Chapter 2
Pathology of Gynecologic Cancer

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Abstract This chapter will discuss the basic pathology of select gynecologic malignancies that occur in older women. First, endometrial cancer will be reviewed, including endometrioid carcinoma, the most common subtype, as well as less common entities such as serous and undifferentiated carcinoma and MMMT. Tamoxifen-associated endometrial cancer as well as Lynch syndrome, an important disorder in endometrial as well as ovarian cancer, will be briefly touched upon. Next, ovarian epithelial malignancies will be discussed with special attention to serous carcinoma and its association with BRCA abnormalities. Endometrioid, clear cell, and mucinous ovarian neoplasms will also be briefly discussed. Finally, the most common carcinomas of the cervix and vulva are reviewed.

Keywords Endometrial carcinoma • Elderly patients • Ovarian carcinoma • Cervical carcinoma • Gynecologic cancer

Endometrial Carcinoma

For almost 30 years, endometrial carcinoma has been divided into two categories based on epidemiology, histology, and clinical behavior. Type I carcinomas consist of low-grade endometrioid tumors (approximately 80 %) which arise in a background of endometrial hyperplasia in pre- or perimenopausal women with estrogen excess and tend to have an indolent clinical course. Type II carcinomas (approximately 20 %), the prototype of which is serous carcinoma, are high-grade estrogen-independent tumors which typically develop in a background of atrophic endometrium in postmenopausal women and have a poor clinical outcome [1].

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Endometrioid Carcinoma

Endometrioid adenocarcinoma is the most common type of endometrial carcinoma, comprising approximately 80 % of the cases. The average age of the patient is approximately 63 years who usually is under the influence of unopposed estrogen stimulation due to obesity, estrogen administration, estrogen-secreting tumors, or anovulatory cycles. Most tumors are low grade, confined to the uterus at the time of diagnosis, and are preceded or coexist with complex endometrial hyperplasia.

Endometrial hyperplasia consists of an increase of the gland to stroma ratio and is divided into four categories based on its behavior as described by Kurman et al. in 1985 [2]: simple hyperplasia, with or without atypia, and complex hyperplasia, with or without atypia. The glands in simple hyperplasia are increased but show little architectural complexity. Complex hyperplasia, however, shows glands with marked glandular complexity including branching, budding, and papillary outpouching. Atypia refers to nuclear abnormalities including nuclear enlargement, rounding, loss of polarity, pleomorphism, prominent nucleolus, and vesicular chromatin. Atypia has been shown to be the most important parameter in this classification as Kurman et al. found that less than 3 % of patients with hyperplasia (simple or complex) without atypia progressed to carcinoma compared to approximately 25 % of the hyperplasias with atypia [2]. Although the diagnosis of atypical hyperplasia has long been plagued with reproducibility issues [3], an alternate classification system has not been widely accepted in clinical practice.

Endometrioid adenocarcinoma found in hysterectomy specimens from patients diagnosed with atypical hyperplasia on endometrial sampling is a frequent finding and has been described to occur in up to 42 % of the patients [4, 5]. Morphologically, carcinoma is distinguished from atypical hyperplasia predominantly based on greater architectural complexity and the absence of intervening stroma between glands.

Endometrioid carcinoma is graded using a 3-tiered system based primarily on architecture and secondarily on cytologic atypia. The FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) grading scheme uses the amount of glandular versus solid architecture present in the tumor to determine grade: Grade 1 shows less than 5% solid architecture, grade 2 has between 5 and 50 % solid architecture, and grade 3 contains a solid component greater than 50 %. If a significant amount of marked cytologic atypia is present, the tumor is then upgraded (from 1 to 2 or 2 to 3). Despite certain limitations, the FIGO grading system does have prognostic utility when applied correctly [6]. There has been interest in applying a binary grading system in which endometrial carcinomas are divided in to low- and high-grade tumors; however, they are not currently used in clinical practice [7–10]. Currently, endometrioid adenocarcinoma is often informally dichotomized into two groups: low grade (FIGO grades 1–2) and high grade (FIGO grade 3). Low-grade endometrioid adenocarcinomas usually have indolent clinical behavior, while FIGO grade 3 endometrioid carcinoma is a high-grade tumor which can show aggressive clinical behavior. It has been

associated with deep myometrial invasion, cervical involvement, and lymphovascular invasion [11]. These tumors may thus be more closely related to other type II cancers. Although some studies have shown a better outcome than other high-grade endometrial carcinomas such as serous or clear cell [12], others have shown similar prognoses [13, 14].

There are a number of different metaplasias that may be present in endometrioid carcinoma, usually in low-grade tumors. These include squamous, spindle cell, mucinous, eosinophilic, and papillary syncytial metaplasias [15, 16]. More infrequently, there may be osteoid or chondroid metaplasia which may mimic a carcinosarcoma [17]. The tumors may also show clear cell or secretory change, sex cord differentiation, or a corded or hyalinized growth pattern [18–20]. These changes are only important in terms of diagnosis, as they may mimic other types of tumors; they have no clinical ramifications.

Different types of myometrial invasion of endometrioid carcinoma have been reported. One of these is the so-called MELF or microcystic, elongated, fragmented pattern of invasion [21] which most frequently occurs in low-grade endometrioid carcinoma. This type of invasion shows a detached glands and tumor cells, often with an attenuated epithelium with a prominent myxoid inflammatory reaction. These tumors have an increased incidence of lymphovascular invasion and possibly lymph node metastases [22, 23]. When present as lymph node metastases, the cells are often single with prominent eosinophilic cytoplasm and can mimic histiocytes [24].

Several different genetic abnormalities have been described in endometrioid carcinoma. These include microsatellite instability, alterations in the gene *PTEN*, and mutations in the genes *PIK3CA*, *KRAS*, and *CTNNB1*. Unlike serous carcinoma, they usually do not show mutations in the gene *Tp53* [25].

Serous Carcinoma

Serous carcinoma of the endometrium is the prototype of Bokhman's type II endometrial cancers as it is usually not associated with estrogen excess, occurs in postmenopausal women, and typically has a poor clinical outcome. It is much less common than endometrioid type and consists of approximately 5–10 % of all endometrial cancers. It is an aggressive subtype of endometrial cancer, often presenting at advanced stage and accounts for a disproportionate amount of deaths and recurrences [26].

Serous carcinoma typically arises in a background of atrophic endometrium or atrophic polyp, as opposed to endometrioid type which is usually present in a background of atypical hyperplasia. It arises in a precursor lesion referred to as endometrial intraepithelial carcinoma (EIC) which is a proliferation of malignant cells, confined to the endometrial surface or glands, without myometrial invasion [27]. The aggressive behavior of this tumor is related to the fact that it may spread

beyond the uterus without invasion into the myometrium. In a large series of patients with uterine serous carcinoma, 32 tumors showed no myometrial invasion; however, surgical staging revealed that 37 % of these tumors had FIGO stage III or IV disease [28].

The tumor suppressor gene *Tp53* has been implicated in the pathogenesis of serous carcinoma as mutations in this gene are present in up to 93 % of uterine serous carcinomas which may be detected by immunohistochemistry [29–31]. Studies have also shown identical p53 mutations in the precursor lesion (EIC) as well as the invasive and metastatic disease [30–32].

Clear Cell Carcinoma

Clear cell carcinoma of the endometrium (ECCC) is a rare entity which has been reported to comprise between 1 and 6 % of endometrial cancers; however, the actual incidence is probably closer to 1 % [33–36]. The discrepancy is due to the fact that many tumors may show clear cell change or similar architectural features, including a papillary growth pattern, resulting in misclassification in many cases. If these types of cases are excluded, unequivocal pure clear cell carcinoma is very rare [33]. ECCC is an example of Bokhman's type II cancers in that it frequently presents in postmenopausal women, often shows a poor clinical outcome, and appears unrelated to estrogen excess.

ECCC may arise in a background of atrophy or a polyp, like serous carcinoma [36, 37]. The most common architectural patterns include papillary, solid, and tubulocystic. There is an oxyphilic variant which shows eosinophilic, rather than clear cytoplasm. These tumors are usually negative for estrogen and progesterone receptors [38, 39]. ECCC has been shown to have a heterogeneous molecular makeup with mutations in *PIK3CA* and *ARID1A* and shows infrequent mutations in *PTEN* and *Tp53* [40].

Undifferentiated Carcinoma

Undifferentiated or dedifferentiated carcinoma is a very aggressive endometrial tumor which has been recently described [41]. It is a tumor in which DNA mismatch repair protein abnormalities have been observed (see section "Lynch Syndrome"). Although some of the abnormalities are sporadic, some of them are associated with Lynch syndrome [42, 43].

Undifferentiated carcinoma is a tumor which shows sheets of discohesive or loosely cohesive cells that may resemble lymphoma. It may also refer to as dedifferentiated when it is associated with a low-grade endometrioid component. It is important for pathologists to recognize these tumors as they appear to have a worse outcome than FIGO grade 3 endometrioid carcinoma and appear to be associated with Lynch syndrome [41, 42].

MMMT (Malignant Mixed Mullerian Tumor/Carcinosarcoma)

MMMTs comprise approximately 2–5 % of uterine malignancies and usually occur in postmenopausal women and have an aggressive clinical course [44]. Although these tumors are biphasic neoplasms consisting of both carcinomatous and sarcomatous components, it is now believed that these are actually variants of carcinoma or "metaplastic" carcinomas. The tumors are usually polypoid endometrial masses. The carcinoma component may be any type of Mullerian carcinoma, and the sarcomatous component may show homologous (leiomyosarcoma, fibrosarcoma) or heterologous (rhabdomyosarcoma, chondrosarcoma) differentiation. Both components are usually high grade.

Tamoxifen and Endometrial Cancer

Tamoxifen is often used in patients with estrogen receptor-positive breast cancer due to its antiestrogenic effects. In the endometrium, however, tamoxifen acts as a weak agonist and is associated with the development of endometrial polyps and endometrial carcinoma [45, 46]. Overall, patients who use tamoxifen have a relative risk of endometrial cancer of approximately seven which appears to be related to the duration of administration [47]. In addition to endometrioid cancers that develop as a result of estrogen exposure, non-endometrioid tumors have also been described including serous carcinoma, clear cell carcinoma, and MMMT [48–50]. Tumors may arise during exposure to tamoxifen or after its discontinuation, a setting in which the incidence of high-grade cancers is increased [51].

Lynch Syndrome

Lynch syndrome (LS) or hereditary non-polyposis colorectal cancer (HNPCC) syndrome is an autosomal dominant condition in which patients develop colorectal, endometrial, and other carcinomas including ovarian, due to a germ line mutation in one of the DNA mismatch repair proteins [52]. While colorectal cancer is the most common tumor to affect these patients, women with LS have up to a 60 and 13% lifetime risk of developing endometrial and ovarian cancer, respectively [53, 54].

The most common DNA mismatch repair proteins to be affected include MLH1, MSH2, MSH6, and PMS2. These proteins function to repair replication errors in repetitive nucleotide sequences, or microsatellites, the deficiency of which frequently results in microsatellite instability (MSI) which may eventually lead to the development of malignancies [55]. Many sporadic endometrial carcinomas show MSI due to mismatch repair deficiency, the majority of which are due to epigenetic *MLH1* promoter methylation in contrast to patients with LS who have a germ line mutation in one of the genes [56, 57].

The development of gynecologic malignancies in LS is often overlooked; however, its recognition is important. In a study of women with LS who developed both gynecologic and colorectal cancers, 51 % had their endometrial or ovarian cancer diagnosed first [58]. In addition, women have an equal or even higher incidence of endometrial cancer than colon cancer, especially those with mutations in *MSH6*, which appears to be frequently associated with endometrial cancer and presentation at an age older than that typically seen in colon cancer [54, 59–62].

In addition to an older age of presentation, many women with Lynch syndrome and endometrial cancer do not have a personal or family history of cancer and are thus undetected with standard screening criteria [63]. Beyond screening at the clinical level, certain pathologic features have been identified in tumors with deficient mismatch repair function. Grossly, it has been noted that the lower uterine segment is an overrepresented location of endometrial cancer associated with Lynch syndrome [42, 64]. Histologically, endometrioid carcinomas are the most common; however, it appears that there is an increased incidence of higher grade tumors and non-endometrioid histologies in younger patients including undifferentiated and clear cell carcinoma [43, 65]. Other pathologic features suggestive of Lynch syndrome include prominent peritumoral lymphocytes, tumor infiltrating lymphocytes, and tumor heterogeneity [42, 66].

When clinical or pathologic factors are present which raise the possibility of Lynch syndrome, the pathologist may perform immunohistochemical studies as a screening tool. This has been found to be a rather sensitive and specific method in detecting patients with the syndrome [67]. If abnormalities are encountered in any of the proteins by immunohistochemistry, the patient is then referred to genetics to undergo confirmatory testing.

Ovarian Carcinoma

Ovarian cancer is the most deadly of the gynecologic malignancies, accounting for approximately half of all mortalities [68]. Although ovarian cancer is traditionally managed as one disease, there is abundant data to support that ovarian cancer is highly heterogeneous with distinct pathogeneses, morphology, and clinical behavior based on histologic subtype.

Serous Carcinoma Including BRCA

Ovarian serous carcinoma (OSC) is the most common ovarian epithelial malignancy, consisting of approximately 80 % of the cases. It carries a poor prognosis due to the fact that up to 95 % of patients present at an advanced stage (FIGO stages II–IV) [69]. Recently, it has become evident that the OSC can be separated into two

categories, based on molecular composition, appearance, and clinical behavior, low-grade serous carcinoma (LGSC) and high-grade serous carcinoma (HGSC).

Despite the existence of different grading schemes (FIGO, World Health Organization [WHO], Gynecologic Oncology Group [GOG], and Shimizu-Silverberg), a single grading system is not currently used universally. Malpica et al. have developed a two-tier grading system specifically for serous carcinoma which evaluates mitotic index and nuclear atypia [70]. Tumors with a uniform nuclear appearance and fewer than 12 mitoses per 10 high-power fields are classified as LGSC, and those with marked cytologic atypia (greater than or equal to 3 times variation in nuclear size) or 12 or more mitoses are classified as HGSC. On multivariate analysis, tumor grade based on this two-tier system was a significant independent prognostic factor of overall survival [70]. Furthermore, this grading system has shown excellent interobserver and intraobserver reproducibility among both gynecologic and general surgical pathologists [71].

In addition to the clinical behavior, molecular studies also support this classification. LGSC is thought to develop in a stepwise progression from cystadenoma and serous borderline tumor (SBT). In fact both SBT and LGSC have been found to have mutations in either KRAS or BRAF in approximately two-thirds of cases [72]. In addition, there are a number of shared allelic imbalances which progressively increase during the development of LGSC from SBT [73]. HGSC, conversely, shows mutations in *Tp*53 in over 80 % of the cases; these are rarely seen in LGSC and SBTs [74, 75]. In addition, SBT and LGSC coexist in approximately two-thirds of the cases, and SBT is rarely seen in association with HGSC [70].

In an effort to identify a precursor of HGSC, women with *BRCA* germ line mutations, a population that is at increased risk for both ovarian and breast cancer, have been extensively studied. *BRCA1* and *BRCA2* are tumor suppressor genes which are involved in DNA repair by homologous recombination and, when lost, additional mutations and genomic instability ensue, which may lead to cancer. It is estimated that at least 10 % of ovarian cancers are due to hereditary susceptibility, and *BRCA* mutations account for the large majority [76]. The lifetime risk of ovarian cancer in patients with a *BRCA1* germ line mutation is approximately 54 %, while the risk for *BRCA2* is 23 % [77]. Due to the increased risk of ovarian cancer, many *BRCA*-positive women have undergone prophylactic bilateral salpingo-oophorectomies, which have been shown to significantly reduce the subsequent development of ovarian cancer by up to 96 % [78, 79].

Occult carcinomas or serous tubal intraepithelial carcinoma (STIC) has been detected in these prophylactic specimens ranging from 2.3 to 17 % of the time [79–84]. A large majority of these STICs have involved the fallopian tube epithelium or, more specifically, the fimbria, which has led to the hypothesis that the majority of HGSCs arise in the fallopian tube. Accordingly, a specific protocol was developed called “SEE-FIM” (sectioning and extensively examining the fimbriated end) [83, 85] in which the tubes are sectioned in a specific manner after fixation and submitted entirely for microscopic examination. This protocol ensures maximum exposure of the fimbrial mucosa in order to detect these occult carcinomas.

In addition to tumors occurring in patients with *BRCA* germ line mutations, sporadic HGSC may also show *BRCA* abnormalities. Specifically, *BRCA* gene

inactivation may occur by several mechanisms including somatic mutation or epigenetic silencing by promoter methylation; these abnormalities have been reported to occur in approximately 30 % of sporadic HGSC [86]. In addition to showing *BRCA* abnormalities, sporadic HGSC has also been shown to have prominent tubal involvement, including the fimbriae. STIC has previously been shown to be present in the majority of tumors classified as primary ovarian, peritoneal, and tubal, some of which have shown identical *Tp53* mutations in both sites [87].

Morphologically, STIC consists of a focus of secretory cells with loss of cilia, cellular stratification or pseudostratification, nuclear enlargement, atypia, mitotic activity disorganization, and loss of polarity [85, 87]. Invasive HGSC can show a wide range of morphologic appearances. The classic appearance is that of a complex papillary architecture with hierarchical branching and slit-like spaces. Other less-described patterns include glandular, cribriform, transitional solid, trabecular, and microcystic. It is for this reason, "serous" is the preferred term as opposed to "papillary serous"; serous carcinoma is not necessarily papillary, and non-serous carcinomas may show papillary architecture. Cytologically, the tumor cells show high nuclear grade.

HGSCs that harbor *BRCA* abnormalities appear to have a characteristic morphologic appearance, particularly those with *BRCA1* germ line mutations and promoter methylation, compared to non-*BRCA* altered cases. A combination of solid, transitional cell-like, or pseudo-endometrioid architecture, the presence of diffuse tumor infiltrating lymphocytes, and high mitotic index have all been significantly associated with *BRCA1* abnormalities [88].

Morphologically, LGSC is not as diverse as HGSC. As described previously, they are usually associated with SBT and have low nuclear grade with a low mitotic index. They often have a micropapillary pattern and may show a distinctive pattern of invasion with small clusters of cells or papillary fronds embedded in stroma with retraction artifact, in addition to the more traditional pattern of destructive stromal invasion.

Endometrioid Carcinoma

Ovarian endometrioid carcinoma (OEC) is the second most common epithelial malignancy, representing approximately 10 % of cases [69]; however, it is the most common carcinoma to present at FIGO stage I, which usually portends a favorable outcome [89].

Many OECs arise in a background of endometriosis and endometrioid borderline tumor. Carcinoma is distinguished from borderline tumor if stromal invasion is identified, either destructive or expansile (confluent growth). Morphologically, OECs resemble those seen in the endometrium. Unlike serous carcinoma, OECs are usually WT1 negative [90, 91]. Like its endometrial counterpart, mutations in *CTNNB-1*, *PIK3CA*, and *PTEN* have been described [91–94]. Microsatellite instability has also been reported in OEC which may be part of the spectrum of Lynch syndrome [95].

Clear Cell Carcinoma

The reported incidence of ovarian clear cell carcinoma (OCCC) has ranged from 3.7 to 12.1 %, [96, 97] in North America, but in Japan, OCCC comprises up to 25 % of ovarian carcinomas [98]. Due to the frequent presence of clear cell change in other ovarian tumors, OCCC is often misdiagnosed. Accurate diagnosis is important in order to improve treatment options, however, as it is well documented that OCCC does not respond to the traditional platinum-based chemotherapy. Most OCCCs present at an early stage (FIGO stages I–II) which confers a favorable prognosis; however, at advanced stage, the prognosis is poor; accordingly all OCCCs are considered to be high grade [98, 99].

OCCC have frequent mutations in *PIK3CA* and *ARID1A* [100–103]. Unlike its serous counterpart, they typically do not show mutations in *Tp53* [100, 104]. Morphologically, OCCC usually arises from endometriosis [105], and occasionally a benign or borderline adenofibroma may be present as well. An oxyphilic variant, or cells with eosinophilic cytoplasm, has been reported. OCCC typically has a combination of growth patterns, including papillary, tubulocystic, and solid. Tumors with papillary architecture may show psammoma bodies; other common features include hyaline globules, an associated lymphoplasmacytic infiltrate, and a characteristic densely hyalinized stroma [106]. OCCCs are typically negative for estrogen and progesterone receptors. A recent immunohistochemical marker, HNF-1beta, has been found to be rather sensitive and specific in OCCC and may serve as a useful tool in its correct classification [107].

Mucinous Carcinoma

In the past, ovarian mucinous carcinomas were reported to be the second most common type of ovarian cancer, accounting for approximately 12 % of the cases [108]. More recently, however, it is clear that these tumors are much less common, comprising only approximately 3 % of primary ovarian carcinomas [69, 109]. This is due to the fact that in older studies, many tumors which were assumed to be primary, especially those at advanced stage, were actually metastases from extraovarian sites. It is now known that the vast majority of tumors that are associated with pseudomyxoma peritonei are of appendiceal origin [110, 111]. Other common mucinous carcinomas to metastasize to the ovary include other gastrointestinal and pancreatobiliary tumors. Factors favoring a metastatic tumor include bilaterality, small size (less than 10–13 cm), surface implants, and an infiltrative pattern of stromal invasion. Factors which favor a primary mucinous neoplasm include unilaterality, larger size, a smooth external surface, and a background mucinous borderline tumor or adenoma [112, 113]. Mucinous carcinomas which are indeed primary to the ovary are usually present at low stage and have a favorable clinical outcome.

Leiomyosarcoma

Leiomyosarcoma, although a rare tumor, is the most common pure sarcoma of the uterus and comprises approximately 1 % of all uterine malignancies [114]. They usually occur in peri- or postmenopausal women, with a mean age of approximately 50–55 years and are highly aggressive neoplasms [115].

Morphologically, the tumor is composed of intersecting fascicles of smooth muscle fibers and usually demonstrate the following malignant features: coagulative or tumor cell necrosis, a mitotic index of more than 10 per 10 high-power fields, and nuclear atypia [116]. Variants include epithelioid and myxoid leiomyosarcoma.

Cervix

Infection by human papilloma virus (HPV) may result in squamous or glandular neoplasia. Squamous cervical intraepithelial neoplasia (CIN) is graded based on the proliferation of immature squamous epithelium. CIN 1, 2, and 3 show neoplastic proliferations in the lower third, lower two-thirds, and entire thickness, respectively, of the squamous epithelium. CIN 1 often shows koilocytes which are wrinkled or "raisinoid" nuclei with perinuclear halos. CIN1 is a low-grade squamous intraepithelial lesion (LSIL), while CIN 2 and CIN3 are high-grade squamous intraepithelial lesions (HSIL), according to the Bethesda classification system. HSILs are caused only by high-risk HPV (HR-HPV), while LSILs may be caused either by low-risk HPV or HR-HPV [117]. Progression to invasive squamous cell carcinoma (SCC) is rare with LSIL (1 %), while HSIL shows higher rates of progression (12 %) [118]. Patients with cervical squamous dysplasia are also at increased risk for dysplasia elsewhere in the female genital tract, especially the vagina [119].

Studies have shown problems with the reproducibility in identifying and grading SILs [120]. Ancillary tests have been developed in order to improve accurate diagnosis. The gene *p16INK4a* is a tumor suppressor gene involved in the pathogenesis of cervical cancer, and its protein product p16 is overexpressed. This protein may be detected by immunohistochemistry with diffuse nuclear and cytoplasmic staining. Thus, in the appropriate setting, p16 is considered to be a surrogate marker for HR-HPV [121–123].

Invasive squamous cell carcinoma (SCC) of the cervix is the most common histologic subtype, accounting for approximately 80 % of the cases and occurs in women with a mean age of 55 years. Like SILs, it is directly related to infection with HPV. The carcinoma is "microinvasive" if the depth of invasion is ≤5 mm and the horizontal component is ≤7 mm. A number of subtypes of SCC have been described including keratinizing, basaloid, papillary, lymphoepithelioma-like, and squamotransitional, all of which have been shown to be associated with HPV [124–127].

Adenocarcinoma in situ (AIS) of the cervix is a glandular dysplasia, also etiologically related to HR-HPV infection and may coexist with SIL [128]. AIS can extend far into the endocervical canal and may be present multifocally more often than SIL [129]. Morphologically, AIS consists of columnar cells with hyperchromatic nuclei and typically shows numerous apical mitotic figures and apoptotic bodies. The subtypes include "usual" type in which mucin is usually present, intestinal type, which shows prominent goblet cells, and "endometrioid" type which has little or no mucin. The term "endometrioid" refers to the histologic appearance; these tumors do not show true endometrioid differentiation. The different subtypes all show infection with HPV and, besides the descriptive nature, have no additional clinical significance. Invasive endocervical adenocarcinoma consists of approximately 20 % of invasive cervical cancer and occurs in women with a mean age of approximately 50 years [130]. The criteria for microinvasive carcinoma are the same as those in SCC. Subtypes of invasive endocervical carcinoma are similar to those seen in AIS.

Vulva

Vulvar carcinoma is a relatively rare tumor, representing approximately 4 % of all cancers of the female genital tract. These tumors occur more frequently in older patients, as approximately two-thirds of cases occur in women over the age of 60 years [131]. There are two types of intraepithelial and invasive squamous neoplasia that affect the vulva, those associated with high-risk HPV and those which are associated with chronic inflammatory skin disorders. Regardless of the underlying lesion, the incidence of associated invasive cancer appears to increase with advanced age [132].

HPV-associated vulvar intraepithelial neoplasia (VIN) or usual VIN (uVIN) includes the warty or basaloid subtypes. This type of VIN usually occurs in younger women [131, 133]. Previously, VIN was graded similar to cervical intraepithelial neoplasia, but in 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) did away with the grading system and recommended that only VIN 2–3 be used for uVIN, due to problems of reproducibility [134–137]. Histologically, uVIN is a proliferation of squamous cells with decreased maturation, increased nuclear to cytoplasmic ratio, pleomorphism, and increased mitotic activity. Warty VIN may have a slightly papillary appearance, while basaloid VIN is usually flat. Approximately 3–6 % of women with treated uVIN eventually develop invasive squamous cell carcinoma (SCC), while up to 15 % of untreated lesions may progress [132, 138, 139]. The warty and basaloid types of SCC invade as sheets or nests of cells and bulbous or jagged nests, respectively. Keratinization may be present, but is usually not as extensive as that seen in non-HPV-associated SCC.

The other type of VIN is known as differentiated or simplex VIN (dVIN) which usually occurs in postmenopausal women and is associated with chronic

inflammatory skin disorders such as squamous hyperplasia and lichen sclerosus (LS); dVIN is typically not associated with HPV [140, 141]. It appears that mutations in the gene *Tp53* may play a role in the pathogenesis [142, 143]. Unlike the usual type of VIN, dVIN is very frequently associated with invasive SCC and has been reported to occur at some point in up to 85 % of cases [144]. Histologically, dVIN and its associated SCC have a different appearance than the warty and basaloid types. In dVIN, the cells appear "differentiated," which contrasts with the appearance of uVIN and also leads to the lesion being underrecognized. The epidermis is usually thickened and is composed of squamous cells with abundant eosinophilic cytoplasm, prominent intercellular bridges, and prominent nucleoli; these changes are more prominent in the basal layers. Invasive SCC arising in this setting is usually keratinizing and has a higher incidence of recurrence compared to HPV-associated SCC [145].

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