of uterine smooth muscle tumors show atypical histologic features that are insufficient for the diagnosis of malignancy or have an unpredictable clinical behavior. These tumors have been designated as smooth muscle tumors of uncertain malignant potential (STUMP), but the term atypical smooth muscle tumors, as introduced by the 2014 WHO classification of tumors,2 seems preferable in view of their favorable behavior in most cases. The latter term simply describes the morphologic findings avoiding the words “uncertain” and “malignant,” which create unnecessary concern for the patient.

In two studies of 41 and 16 cases of “STUMP,” only 3 (7%) and 2 (12%) patients developed recurrences, respectively. Recurrence occurred, several years after hysterectomy, in the form of “STUMP” in three cases and as leiomyosarcoma in the other two. All five patients were alive and disease free after prolonged follow-up.13,14 As indicated previously, when account is taken of mitotic count, myometrial invasion, nuclear atypia, tumor cell necrosis, size of tumor, and age of the patient, tumors can be allocated to benign or malignant categories with greater certainty and the term “of uncertain malignancy” can be avoided in most cases.1,2

6 | FALLOPIAN TUBE

Tumors of the fallopian tube are rare. Most primary malignancies are carcinomas, with peak incidence among women aged 50–60 years. Recent observations suggest that some cases of high-grade serous carcinoma of the ovary (see below) may arise from the fimbriated end of the fallopian tube. Tubal carcinomas behave similarly to ovarian carcinoma and frequently appear as a solid mass in the wall of a grossly dilated tube, but may sometimes only be identified upon microscopic examination. The tumor is bilateral in 25% of cases. Prognosis is poor, as the disease is almost always detected at advanced stage.1,2 These tumors are treated like an ovarian cancer.

6.1 | Risk reducing salpingo-oophorectomy

An increasingly common indication for salpingectomy is prophylactic for patients who have BRCA1/2 mutations, a personal history of breast cancer, or strong family history of breast and/or tubo-ovarian cancer. Typically the specimen is grossly unremarkable, however these fallopian tubes, along with the corresponding ovaries, should be submitted entirely for histologic examination.1,2 Prophylactic salpingectomy is becoming standard at the time of hysterectomy and emerging data suggest a significant reduction in ovarian cancer risk when the fallopian tubes are removed.15
The protocol for sectioning and extensively examining the fimbriated end (SEE-FIM protocol) (Fig. 10) was developed for processing risk-reducing salpingo-oophorectomy specimens. The entire tube is initially fixed for at least 4 hours to prevent denuding of the mucosal epithelial cells. Then, the fimbriated end is amputated from the proximal tube and sectioned longitudinally into multiple (at least four) sections and the entire tube is submitted for histologic review.

7 | OVARY

7.1 | Ovarian tumors

There are many types of ovarian tumors including benign, borderline, and malignant types. About two-thirds occur in women of reproductive age. Approximately 80% of ovarian tumors are benign. Almost 90% of malignant and borderline tumors are diagnosed after the age of 40 years.

Ovarian tumors are classified by the ovarian cell type of origin. Most are common epithelial tumors (approximately 60%). Other important groups are germ cell tumors (30%), sex cord/stromal tumors (8%), and tumors metastatic to the ovary. Common epithelial tumors account for about 90% of ovarian malignancies, high-grade serous adenocarcinoma being the most common (70%). Some cases of high-grade serous carcinomas may arise in the fallopian tubes.

Ovarian cancer is the second most frequent gynecologic malignancy after endometrial cancer and carries a higher mortality rate than all other female genital cancers combined. It is difficult to detect early in its evolution when it is still curable and, as such, over three-fourths of patients already have extraovarian tumor spread to the pelvis or abdomen at the time of diagnosis.

7.2 | Epithelial tumors

Tumors of common epithelial origin can be broadly classified, according to cell proliferation, degree of nuclear atypia, and presence or absence of stromal invasion: (1) benign; (2) borderline malignancy; and (3) carcinoma.

Common epithelial neoplasms most commonly affect nulliparous women and occur least frequently in women in whom ovulation has been suppressed (e.g. by pregnancy or oral contraceptives). Whereas the lifetime risk of developing ovarian cancer in the general population is 1.6%, women with one-first-degree relative with ovarian cancer have a 5% risk. Also, women with a family history of ovarian carcinoma are at greater risk of breast cancer and vice versa. Defects in repair genes implicated in hereditary breast cancers, BRCA-1 and BRCA-2, are incriminated in familial ovarian cancers as well. As for endometrial carcinoma, women with hereditary nonpolyposis colon cancer (HNPCC) are also at greater risk of ovarian cancer.

Epithelial ovarian tumors are primarily classified according to cell type into serous, mucinous, endometrioid, clear cell, transitional, and squamous cell tumors. However, none of these cells are found in the normal ovary and their development has long been attributed to müllerian “neometaplasia” of the ovarian surface epithelium (mesothelium). During embryonic life, the pelvic cavity is lined by mesothelium which also covers the gonadal ridge. The same mesothelial lining gives rise to müllerian ducts, from which the fallopian tubes, uterus, and vagina arise (Fig. 11). Thus, the tumor cells would resemble morphologically the epithelia of the fallopian tube, endometrium, or endocervix. Recently, it has been hypothesized that cytokeratin7-positive embryonic/stem cells would give rise to immunophenotypically distinct neoplastic progeny, which would support the old concept of “müllerian neometaplasia.” Besides the mesothelial origin, there is now compelling evidence that a number of what have been thought to be primary ovarian cancers actually originate in other pelvic organs and involve the ovary secondarily. In fact, it has been shown that some high-grade serous carcinomas arise from precursor epithelial lesions in the distal fimbriated end of the fallopian tube, whereas endometrioid and clear cell carcinomas originate from ovarian endometriosis.

7.3 | Borderline tumors

Borderline tumors show epithelial proliferation greater than that seen in their benign counterparts and variable nuclear atypia; however, in contrast to carcinomas, there is absence of stromal invasion, and their prognosis is much better than that of carcinomas.

Serous borderline tumors generally occur in women aged 20–50 years (average, 46 years). Serous tumors are more commonly bilateral (34%) than mucinous ones (6%) or other types. The tumors vary in size, although mucinous tumors may be gigantic. Serous borderline tumors have one or more cysts lined to varying extents by papillary projections, ranging from fine and exuberant to grapelike clusters. These structures show: (1) epithelial stratification; (2) moderate nuclear atypia; and (3) mitotic activity. By definition, the presence of more than focal microinvasion (i.e. discrete nests of epithelial cells <3 mm into the ovarian stroma) identifies a tumor as low-grade serous carcinoma (LGSC), rather than a borderline tumor.
Despite the lack of ovarian stromal invasion, serous borderline tumors—particularly those with exophytic growth—can implant on peritoneal surfaces (Fig. 12A) and, rarely, (about 10% of peritoneal implants), progress to LGSC and invade the underlying tissues (Fig. 12B). Histopathologically, invasive peritoneal implants and LGSC are identical lesions only distinguished by the timing of the disease and the volume of the tumor. Whereas invasive implants are early superficial lesions of microscopic or small macroscopic size (≤1–2 cm), LGSC frequently presents as bulky disease (peritoneal carcinomatosis).1,2,16

Surgical cure is almost always possible if the serous borderline tumor is confined to the ovaries. Even if it has spread to the pelvis or abdomen, 90% of patients are alive after 5 years. Although there is a significant rate of late recurrence, the tumors rarely recur beyond 10 years. Late progression to low-grade serous carcinoma has been reported in approximately 7% of cases.1,2,16 After fertility-sparing surgery, mucinous borderline tumors may "recur" as carcinomas in the contralateral ovary; however, such tumors should be considered independent primary tumors.18,19

7.4 | Malignant epithelial tumors (carcinomas)

Carcinomas of the ovary are most common in women aged 40–60 years, and are rare under the age of 35 years. Based on light microscopy and molecular genetics, ovarian carcinomas are classified into five main subtypes, which, in descending order of frequency, are: high-grade serous carcinomas (>70%), endometrioid carcinomas (10%), clear cell carcinomas (10%), mucinous carcinomas (3%–4%), and low-grade serous carcinomas (<5%).16 (Table 2). These subtypes, which account for 98% of ovarian carcinomas, can be reproducibly diagnosed and are inherently different diseases, as indicated by differences in epidemiologic and genetic risk factors, precursor lesions, patterns of spread, molecular events during oncogenesis, responses to chemotherapy, and outcomes. With progress toward subtype-specific management of ovarian cancer, accurate subtype assignment is becoming increasingly important.

7.4.1 | Serous carcinomas

7.4.1.1 | Molecular pathogenesis

Low-grade and high-grade serous carcinomas are fundamentally different tumors. Whereas low-grade tumors are frequently associated with serous borderline tumors and have mutations of KRAS or BRAF oncogenes, high-grade serous carcinomas lack ovarian precursor lesions and have a high frequency of mutations in TP53, but not in KRAS or BRAF. Interestingly, carcinomas arising in patients with germline BRCA1 or BRCA2 mutations (hereditary ovarian cancers) are almost invariably the high-grade serous type and commonly have TP53 mutations. An undetermined number of BRCA1- or BRCA2-related tumors arise from the epithelium of the fimbriated end of the fallopian tube, suggesting that at least some sporadic high-grade ovarian and "primary" peritoneal serous carcinomas may actually develop from the distal fallopian tube and "spill over" onto the adjacent tissues (Table 2).1,16

7.4.1.2 | Pathology

High-grade serous carcinomas are the most common ovarian cancers and most patients present with advanced stage disease (approximately 80%). Two-thirds of serous cancers with extraovarian spread are bilateral. They are predominantly solid masses, usually with necrosis and hemorrhage and typically show obvious stromal invasion. Most tumors have a high nuclear grade with highly cellular papillae and solid areas (Fig. 13A). The mitotic rate is very high. Psammoma
bodies are often present. Ovarian cancers formerly designated as transitional cell carcinomas represent histologic variants of high-grade serous carcinoma and carry TP53 mutations.

Low-grade serous carcinomas show irregular stromal invasion with small, tight nests of tumor cells within variable desmoplasia. The uniformity of the nuclei is the principal criterion for distinguishing low- and high-grade serous carcinomas (Fig. 13B). Low-grade serous carcinomas rarely progress to high-grade tumors.

### 7.4.2 | Mucinous carcinoma

#### 7.4.2.1 | Molecular pathogenesis

Mucinous ovarian tumors are often heterogeneous. Benign, borderline, noninvasive, and invasive carcinoma components may coexist within the same tumor. Such a morphologic continuum suggests that tumor progression occurs from cystadenoma and borderline tumor to noninvasive, microinvasive, and invasive carcinomas. This hypothesis is supported by KRAS mutations in mucinous tumors: 56% of cystadenomas and 85% of carcinomas express mutated KRAS, with borderline tumors being intermediate (Table 2).

#### 7.4.2.2 | Pathology

Mucinous carcinomas are usually large, unilateral, multilocular cystic masses containing mucinous fluid. They often exhibit papillary architecture (Fig. 13C). Since benign and malignant components may coexist within a single specimen, these tumors should be sampled extensively. Mucinous tumors are bilateral in only 5% of the cases; thus, finding bilateral or unilateral mucinous tumors smaller than 10 cm should raise suspicion of metastases from a mucinous carcinoma elsewhere (e.g., gastrointestinal tract).

The category of mucinous borderline tumor with intraepithelial carcinoma is reserved for tumors that lack architectural features of invasive carcinoma but, focally, show unequivocally malignant cells lining glandular spaces. Mucinous borderline tumors with intraepithelial carcinoma have a very low likelihood of recurrence.

Mucinous carcinomas showing expansile or confluent glandular growth appear to have a more favorable prognosis than mucinous carcinomas with destructive stromal invasion. The combination of extensive infiltrative stromal invasion, high nuclear grade, and tumor rupture should be considered a strong predictor of recurrence for Stage I mucinous carcinomas.

Pseudomyxoma peritonei is a clinical condition of abundant gelatinous or mucinous ascites in the peritoneum, fibrous adhesions, and frequently mucinous tumors involving the ovaries. The appendix is also involved by a similar mucinous tumor in 60% of the cases and appears normal in the remaining 40%. Current data suggest that in most cases the ovarian tumors are metastases from the appendiceal lesions.

### 7.4.3 | Endometrioid carcinoma

Endometrioid adenocarcinoma histologically resembles its uterine counterpart (Fig. 13D), may have areas of squamous differentiation, and is second only to serous adenocarcinoma in frequency. It accounts for 10% of all ovarian cancers. These tumors occur most commonly after menopause. Up to half of these cancers are bilateral and, at diagnosis, most tumors are either confined to the ovary or within the pelvis.

#### 7.4.3.1 | Molecular pathogenesis

Endometrioid carcinomas are thought to arise by malignant transformation of endometriosis, and not from ovarian surface epithelium. The most common genetic abnormalities in sporadic endometrioid carcinoma of the ovary are somatic mutations of the ARID1A, β-catenin (CTNNB1), and PTEN genes and microsatellite instability. Endometrioid borderline tumors also have CTNNB1 (β-catenin gene) mutations (Table 2).

#### 7.4.3.2 | Pathology

Although they may be cystic, most endometrioid carcinomas are largely solid with areas of necrosis. These tumors are graded like their uterine counterparts. Between 15% and 20% of patients also harbor a uterine endometrioid carcinoma. Strong data suggest that...
most of these cases arise independently, although some may be
metastases from one or the other. This distinction has important
prognostic implications.1,2

### 7.4.4 Clear cell carcinoma

This enigmatic ovarian cancer is closely related to endometrioid
adenocarcinoma, and often occurs in association with endometriosis.
It constitutes 5%–10% of all ovarian cancers usually occurring after
menopause. The most common genetic abnormalities are somatic
mutations of the ARID1A, PTEN, and PIK3CA genes.1,16

Although patients typically present with Stage I or II disease, clear
cell carcinomas have a poor prognosis compared with other
low-stage ovarian carcinomas. Clear cell carcinomas of the ovary resemble
their counterparts in the vagina, cervix, and corpus; they show
sheets or tubules of malignant cells with clear cytoplasm (Fig. 13E).

#### 7.4.4.1 Clinical features

By the time ovarian cancers are diagnosed, many have metastasized
to (i.e. implanted on) the surfaces of the pelvis, abdominal organs,
or bladder. Ovarian tumors have a tendency to implant in the peritoneal
cavity on the diaphragm, paracolic gutters, and omentum. Lymphatic
spread is preferentially to para-aortic lymph nodes near the origin of
the renal arteries and to a lesser extent to external iliac (pelvic) or
inguinal lymph nodes.1,2

Survival for patients with malignant ovarian tumors is generally
poor. The most important prognostic index is the surgical stage of the
tumor at the time it is detected.20 Overall, 5-year survival is only 35%.
Prognostic indices for epithelial tumors also include histologic type
(grade) and the size of the residual neoplasm.

Surgery is the mainstay of therapy. It removes the primary tumor,
establishes the diagnosis, and determines the extent of spread. The
peritoneal surfaces, omentum, liver, subdiaphragmatic recesses, and
all abdominal regions must be visualized, and as much metastatic
tumor removed as possible. Adjuvant chemotherapy is used to treat
distant occult sites of tumor spread.

### 7.5 Germ cell tumors

Tumors derived from germ cells make up one-fourth of ovarian
tumors. In adult women, ovarian germ cell tumors are virtually all
benign (mature cystic teratoma, dermoid cyst), but in children and
young adults, they are largely cancerous. In children, germ cell tumors
are the most common ovarian cancer (60%); they are extremely rare
after menopause. Rarely, germ cell tumors may arise from pre-existing
somatic neoplasms of the female genital tract. In these cases, the terato
toid tumors derive most likely from a pluripotent stem cell population
of somatic neoplasms.1,2

Neoplastic germ cells may differentiate along several lines producing:

1. Dysergerminomas are composed of neoplastic germ cells, similar
to oogonia of fetal ovaries. After dysergerminomas the differentiation
is typically extraembryonic or embryonic
2. Teratomas differentiate toward somatic (embryonic or adult) tissues.
3. Yolk sac tumors form extraembryonic endoderm and mesenchyme
and, less frequently, embryonic endodermal derivatives (intestine
and liver).
4. Choriocarcinomas feature cells similar to those covering the
placental villi.

Malignant germ cell tumors in women older than 40 years usually
result from transformation of one of the components of a benign
cystic teratoma. Malignant germ cell tumors tend to be highly
aggressive; however, with current chemotherapy, survival rates for
many exceed 80%.1,2

Recent stem cell research has provided several highly diagnostic
pluripotency markers, including transcription factors (SALL4,
LIN28, OCT3/4, and SOX2) and cytoplasmic/membranous proteins

#### TABLE 2 Main types of ovarian carcinoma.

|                         | High-grade serous | Low-grade serous | Mucinous     | Endometrioid | Clear cell |
|-------------------------|-------------------|------------------|--------------|--------------|------------|
| Usual stage at diagnosis| Advanced          | Early or advanced| Early        | Early        | Early      |
| Presumed tissue of origin/precursor lesion| Tubal metaplasia in inclusions of ovarian surface epithelium or fallopian tube | Serous borderline tumor | Adenoma-borderline-carcinoma sequence; teratoma | Endometriosis, adenofibroma | Endometriosis, adenofibroma |
| Genetic risk           | BRCA1/2           | ?                | ?            | HNPCC        | ?          |
| Significant molecular abnormalities| p53 and BRCA pathways | B-RAS or K-RAS | K-RAS HER2 | PTEN, β-catenin, ARID1A, PIK3CA | HNF-1β, ARID1A, PIK3CA, PTEN |
| Proliferation          | High              | Low              | Intermediate | Low          | Low        |
| Response to primary chemotherapy | 80%             | 26%–28%          | 15%          | ?            | 15%        |
| Prognosis              | Poor              | Favorable        | Favorable    | Favorable    | Intermediate |
(glypican-3) that are sequentially expressed in malignant germ cell tumors according to their differentiation stage.¹²

7.5.1 | Dysgerminoma

Dysgerminoma is the ovarian counterpart of testicular seminoma, and is composed of primordial germ cells. It accounts for less than 2% of ovarian cancers in all women. Most patients are between 10 and 30 years. The tumors are bilateral in about 15% of cases.

7.5.1.1 | Pathology

Dysgerminomas are often large and firm and have a bosselated external surface. The cut surface is soft and fleshy. They contain large nests of monotonously uniform tumor cells that have clear glycogen-filled cytoplasm and irregularly flattened central nuclei. Fibrous septa containing lymphocytes traverse the tumor.¹²

The tumor cells show diffuse nuclear expression for the stem cell/primitive germ cell nuclear transcription factors OCT3/4, NANOG, and SALL4. The majority of dysgerminomas show isochromosome 12p. c-Kit mutations are seen in 25%-50% of tumors, most commonly in exon 17, not in the exon 11 location that confers susceptibility to imatinib therapy.

Dysgerminomas are treated surgically; 5-year survival for patients with Stage I tumor approaches 100%. Because the tumor is highly responsive to chemotherapy, even for higher-stage tumors 5-year survival rates still exceed 90%.

7.5.2 | Teratoma

Teratoma is a tumor of germ cell origin that differentiates toward somatic structures. Most teratomas contain tissues from at least two, and usually all three, embryonic layers. Immature teratomas contain elements derived from the three germ layers. However, unlike mature cystic teratomas, immature teratomas contain embryonal tissues. These tumors account for 20% of malignant tumors in women under the age of 20. Microscopically, they show multiple components such as immature neural tissue (neuroepithelial rosettes and glia), glands, and other structures found in mature cystic teratomas. Grading is

![FIGURE 13](Representative examples of the five main types of ovarian carcinoma, which together account for 98% of cases: (A) High-grade serous carcinoma; (B) Low-grade serous carcinoma; (C) Mucinous carcinoma; (D) Endometrioid carcinoma; and (E) Clear cell carcinoma.)
based on the amount of immature tissue present. Survival correlates with tumor grade.1,2

7.5.3 | Yolk sac tumor

Yolk sac tumors are highly malignant neoplasms of women under the age of 30 that histologically resemble the endoderm and mesenchyme of the primitive yolk sac (extra-embryonal) and embryonal somatic tissues (intestine and liver). They are typically large, with extensive necrosis and hemorrhage. The most common histotype is the reticular form. Schiller-Duval bodies are characteristic. They consist of papillae that protrude into spaces lined by tumor cells, resembling the glomerular spaces. The papillae are covered by a mantle of embryonal cells and contain a fibrovascular core and a central blood vessel.

Yolk sac tumor secretes α-fetoprotein that should be stained for in all germ cell tumors. Detection of α-fetoprotein in the blood is useful for diagnosis and for monitoring the effectiveness of therapy. Once uniformly fatal, 5-year survival with chemotherapy for Stage I yolk sac tumors exceeds 80%.1,2

7.5.4 | Choriocarcinoma

Choriocarcinoma of the ovary is a rare tumor that mimics the epithelial covering of placental villi, namely, cytotrophoblast and syncytiotrophoblast. The pregnancy test is positive and the elevated serum level of human chorionic gonadotropin may lead to precocious sexual development in young girls or menstrual abnormalities in older patients. In women of reproductive age, however, it may also be a metastasis from an intrauterine gestational tumor. The tumor is unilateral, solid, and widely hemorrhagic. Although highly aggressive, it responds well to chemotherapy.1,2

7.6 | Sex cord/stromal tumors

These tumors represent 10% of ovarian tumors, vary from benign to low-grade malignant, and may differentiate toward female (granulosa and theca cells) or male (Sertoli and Leydig cells) structures.1,2

7.7 | Granulosa cell tumor

Granulosa cell tumors are the prototypical functional neoplasms of the ovary associated with estrogen secretion. They should be considered low-grade malignancies because of their potential for local spread and the rare occurrence of distant metastases.

Most granulosa cell tumors occur after menopause (adult form) and are unusual before puberty. A juvenile form occurs in children and young women and has distinct clinical and pathologic features (hyperestrinism and precocious puberty).

7.7.1 | Pathology

Adult-type granulosa cell tumors are large and focally cystic to solid. The cut surface shows yellow areas, due to lipid-rich luteinized granulosa cells, white zones of stroma, and focal hemorrhages. Random nuclear arrangement about a central degenerative space (Call-Exner bodies) gives a characteristic follicular pattern. Tumor cells secrete α-inhibin, a protein that suppresses pituitary release of follicle-stimulating hormone (FSH). Besides α-Inhibin, calretinin, and FOXL2 are the most important positive immunoreactions.1,2

The most common chromosomal abnormalities are trisomy 12, trisomy 14, monosomy 16, deletion of 16q, and monosomy 22. Missense somatic point mutations in the FOXL2 gene (402 C to G) are found in over 90% of adult granulosa cell tumors.

7.7.2 | Clinical features

Three-fourths of granulosa cell tumors secrete estrogens. Thus, endometrial hyperplasia is a common presenting sign. Endometrial adenocarcinoma may develop if a functioning granulosa cell tumor remains undetected. At diagnosis, 90% of granulosa cell tumors are within the ovary (Stage I). Over 90% of these patients survive 10 years. Tumors that have extended into the pelvis and lower abdomen have a poorer prognosis. Late recurrence after surgical removal is not uncommon after 5–10 years and is usually fatal.1,2

7.8 | Sertoli-Leydig cell tumors

Ovarian Sertoli-Leydig cell tumors are rare androgen-secreting mesenchymal neoplasms of low malignant potential that resemble embryonic testis. Tumor cells typically secrete weak androgens (dehydroepiandrosterone). Sertoli-Leydig cell tumors occur at all ages but are most common in young women of childbearing age. They vary from well to poorly differentiated and some have heterologous elements (e.g. mucinous glands and, rarely, even skeletal muscle and cartilage).

Mutations in DICER1, a gene encoding an RNase III endoribonuclease, are found in 60% of Sertoli-Leydig cell tumors. Germline mutations in this gene are seen in familiar multinodular goiter with Sertoli-Leydig tumor, and tumor susceptibility includes pleuropulmonary blastoma in childhood. Sertoli-Leydig cell tumor has been reported in association with cervical embryonal rhabdomyosarcoma in four patients.21

Nearly half of all patients with Sertoli-Leydig cell tumors exhibit signs of virilization. Initial signs are often defeminization, manifested as breast atrophy, amenorrhea, and loss of hip fat. Once the tumor is removed, these signs disappear or at least lessen. Well-differentiated tumors are virtually always cured by surgical resection, but poorly differentiated ones may metastasize.1,2

7.9 | Steroid cell tumor

Steroid cell tumors of the ovary, also called lipid cell tumors, are composed of cells that resemble lutein cells, Leydig cells, and adrenal cortical cells. Most steroid cell tumors are hormonally active, usually with androgenic manifestations.
7.10 | Tumors metastatic to the ovary

About 3% of cancers found in the ovaries arise elsewhere, mostly in the large intestine, breast, endometrium, and stomach, in descending order. These tumors vary from microscopic lesions to large masses. Metastatic tumors large enough to cause symptoms originate most often in the colon and may be estrogen secreting as they activate the ovarian stroma.

Krukenberg tumors are metastases to the ovary, composed of nests of mucin-filled “signet-ring” cells in a cellular stroma derived from the ovary. The stomach is the primary site in 75% of cases and most of the rest are from the colon.1,2

Bilateral ovarian involvement and multinodularity suggest a metastatic carcinoma, and both ovaries are grossly involved in 75% of cases.

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JP and DM reviewed and updated the pathology chapter published in the 2015 Cancer Report.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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