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FIGO CANCER REPORT 2012

# Pathology of cancers of the female genital tract

Jaime Prat

*Department of Pathology, Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Spain*

## 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 gynecological cancers to assure that their reports communicate clinically relevant information. On the other hand, full comprehension of the pathology report by the gynecological oncologist requires familiarity with the terminology used in gynecological pathology as well as the techniques of gross examination. This chapter summarizes the pathological features of the most common gynecological malignancies as well as an approach for processing gynecological biopsies and surgical specimens. Both the gross examination and the histopathology are guided by the clinical principles necessary for patient management.

## 2. Vulva

### *2.1. Malignant tumors and premalignant conditions*

#### *2.1.1. Squamous cell carcinoma*

Carcinoma of the vulva accounts for 3% 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 2 groups: keratinizing squamous cell carcinomas unrelated to HPV (>70% of cases), and warty and basaloid carcinomas associated with high-risk HPV (<25% of cases) [1,2].

**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 (VIN) or VIN simplex (Fig. 1A), which carries a high risk of cancer development. In contrast, the less common HPV-associated warty and basaloid carcinomas develop from a precursor lesion called undifferentiated or classic VIN (Fig. 1B). HPV-associated VIN lesions have a low risk of progression to invasive carcinomas (approximately 6%), except in older or immunosuppressed women [1,2].

**Pathology:** VIN may be single or multiple, and macular, papular, or plaque-like. Histologic grades are labeled VIN I, II, and III, corresponding to mild, moderate, and severe dysplasia, respectively. However, grade III – which includes squamous cell carcinoma in situ [CIS] – is by far the most common.

Keratinizing squamous cell carcinomas usually follow differentiated VIN (VIN simplex). 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 grow slowly, extending to contiguous skin, vagina, and rectum. They metastasize initially to superficial inguinal lymph nodes, and then to deep inguinal, femoral, and pelvic lymph nodes [1,2].

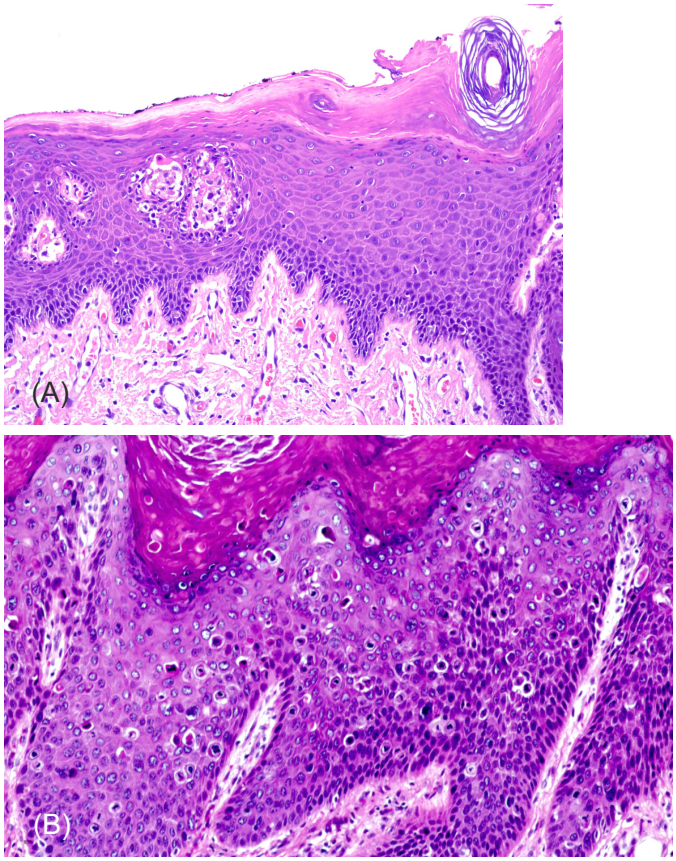


**Fig. 1.** Vulvar intraepithelial neoplasia (VIN). (A) Well-differentiated (simplex) type. The atypia is accentuated in the basal and parabasal layers. There is striking epithelial maturation in the superficial layers. (B) HPV-related undifferentiated (classic) VIN. Beneath a hyperkeratotic surface the epithelial cells are atypical. There are numerous mitoses.

**Clinical features:** The 2009 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 perineal structures (lower third) as Stage II, tumors with positive inguinofemoral lymph nodes as Stage III, and tumors invading perineal structures (upper third) or distant metastasis as Stage IV. Tumor grade and number, size, and location of lymph node metastases determine survival. Better-differentiated tumors have a better mean survival, approaching 90% if nodes

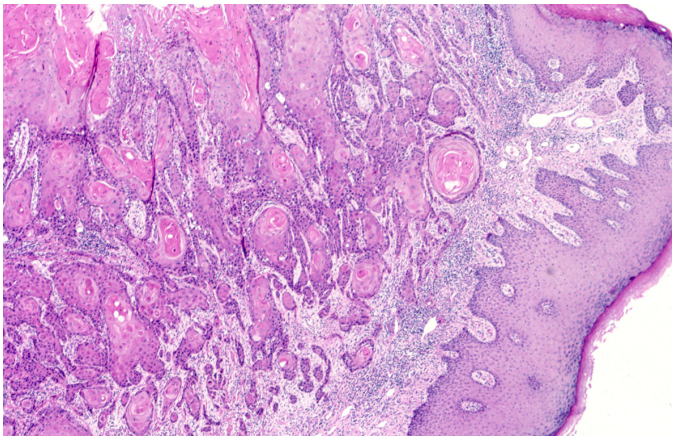

**Fig. 2.** Keratinizing squamous cell carcinoma of vulva. Nests of neoplastic squamous cells, some with keratin pearls, are evident.

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 [3].

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 generally good, with an overall 5-year survival of 70% [1].

#### *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.

#### *2.1.5. Extramammary Paget disease*

The disorder usually occurs on the labia majora in older women. The lesion is large, red, moist, and 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 only rarely associated with carcinoma of the skin adnexa. Metastases rarely occur, so treatment requires only wide local excision or simple vulvectomy [1,2].

### *2.2. Gross description and processing of specimens*

#### *2.2.1. Excisional biopsies*

Biopsies of the vulva should be handled like skin biopsies. Assess the deep and lateral resection margins.

#### *2.2.2. Wide local excision*

In general, wide local excisions are performed for noninvasive neoplasms such as VIN 3 or Paget disease of the vulva, as well as superficially invasive (less than 1 mm) Stage I carcinomas. Orientation is critical in these specimens. Describe and measure the lesions, distances to resection margins, and the anatomic structures involved. As intraepithelial lesions are often multifocal and difficult to discern macroscopically, all surgical resection margins (peripheral and deep) should be evaluated microscopically [1].

#### *2.2.3. Simple (or total) vulvectomy*

This includes the entire vulva and subcutaneous fat (dissection to deep fascia). It is typically performed for noninvasive neoplasms that widely involve the vulva. The resection margins must be thoroughly evaluated [1].

#### *2.2.4. Radical vulvectomy*

Radical vulvectomy consists of vulva excised to the deep fascia of the thigh, the periosteum of the pubis, and the inferior fascia of the urogenital diaphragm. It is usually performed together with at least an inguinal lymph node dissection, which may be included en bloc with the vulvectomy. Total radical vulvectomies have largely been replaced in favor of more limited excisions, but sufficient to completely excise the primary tumor with a minimum 1 cm margin. The gross description should include the size, location, depth of invasion, and all resection margins, including perianal and vaginal margins. Depth of invasion should be measured from the epithelial–stromal junction of the adjacent dermal papilla to the deepest point of tumor invasion. Separate lymph nodes into superficial and deep groups, and submit them entirely for histologic examination [1].

## 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. 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 old. 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 decreased cervical carcinoma by 50% to 85%; however, worldwide cervical cancer remains the second most common cancer in women.

### *4.2. Cervical intraepithelial neoplasia*

Cervical intraepithelial neoplasia (CIN) is a spectrum of intraepithelial changes that begins with minimal atypia and progresses

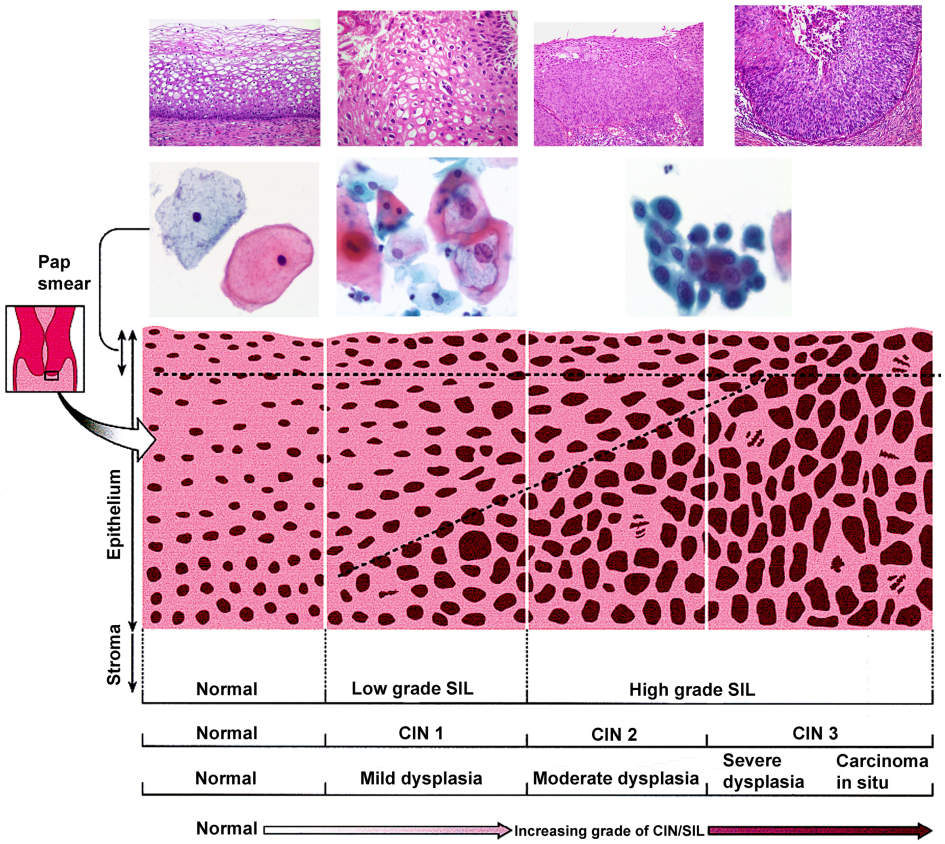


**Fig. 3.** Interrelations of naming systems in precursor cervical lesions. This chart integrates multiple aspects of the disease. It illustrates the changes in progressively more abnormal disease states and provides translation terminology for the dysplasia/carcinoma in situ (CIS) system, cervical intraepithelial neoplasia (CIN) system, and the Bethesda System. The scheme also illustrates the corresponding cytologic smear resulting from exfoliation of the most superficial cells as well as the equivalent histopathologic lesions (top). SIL, squamous intraepithelial lesion.

through stages of greater intraepithelial abnormalities to invasive squamous cell carcinoma. The terms CIN, dysplasia, CIS, and squamous intraepithelial lesion (SIL) are commonly used interchangeably [1,2] (Fig. 3).

**Epidemiology and molecular pathogenesis:** HPV infection leads to CIN and cervical cancer (Fig. 4). Low-grade CIN 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 CIN, 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. HPV types 16 and 18 are found in 70% of invasive cancers; the other high-risk types account for another 25% [4].

**Pathology:** 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. CIN 3 is synonymous with severe dysplasia and CIS. The sequence of histologic changes from CIN 1 to CIN 3 is shown in Fig. 3 [1,2].

**Clinical features:** The mean age at which women develop CIN is 24–27 years for CIN 1 and CIN 2, and 35–42 years for CIN 3. Based on morphologic criteria, half of cases of CIN 1 regress, 10% progress to CIN 3, and less than 2% become invasive cancer. The average time for all grades of dysplasia to progress to CIS is about 10 years. At

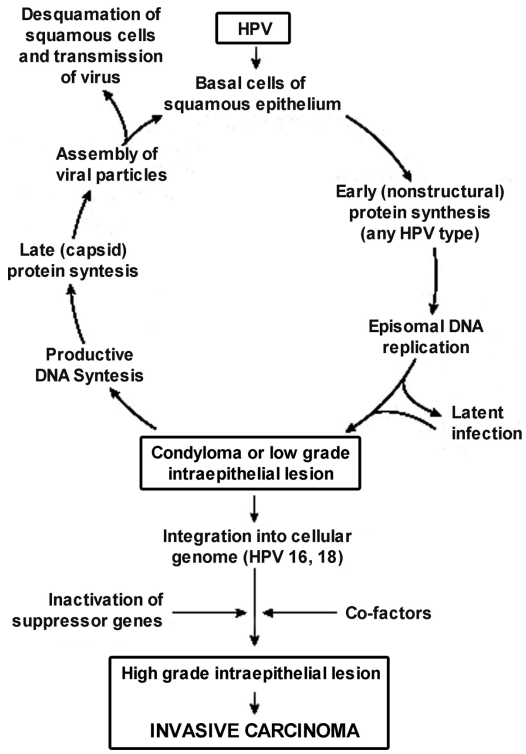


**Fig. 4.** Role of HPV in the pathogenesis of cervical neoplasia.

least 20% of cases of CIN 3 progress to invasive carcinoma in that time [1].

When CIN is discovered, colposcopy, together with a Schiller test, delineates the extent of the lesion and indicates areas to be biopsied. Diagnostic endocervical curettage also helps to determine the extent of endocervical involvement. Women with CIN 1 are often followed conservatively (i.e. repeated Pap smears plus close follow-up). High-grade lesions are treated according to the extent of disease. LEEP (loop electrosurgical excision procedure), cervical conization (removal of a cone of tissue around the external os), cryosurgery, and (rarely) hysterectomy may be done [1].

### 4.3. Microinvasive squamous cell carcinoma

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

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

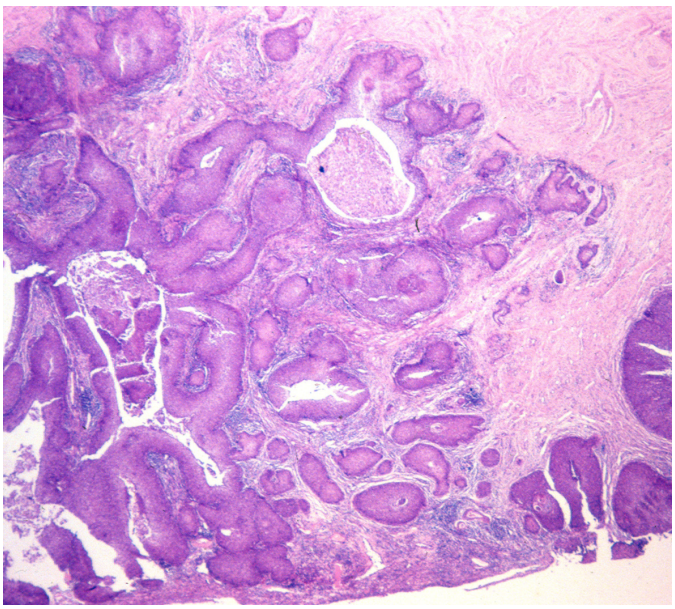

**Fig. 5.** Microinvasive squamous cell carcinoma. The tumor invades 5 mm deep and 4 mm wide. This tumor is stage IA2 according to FIGO's classification.

The earliest invasive changes ("early stromal invasion" or ESI) appear as tiny irregular epithelial buds emanating from the base of CIN 3 lesions. These small (<1 mm) tongues of neoplastic epithelial cells do not affect the prognosis of CIN 3 lesions; hence, both can be treated similarly with conservative surgery. In the 2009 FIGO classification, ESI was excluded from Stage IA1. Some gynecologic oncologists further limit microinvasive carcinoma to tumors lacking vascular invasion. Lymph node metastases are found in only 3%–5% of Stage IA2 microinvasive tumors. Conization or simple hysterectomy generally cures microinvasive cancers less than 3 mm deep [1–3].

### 4.4. Invasive squamous cell carcinoma

**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 stroma and cause diffuse enlargement of the cervix. 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 by direct extension, through lymphatic vessels and only rarely by the hematogenous route. Local extension into surrounding tissues (parametrium) results in ureteral compression (Stage IIIB); the corresponding clinical complications are hydroureter, hydronephrosis, and renal failure secondary to ureteric obstruction – the most common cause of death (50% of patients). Bladder and rectal involvement (Stage IVA) may lead to fistula formation. Metastases to regional lymph nodes involve paracervical, hypogastric, and external iliac nodes. Overall, tumor growth and spread are relatively slow, since the average age for patients with Stage 0 tumor (CIN 3) is 35–40 years; for stage IA, 43 years; and for stage IV, 57 years [1–3].

**Clinical features:** The Pap smear remains the most reliable screening test for detecting cervical cancer.

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 wall, 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 [1–3].

### 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 are of the endocervical cell (mucinous) type. These tumors are often associated with adenocarcinoma in situ and are frequently infected with HPV types 16 and 18 [1,2].

Adenocarcinoma in situ (AIS) generally arises by the squamo-columnar junction and extends into the endocervical canal. Associated high-grade squamous cell CIN occurs in 40% of cases of AIS. Invasive adenocarcinoma typically presents as a polypoid or papillary mass. Adenocarcinoma of the endocervix spreads by local invasion and lymphatic metastases, but overall survival is somewhat worse than for squamous carcinoma.

### 4.6. Gross description and processing of specimens

#### 4.6.1. Punch biopsies

Biopsies are usually colposcopically directed. The best specimens are at least several millimeters long with underlying stroma to a depth of 2–4 mm.

#### 4.6.2. Endocervical curettage

Endocervical curettage is performed to evaluate the presence of glandular neoplasms, cervical squamous neoplasia involving the endocervical canal, or to determine whether endometrial carcinoma has spread into the cervix.

#### 4.6.3. 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 often done with laser or low-voltage, large-loop diathermy methods (LEEP). Trachelectomy may also be performed as a therapeutic procedure for early-stage invasive carcinomas of the cervix. A trachelectomy is a more extensive version of a cone excision, as the entire cervix is removed, with or without a vaginal cuff.

The cone biopsy is a roughly cone-shaped excision of the uterine cervix to include a portion of exocervix, external os with the entire transformation zone, and endocervical canal with varying amounts

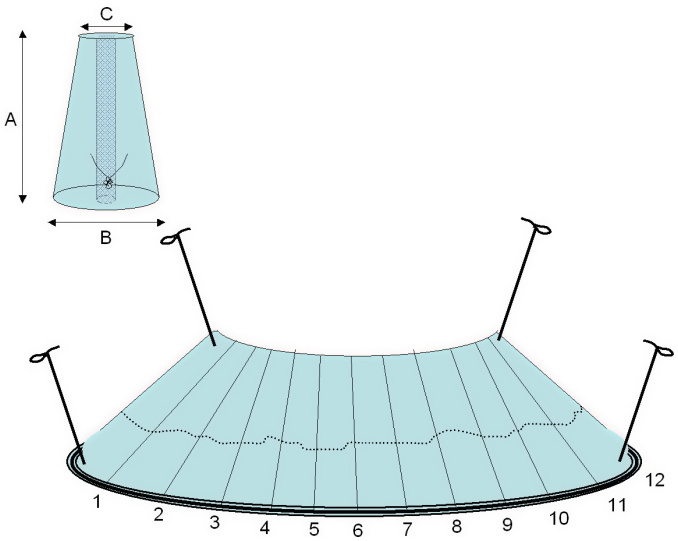


**Fig. 6.** Cervical cone biopsy/excision. The craniocaudal length (A) and diameter (B) should be measured; and both the radial (A) and endocervical (C) margins need to be assessed (with differential inking). Use a stitch to designate 12 o'clock, open cone and pin out to fix, and then block in the entire specimen sequentially. Figure reproduced with permission courtesy of BE Howitt and GL Mutter, Boston, MA, USA.

of deep tissue. The surgeon should note the 12 o'clock position with a black suture or circumference and thickness if received opened. For a trachelectomy specimen, the presence of vaginal cuff should be documented and measured.

Fixation for 3 hours before cutting is usually adequate. Serially cut sections should be sequentially submitted. Submit the entire specimen in a clockwise direction beginning at 1 o'clock (Fig. 6). Both the ectocervical and endocervical edges of the cone specimen need to be assessed [1].

#### *4.6.4. Hysterectomy for malignant cervical disease*

Simple hysterectomy is performed for high-grade intraepithelial neoplasms and many microinvasive cancers. Radical hysterectomy (removal of paracervical soft tissue) is common for Stage I squamous carcinomas and for some Stage 2A tumors.

For uteri removed for the treatment of CIN, amputate the cervix at least 1.0 cm above the level of the external os and process in the way that has been described above for a cone biopsy. Often, one section from each quadrant may be sufficient. Each section should be full thickness to include the endocervical mucosa, squamocolumnar junction, exocervix, and outer adventitia. Submit all of the parametrial tissue since this represents the lateral and most significant resection margin. Separate and group lymph nodes as right and left, further by location (internal iliac, external iliac, obturator, etc.) [1].

## 5. Corpus uteri

### *5.1. Endometrial hyperplasia*

Endometrial hyperplasia forms a morphologic continuum of abnormal proliferation ranging from focal glandular crowding or simple hyperplasia to well-differentiated adenocarcinoma.

**Pathology:** There are two classifications of endometrial hyperplasia: (1) the 2003 World Health Organization (WHO) scheme; and (2) the benign hyperplasia–endometrial intraepithelial neoplasia (EIN) schema. The former emphasized abnormal glandular architecture and focused on cytologic atypia as the most important prognostic feature:

- Simple hyperplasia: This proliferative lesion shows minimal glandular complexity and crowding and no cytologic atypia. The epithelium is usually one cell layer thick and the stroma between the glands is abundant. Of these, 1% progress to adenocarcinoma.
- Complex hyperplasia: This variant exhibits marked glandular complexity and crowding but no cytologic atypia. The stroma between the glands is scanty. Adenocarcinoma develops in 3%.
- Complex atypical hyperplasia (CAH): This lesion shows marked glandular crowding, often as back-to-back glands, and cytologic atypia. Epithelial cell nuclei are large and hyperchromatic with prominent nucleoli. Of these, 25% progress to adenocarcinoma, which is almost always of the endometrioid type [1,2].

EIN refers to a monoclonal neoplastic growth of genetically altered cells with greatly increased risk of becoming the endometrioid type of endometrial adenocarcinoma. The main diagnostic criterion of EIN is that gland area exceeds that of stroma (volume percentage stroma <55%). Women diagnosed with EIN have a 39% chance of having endometrial cancer diagnosed within 1 year. Thus, in most cases the cancer is already present at the time of the initial biopsy [1,2].

**Clinical features:** Hysterectomy is usually the therapy of choice if a woman does not want more children. Women who want more children or those with high operative risks may be treated with progestins.

### *5.2. Endometrial adenocarcinoma*

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" carcinoma). Type II tumors are not associated with estrogen stimulation or hyperplasia, readily invade myometrium and vascular spaces, and are highly lethal [1].

Endometrial cancer is the most common extracolonic cancer in women with hereditary nonpolyposis colon cancer syndrome, a defect in DNA mismatch repair that is also associated with breast and ovarian cancers [5].

**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 [5].

Five 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 β-catenin (*CTNNB1*) 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 [5].

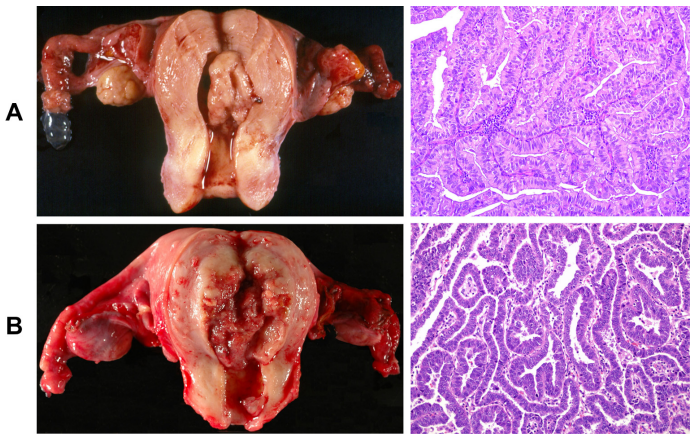


**Fig. 7.** Adenocarcinoma of the endometrium. (A) Endometrioid carcinoma. Polypoid tumor with only superficial myometrial invasion (left). Well-differentiated (grade 1) adenocarcinoma. The neoplastic glands resemble normal endometrial glands (right). (B) Nonendometrioid carcinoma. Large hemorrhagic and necrotic tumor with deep myometrial invasion (left). Nonendometrioid (serous) carcinoma exhibiting stratification of anaplastic tumor cells and abnormal mitoses (severe cytologic atypia) (right).

**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, β-catenin | p53 mutations, loss of heterozygosity |

**Pathology:**

- *Endometrioid adenocarcinoma 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 3 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 [1–3].
- *Nonendometrioid endometrial carcinomas*: They are aggressive as a group, and histologic grading is not clinically useful, all cases being considered high grade.
  - Serous adenocarcinoma histologically resembles, and behaves like, serous adenocarcinoma of the ovary (Fig. 8B, below). It often shows transtubal spread to peritoneal surfaces. An in situ 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.
  - Clear cell adenocarcinoma 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.
  - 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% [1,2].

**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. Postoperative radiation is considered if: (1) the tumor is poorly differentiated or nonendometrioid in type; (2) myometrium is deeply invaded; (3) the cervix is involved; or (4) lymph nodes contain metastases.

Survival in endometrial carcinoma is related to multiple factors: (1) stage, histotype and, for endometrioid tumors, grade; (2) age; and (3) other risk factors, such as progesterone receptor activity, depth of myometrial invasion, 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. Tumors that have penetrated the myometrium or invaded lymphatics are more likely to have spread beyond the uterus. Endometrial cancers involving the cervix have a poorer prognosis. Spread outside the uterus entails the worst outlook [6].

### 5.3. Low-grade endometrial stromal sarcomas

These tumors 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. Higher-grade sarcomas originating in the endometrium are designated as undifferentiated endometrial sarcoma [1,2].

**Clinical features:** Many years may elapse before low-grade endometrial stromal sarcomas 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

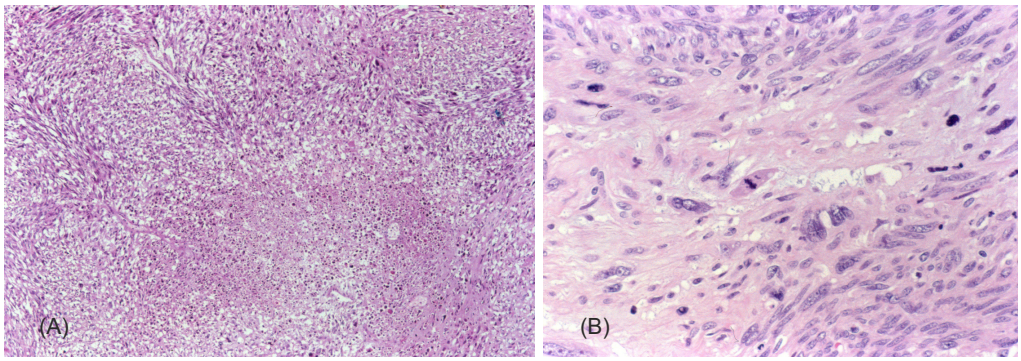


**Fig. 8.** Leiomyosarcoma of the uterus. (A) A zone of coagulative tumor necrosis appears demarcated from the viable tumor. (B) The tumor shows considerable nuclear atypia and abundant mitotic activity.

by lung metastases. Prolonged survival and even cure are feasible, despite metastases. By contrast, undifferentiated endometrial sarcomas recur early, generally with widespread metastases. Low-grade endometrial stromal sarcomas can be successfully treated with surgery and progestin therapy, with an expectation of 90% survival 10 years after diagnosis [1,2].

### *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, in which both epithelial and stromal elements are malignant and which is highly aggressive. One-fourth of patients with adenosarcoma 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].

**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), cellular atypia, and geographical necrosis are the best diagnostic criteria (Figs. 8A,B).

Myxoid and epithelioid leiomyosarcomas may contain only 5 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].

### *5.6. Gross description and processing of specimens*

#### *5.6.1. Endometrial biopsy*

Tissue from an endometrial biopsy (curettage or outpatient sampler) should be embedded in its entirety. A single hematoxylin and eosin section is often sufficient for diagnostic purposes.

#### *5.6.2. Malignant uterine disease*

Evaluate all specimens with a preoperative diagnosis of malignancy for residual tumor. If present, determine the maximum depth of myometrial invasion and cervical involvement (mucosal or stromal).

The gross description must include the size, location, distribution (focal or diffuse), and depth of myometrial invasion (Fig. 9). Sample

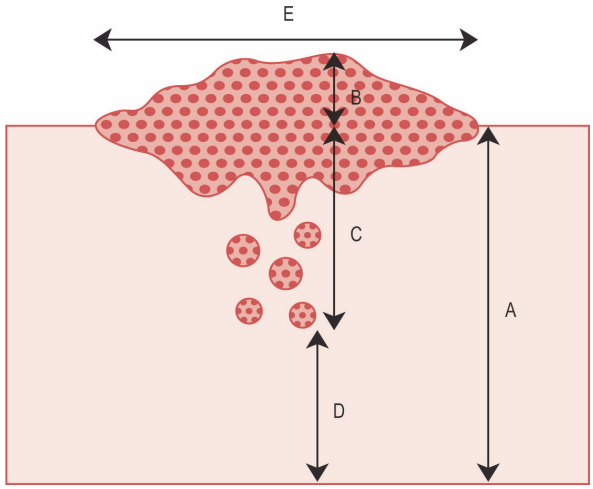


**Fig. 9.** Endometrial carcinoma. Measurements of depth to which tumor invades. (A) Full thickness of myometrial wall, measured from where endometrium adjacent to tumor is normal (or hyperplasic). (B) Component of tumor exophytic and rising above imaginary line drawn between adjacent normal endometrium. (C) Depth of invasion. (D) Tumor-free zone. (E) Width of tumor. A tumor is generally reported as measuring $n \times n \times n$ and 'C' cm invasive into a wall 'A' cm thick. Reproduced with permission from Robboy et al. [1].

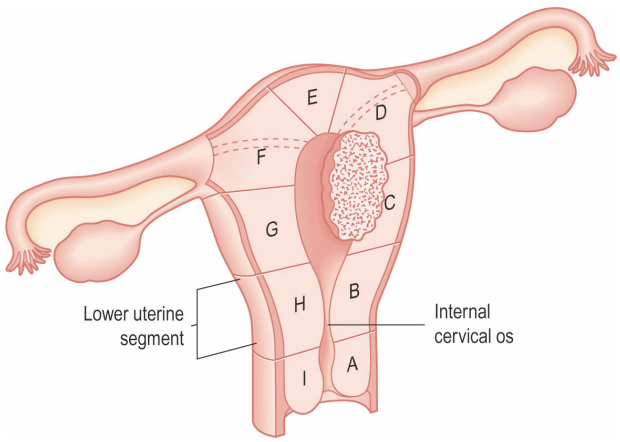


**Fig. 10.** Technique for sectioning the uterus. Sampling includes cervix (e.g. A, I); margins adjacent and deep to a tumor (e.g. C, D); lower uterine segment and uppermost endocervix (e.g. B, H) – for example, to determine whether an endometrial cancer involves the cervix, thus upstaging it; the wall for adenomyosis (e.g. D, F); and endometrium with areas partially or totally seemingly free of tumor (e.g. C, G). Reproduced with permission from Robboy et al. [1].

the uninvolved endometrium, including the lowermost margin of the neoplasm (Fig. 10). At least one microscopic section should permit measurement of the greatest depth of tumor invasion.

Lymphadenectomy may be included in the staging of endometrial carcinoma. Careful dissection of lymphadenectomy specimens, with submission of all possible lymph nodes is necessary [1].

## 6. Fallopian tube

Tumors of the fallopian tube are rare. Most primary malignancies are adenocarcinomas, 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].

### *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 (Fig. 11) [1,2].

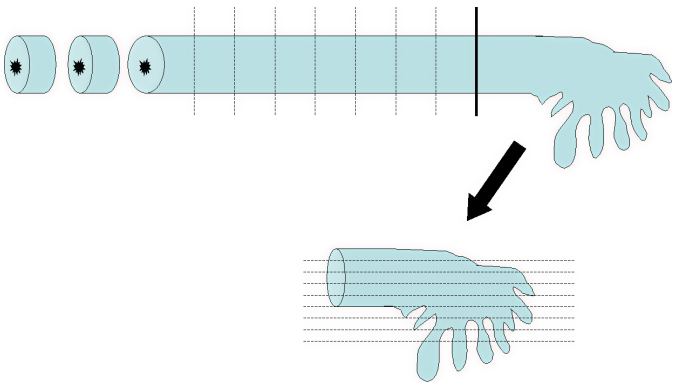

**Fig. 11.** Sectioning and extensively examining the fimbriated end (SEE-FIM protocol) for cutting in a fallopian tube specimen. Cross-sections cut at approximately 3 mm intervals of the length of the tube, and the fimbriated end amputated and cut in the longitudinal axis at 1–2 mm intervals. Figure reproduced with permission courtesy of BE Howitt and GL Mutter, Boston, MA, USA.

## 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 [1,2,7].

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.

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. As it is difficult to detect early in its evolution when it is still curable, over three-fourths of patients already have extraovarian tumor spread to the pelvis or abdomen at the time of diagnosis [1,2,7].

### *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) of borderline malignancy (also called of low malignant potential); and (3) malignant.

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 for 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 for breast cancer and vice versa. Defects in repair genes implicated in hereditary breast cancers, *BRCA1* and *BRCA2*, are incriminated in familial ovarian cancers as well. As for endometrial carcinoma, women with hereditary nonpolyposis colon cancer (HNPCC) are also at greater risk for ovarian cancer [1,2,7].

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 celomic 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. 12). Thus, the tumor cells would resemble morphologically the epithelia of the fallopian tube, endometrium, or endocervix. Although the mesothelial origin cannot be excluded, 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 proposed that high-grade serous carcinoma 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].

### *7.3. Borderline tumors (tumors of low malignant potential)*

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 [1,2].

Despite the lack of ovarian stromal invasion, serous borderline tumors, particularly those with exophytic growth, can implant on peritoneal surfaces (Fig. 13A) and, rarely (about 10% of peritoneal implants), progress to LGSC and invade the underlying tissues (Fig. 13B). 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) [1,2,7].

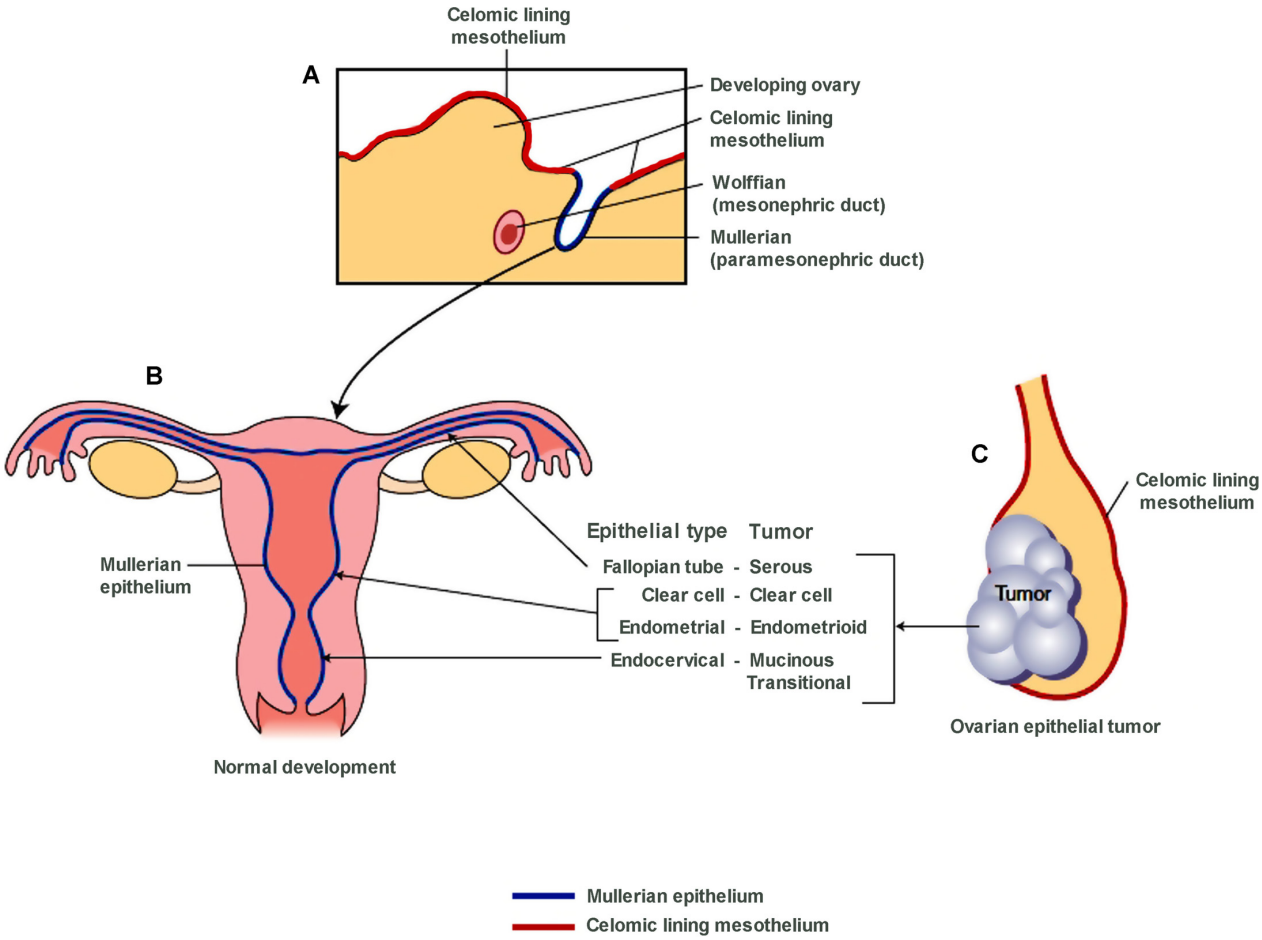


**Fig. 12.** Histogenesis of ovarian epithelial tumors.

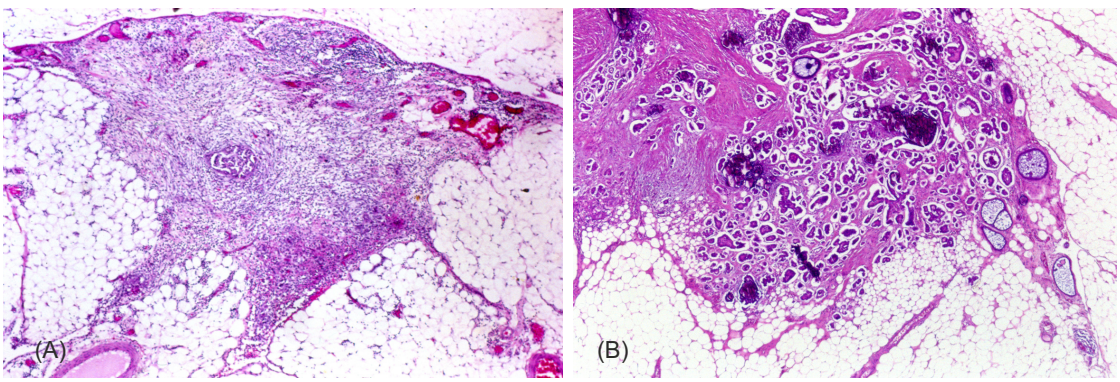


**Fig. 13.** Peritoneal implants of serous borderline tumor. (A) Noninvasive desmoplastic implant. The implant invaginates between adjacent lobules of omental fat. A few nests of tumor cells are present within a loose fibroblastic stroma. (B) Invasive omental implant. The tumor glands and papillae appear disorderly distributed within a dense fibrous stroma and resemble a low-grade serous carcinoma.

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 [1,2,7].

### *7.4. Malignant epithelial tumors (carcinomas)*

Carcinomas of the ovary are most common in women aged 40–60 years old, and are rare under the age of 35 years. Based on light microscopy and molecular genetics, ovarian carcinomas are classified into 5 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%) [7] (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.

**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 pRb pathways | BRAF or K-ras | K-ras | PTEN, β-catenin, *ARID1A* *PIK3CA* K-ras MI | HNF-1β *ARID1A* *PIC3CA* |
| Proliferation | High | Low | Intermediate | Low | Low |
| Response to primary chemotherapy | 80% | 26%–28% | 15% | ? | 15% |
| Prognosis | Poor | Favorable | Favorable | Favorable | Intermediate |

*7.4.1. Serous adenocarcinomas*

**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 p53, 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 p53 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) [7].

**Pathology:** High-grade serous carcinomas (commonly called "cystadenocarcinomas") 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. 14A). The mitotic rate is very high. Psammoma bodies are often present [7].

Low-grade serous carcinomas show irregular stromal invasion by 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. 14B). Low-grade serous carcinomas rarely progress to high-grade tumors [7].

*7.4.2. Mucinous adenocarcinoma*

**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) [1,2,7].

**Pathology:** Mucinous carcinomas are usually large, unilateral, multilocular cystic masses containing mucinous fluid. They often exhibit papillary architecture (Fig. 14C). 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 [1,2].

Mucinous adenocarcinomas 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 adenocarcinomas [1,2].

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 [1,2].

*7.4.3. Endometrioid adenocarcinoma*

Endometrioid adenocarcinoma histologically resembles its uterine counterpart (Fig. 14D), 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 [1,2].

**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 β-catenin gene mutations (Table 2) [7].

**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].

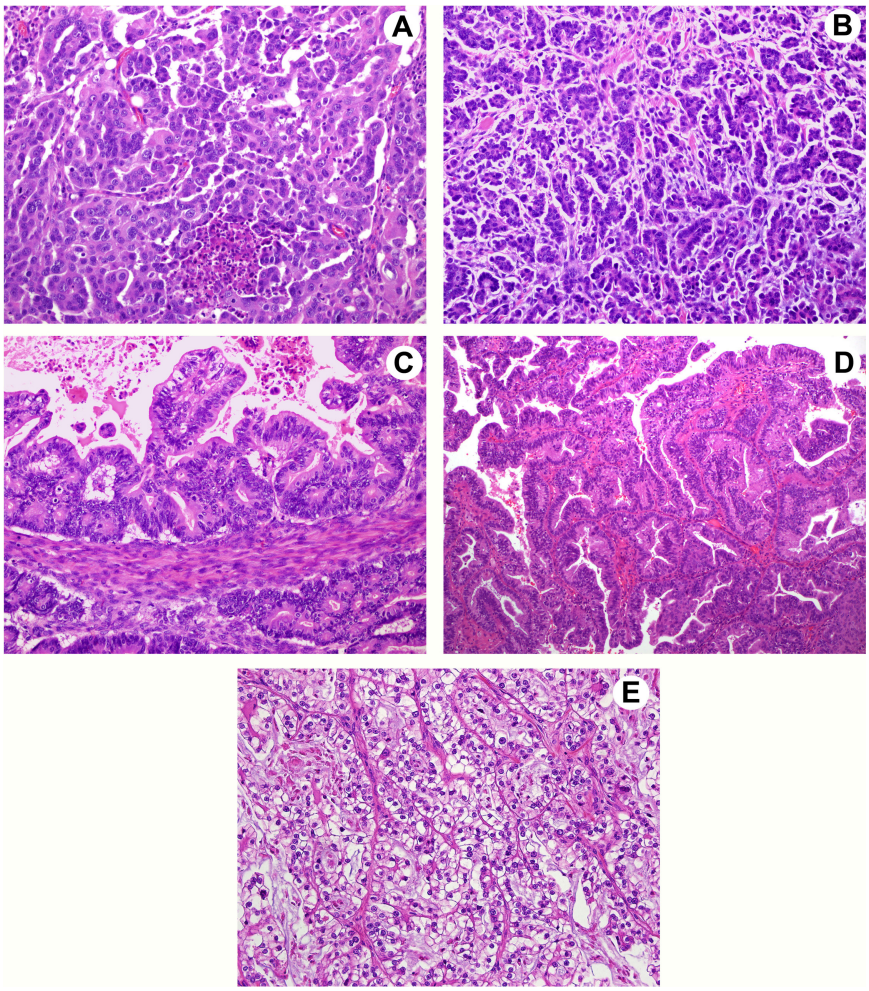


**Fig. 14.** Representative examples of the 5 main types of ovarian carcinoma, which together account for 98% of cases: (A) High-grade serous carcinoma; (B) Low-grade serous carcinoma; (C) Mucinous carcinoma; (D) Endometrioid carcinoma; (E) Clear cell carcinoma.

*7.4.4. Clear cell adenocarcinoma*

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* and *PIK3CA* genes [1,2,7].

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. 14E).

**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. 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, which removes the primary tumor, establishes the diagnosis, and determines the extent of spread, is the mainstay of therapy. 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 [1,2].

*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 rare after menopause [1,2].

Neoplastic germ cells may differentiate along several lines producing:

- Dysgerminomas are composed of neoplastic germ cells, similar to oogonia of fetal ovaries.
- Teratomas differentiate toward somatic (embryonic or adult) tissues.
- Yolk sac tumors form extraembryonic tissue, like placental mesenchyme or its precursors.
- 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].

#### 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.

**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 [1,2].

Dysgerminomas are treated surgically; 5-year survival for patients with Stage I tumor approaches 100%. Because the tumor is highly radiosensitive and also responsive to chemotherapy, even for higher-stage tumors 5-year survival rates still exceed 80%.

#### 7.5.2. Teratoma

Teratoma is a tumor of germ cell origin that differentiates toward somatic structures. Most teratomas contain tissues from at least 2, and usually all 3, embryonic layers. Immature teratomas contain elements derived from the 3 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 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 tumors of women under the age of 30 that histologically resemble the mesenchyme of the primitive yolk sac. 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. 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. Young girls may show precocious sexual development, menstrual irregularities, or rapid breast enlargement. 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 to chemotherapy [1,2].

### 7.6. Sex cord/stromal tumors

They 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).

**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 inhibin, a protein that suppresses pituitary release of follicle-stimulating hormone (FSH) [1,2].

**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).

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.

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.

### 7.11. Gross description and processing of specimens

#### 7.11.1. Large cystic or neoplastic ovaries

Document whether the ovarian tumor is received intact or ruptured and learn whether the rupture occurred intraoperatively. Many ovarian tumors are cystic and all locules should be opened. Include the capsule and tumor, and include tumor with adjacent normal parenchyma. Generally, about one block per 2 cm of greatest tumor dimension will suffice. Look for the fallopian tube, which may be incorporated in or stretched over the tumor mass/cyst. It may contain coexistent neoplasia. Germ cell tumors should be sampled extensively [1].

#### 7.11.2. Staging operations

Close cooperation between surgeon and pathologist is needed. General guidelines for the surgeon include:

1. Evaluate the ovarian mass to exclude metastasis from colon, stomach, or elsewhere. Note penetration through capsule and biopsy areas of adherence.
2. Obtain ascitic fluid or saline washings for cytology.
3. Inspect all peritoneal surfaces. Prove that apparent implants are malignant by frozen section, or submit multiple samples for permanent section, or both. Inspect the diaphragm, with biopsy of visible lesions or scrapings for cytology.
4. Confirm accuracy of apparent Stage I or II disease by generous omental biopsy and biopsy of palpable pelvic and para-aortic nodes.
5. After excision, mark the specimen indicating for the pathologist the site of rupture and/or area(s) of adherence. Record residual disease location and estimate extent.

Specimens submitted for pathologic examination are likely to include:

- Uterus with attached or separately submitted adnexa, preferably delivered fresh to the pathologist immediately. Before fixation, open the uterine cavity, keeping in mind the possibility of a coexisting endometrial carcinoma or hyperplasia. Scrutinize the uterine serosal surface for tumor deposits and section any adhesions to exclude microscopic metastases (since these will raise the FIGO stage from at least Stage I to at least Stage IIA).
- Omentum. Slice finely, looking for tumor deposits and block these. If none is found, sample any unusually firm areas. One to two blocks should be sufficient. In over 20% of cases, the grossly normal omentum will disclose microscopic foci of tumor.
- Pelvic and/or para-aortic lymph nodes. Block all lymphoid tissue.
- Peritoneal biopsies. These are often very small and should be handled accordingly.
- Peritoneal washings. The surgeon collects these by saline irrigation from the left and right paracolic gutters, subdiaphragmatic region, and pouch of Douglas. These fluids should be processed by cytology and cell block. Ascitic fluid is treated similarly [1].

## 8. Gestational trophoblastic disease

The term gestational trophoblastic disease is a spectrum of disorders with abnormal trophoblast proliferation and maturation, as well as neoplasms derived from trophoblast.

### 8.1. Complete hydatidiform mole

Complete hydatidiform mole is a placenta with grossly swollen chorionic villi, resembling bunches of grapes, and showing varying degrees of trophoblastic proliferation. Villi are enlarged, often exceeding 5 mm in diameter.

**Molecular pathogenesis and etiologic factors:** Complete mole results from fertilization of an empty ovum that lacks functional maternal DNA. Most commonly, a haploid (23,X) set of paternal chromosomes introduced by monospermy duplicates to 46,XX, but dispermic 46,XX and 46,XY moles also occur. Moles characteristically lack maternal chromosomes. Paternally imprinted genes, such as *p57,* in which only the maternal allele is expressed, are not expressed in villous trophoblasts of androgenetically derived complete moles. Since the embryo dies at a very early stage, before placental circulation has developed, few chorionic villi develop blood vessels and fetal parts are absent. Women with a prior hydatidiform mole have a 20-fold greater risk of a subsequent molar pregnancy than the general population [1,2].

**Pathology:** Microscopically, many individual villi have cisternae. Trophoblast is hyperplastic and composed of syncytiotrophoblast, cytotrophoblast, and intermediate trophoblast. Considerable cellular atypia is present.

**Clinical features:** Serum hCG levels are markedly elevated, and increase rapidly. Complications of complete mole include uterine hemorrhage, disseminated intravascular coagulation, uterine perforation, and trophoblastic embolism. The most important complication is development of choriocarcinoma, which occurs in about 2% of patients.

Treatment consists of suction curettage of the uterus under ultrasound guidance and an oxytocic infusion and subsequent monitoring of serum hCG levels. Up to 20% of patients require adjuvant chemotherapy for persistent disease, and 100% cure rate is expected even under these circumstances.

### 8.2. Invasive hydatidiform mole

The villi of a hydatidiform mole may only enter the superficial myometrium or they may invade the uterus, and even the broad ligament. They tend to enter dilated venous channels of the myometrium and one-third spread to distant sites, mostly the lungs. Uterine perforation is a major complication, but occurs in only a minority of cases [1,2].

### 8.3. Gestational choriocarcinoma

Choriocarcinoma occurs in 1 of 160 000 normal gestations, 1 of 15 000 spontaneous abortions, 1 of 5000 ectopic pregnancies, and 1 of 40 complete molar pregnancies. Unlike most other cancers, choriocarcinomas lack intrinsic tumor vasculature. Thus, the tumors are typically necrotic and hemorrhagic and viable tumor is confined to the rim of the neoplasm. There is a dimorphic population of cytotrophoblast and syncytiotrophoblast, with varying degrees of intermediate trophoblast. hCG is localized to the syncytiotrophoblastic element. By definition, tumors containing any villous structures, even if metastatic, are considered hydatidiform mole and not choriocarcinoma [1,2].

Choriocarcinoma invades mainly through venous sinuses in the myometrium. It metastasizes widely via the bloodstream, especially to lungs (over 90%), brain, gastrointestinal tract, liver, and vagina. With current chemotherapy, recognition of risk factors (high hCG levels and prolonged interval since antecedent pregnancy), and early treatment, most patients are cured.

### 8.4. Placental site trophoblastic tumor

Placental site trophoblastic tumors are the least common trophoblastic tumors, and are mainly composed of intermediate trophoblastic cells. Mononuclear and multinuclear trophoblast may be present as sheets of cells interspersed among myometrial cells. No chorionic villi are seen. Placental site trophoblastic tumor is distinguished from choriocarcinoma by its monomorphic (intermediate) trophoblastic proliferation, unlike the dimorphic pattern of trophoblast in choriocarcinoma. Most trophoblastic

cells express human placental lactogen (hPL), but a few express hCG [1,2].

Placental site trophoblastic tumor must be excised completely (hysterectomy) to prevent local recurrence. It sometimes metastasizes and may be fatal. Large tumors and mitotic indices of more than 5 mitoses/10 HPFs are associated with worse prognosis.

## Conflict of interest

The author has no conflicts of interest to declare.

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