Cervical Adenocarcinomas
A Heterogeneous Group of Tumors With Variable Etiologies and Clinical Outcomes
Anjelica Hodgson, MD; Kay J. Park, MD

Context.—Cervical adenocarcinomas are a heterogeneous group of tumors with varying morphologies, etiologies, molecular drivers, and prognoses, comprising approximately 25% of all cervical cancers. Unlike cervical squamous cell carcinoma, adenocarcinomas are not uniformly caused by high-risk human papillomavirus (HPV) infection and, therefore, would not necessarily be prevented by the HPV vaccine.

Objective.—To provide a review of endocervical adenocarcinoma subtypes and, when appropriate, discuss precursor lesions, etiologies, molecular genetics, and ancillary studies within the context of clinical care. Some historical perspectives will also be provided.

Data Sources.—Data sources included published peer-reviewed literature and personal experiences of the senior author.

Conclusions.—Endocervical adenocarcinomas are a histologically diverse group of tumors with various causes and molecular drivers, not all related to HPV infection. Distinguishing them has important implications for treatment and prognosis as well as strategies for prevention.


Cervical cancer was once one of the most common malignancies to affect women in the United States, but with the advent of Papanicolaou test screening in the mid-20th century, a sharp decline in the rate of cervical cancer and associated deaths has been noted. Today, cervical cancer ranks as the 14th most common cancer to affect women in the United States and the third most common cancer to affect women worldwide.1 Most cervical cancers are composed of squamous cell carcinoma caused by human papillomavirus (HPV) infection; however, adenocarcinoma of the cervix appears to be increasing in both true and relative incidence.2,3 Unlike squamous cell carcinoma, adenocarcinoma of the cervix comprises a heterogeneous group of tumors not universally associated with HPV infection. These tumors demonstrate varying morphologies, etiologies, and prognoses. This review will cover classification of endocervical adenocarcinomas, associated precursor lesions, pathogenesis, and the latest available data of molecular and immunohistochemical findings. Where applicable, a historical perspective will also be provided.

CLASSIFICATION OF ENDOCERVICAL ADENOCARCINOMAS

According to the most recent WHO (World Health Organization) Classification of Tumors of Female Reproductive Organs published in 2014, endocervical adenocarcinomas are classified from descriptive morphologic characteristics, primarily cytoplasmic features.4 This classification suffers from vague definitions and does not reflect our current understanding of endocervical glandular neoplasia. A recent novel classification system based on etiology and biologic behavior was proposed to provide an updated framework for classification of endocervical adenocarcinomas. The International Endocervical Adenocarcinoma Criteria and Classification (IECC)5 categorizes endocervical adenocarcinomas by the presence or absence of HPV infection–related features: easily identified apical mitotic figures and apoptotic bodies. HPV-associated adenocarcinomas are further subdivided by clear definitions centered around cytoplasmic features, while HPV-unassociated adenocarcinomas are subclassified based on established published criteria.5 It has been suggested by the authors of that study that the IECC, given its etiologically based framework and clear definitions, would replace the current WHO classification should ongoing validation, genomic, and clinical outcome studies support it. The WHO and IECC systems are summarized in Table 1, and each of the known distinct morphologic subtypes is described herein.

HPV-ASSOCIATED ADENOCARCINOMAS

Usual Type Endocervical Adenocarcinoma

According to both the WHO and the IECC systems, usual type endocervical adenocarcinoma (UEA) is the most common subtype, accounting for 75% of all invasive adenocarcinomas.
endocervical adenocarcinomas.6 Historically, these tumors were termed endocervical type, and grouped under the mucinous category. According to the current WHO classification, these tumors are characterized by round or oval glands with “relative mucin depletion.” Cribriform or papillary architecture may be seen. Cytologically, the tumor nuclei are enlarged and display pseudostratification, elongation, and hyperchromasia. Apical mitotic figures and apoptotic bodies are readily visible, as are prominent nucleoli. The IECC defines these tumors as having between 0% and 50% of cells with appreciable intracytoplasmic mucin; with or without benign-appearing squamous differentiation5 (Figure 1, A and B).

Owing to their relative mucin depletion and pseudostratified nuclei, confusion with endometrial endometrioid adenocarcinoma (EEA) is not uncommon. In distinguishing these lesions from UEA, tumor location, HPV status, and immunohistochemistry can be used to adjudicate tumor origin. EEA is typically positive for high-risk HPV by messenger ribonucleic acid (mRNA) in situ hybridization and displays diffuse, block-like positivity for p16 by immunohistochemistry (Figure 1, C and D). Mononuclear carcinoma embryonic antigen (CEA) also usually shows positivity. In contrast, EEA is typically positive for vimentin and estrogen receptor (ER)/progesterone receptor (PR). It should be noted however, that there can be significant overlap of immunohistochemical profiles between EEA and EEA and that dependence should not be placed on a single immunohistochemical marker; rather, a panel should always be used. Deoxyribonucleic acid (DNA) mismatch repair (MMR) proteins (MLH1, PMS2, MSH2, MSH6) may also be potentially helpful when 1 or more are lost in tumor cells, as this would indicate an EEA with microsatellite instability.

**Mucinous Adenocarcinoma, Including Not Otherwise Specified, Intestinal, and Signet Ring Cell Types**

The WHO classification for mucinous endocervical adenocarcinomas is heterogeneous, and includes both HPV-associated (not otherwise specified [NOS], intestinal, and signet ring cell types) and HPV-unassociated (gastric type) tumors. Like all HPV-associated tumors as determined by the IECC, these neoplasms have apical mitoses and apoptotic bodies. They are further subclassified by the amount of tumor cells with evident intracytoplasmic mucin into NOS (>50% of tumor cells with intracytoplasmic mucin; Figure 2, A), intestinal type (>50% of cells with goblet morphology; Figure 2, B and C), or signet ring cell type (>50% of tumor cells with signet ring morphology; Figure 2, D).5 Mucinous and usual type features often coexist.

**Villoglandular Adenocarcinoma**

Villoglandular adenocarcinoma of the endocervix is a rare, well-differentiated subtype of HPV-associated adenocarcinoma. Like villoglandular neoplasms elsewhere in the gynecologic tract, these neoplasms are microscopically characterized by thin villous and papillary cores lined by cells with usual type cytomorphology and no more than moderate atypia. No morphologically distinct precursor lesions have been described.

**Invasive Stratified Mucin-Producing Carcinoma**

Stratified mucin-producing intraepithelial lesion (SMILE) is an in situ cervical lesion that arises from reserve cells of the cervical transformation zone, and thought to be distinct from conventional adenocarcinoma in situ (AIS) and squamous intraepithelial lesions.9 Morphologically, SMILE is characterized by immature epithelium with conspicuous intracytoplasmic mucin stratified throughout its thickness but without overt gland formation (Figure 3, A). In the original description, SMILEs were associated with other in situ lesions including AIS and squamous intraepithelial lesion (Figure 3, B), as well as different forms of invasive carcinoma; therefore, it was concluded that this lesion represented a marker for phenotypic instability.9 Ultrastructural examination has suggested that these lesions are more closely related to endocervical glandular neoplasia rather than squamous dysplasia.16 Several studies have evaluated the cytocologic11–14 and histologic features15 of SMILEs, and it has been recommended that these lesions should be managed like AIS,15 with dilemmas regarding treatment acknowledged in the clinical literature.16

A corresponding invasive form of SMILE has been recently described, termed invasive stratified mucin-producing carcinoma, or iSMILE.17 In the seminal article, these invasive tumors were described as nests of stratified columnar cells with peripheral palisading, variable amounts of intracytoplasmic mucin, and evident HPV infection–related features with apical mitotic figures and apoptotic bodies, similar to SMILE (Figure 3, A through F).17 In addition, a neutrophilic

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**Table 1. Classifications of Endocervical Adenocarcinoma by World Health Organization (WHO) and International Endocervical Criteria and Classification (IECC)**

<table>
<thead>
<tr>
<th>WHO</th>
<th>HPV-Associated Adenocarcinomas</th>
<th>HPV-Unassociated Adenocarcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocervical adenocarcinoma, usual type</td>
<td>Usual type</td>
<td>Gastric type</td>
</tr>
<tr>
<td>Mucinous carcinoma, NOS</td>
<td>Mucinous, NOS</td>
<td>Mesonephric carcinoma</td>
</tr>
<tr>
<td>Mucinous carcinoma, gastric type</td>
<td>Mucinous, intestinal type</td>
<td>Serous carcinoma</td>
</tr>
<tr>
<td>Mucinous carcinoma, intestinal type</td>
<td>Mucinous, signet ring cell type</td>
<td>Clear cell carcinoma</td>
</tr>
<tr>
<td>Mucinous carcinoma signet ring cell type</td>
<td>Villoglandular type</td>
<td>Endometrioid adenocarcinoma</td>
</tr>
<tr>
<td>Villoglandular carcinoma</td>
<td>iSMILE</td>
<td>Adenocarcinoma, NOS</td>
</tr>
<tr>
<td>Mesonephric carcinoma</td>
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<tr>
<td>Serous carcinoma</td>
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<td>Clear cell carcinoma</td>
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<tr>
<td>Endometrioid carcinoma</td>
<td></td>
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<tr>
<td>Adenocarcinoma, NOS</td>
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</tbody>
</table>

Abbreviations: HPV, human papillomavirus; iSMILE, invasive stratified mucin-producing carcinoma; NOS, not otherwise specified.
infiltrate was noted in most cases (Figure 3, C and D). Subsequent studies evaluating the morphologic and immunohistochemical features, as well as HPV status of iSMILE, have been reported and describe a variety of patterns including pure composition or admixture with usual type, mucinous, signet ring, glassy cell, or squamoid areas.\textsuperscript{18} Immunohistochemically, most of these tumors are diffusely positive for p16 (Figure 3, G), with varying percentages of positivity for paired-box 8 (PAX8), p63, p40 (Figure 3, H), hepatocyte nuclear factor 1 homeobox B (HNF1-β), U3 small nucleolar ribonucleoprotein protein (IMP3), and GATA binding protein 3 (GATA3). Anti-mucin MGGMC-1 (clone: HIK1083), special AT-rich sequence–binding protein 2 (SATB2), caudal-related homeobox gene 2 (CDX2), and androgen receptor consistently show negativity.\textsuperscript{10,18} HPV in situ hybridization detects high-risk HPV consistently in these tumors (Figure 3, I).\textsuperscript{5}

Although SMILE is mentioned in the 2014 WHO classification, iSMILE was not described at the time of publication. As such, it is included as an HPV-associated adenocarcinoma in the IECC.\textsuperscript{5}

**NON–HPV-ASSOCIATED ADENOCARCINOMAS**

**Gastric Type Endocervical Adenocarcinoma**

Gastric type endocervical carcinoma (GEA) was included in the 2014 WHO classification, and recent studies have shown that these tumors are the second most common subtype of endocervical adenocarcinoma.\textsuperscript{5} It is now known that within the spectrum of gastric type adenocarcinoma is minimal deviation adenocarcinoma (MDA), also referred to as adenoma malignum. This is an entity that has long been known to be a particularly aggressive type of endocervical adenocarcinoma, in spite of its deceptively bland morphology. Remarkably, cervical lesions matching the description of MDA were described in the European literature dating back to 1870.\textsuperscript{19} The first report in the English literature was published in *Cancer* in 1963 by McKelvey and Goodlin\textsuperscript{20} who noted that, despite its “innocent histological pattern,”

![Figure 1. Usual type endocervical adenocarcinoma. A and B, Apical mitotic figures and apoptotic bodies seen at scanning magnification with round to oval glands with focal cribriform pattern, lined by cells with enlarged, pseudostratified, and hyperchromatic nuclei and “mucin-depleted” appearance. C, High-risk human papillomavirus (HPV) in situ hybridization positive. D, p16 positive (hematoxylin-eosin, original magnifications ×40 [A] and ×100 [B]; original magnification ×100 [C and D]).](image-url)

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these neoplasms were almost always fatal and were resistant to common therapeutic approaches. In 1998, Ishii and colleagues published the first histochemical study to link MDA with gastric type mucin. Subsequently, the seminal article by Kojima et al described mucinous adenocarcinomas of the cervix with gastric morphology and immunophenotype, showing that these tumors had poor outcomes that were significantly worse than nongastric types. They defined gastric differentiation morphologically as tumor cells that have distinct cell borders and voluminous clear or pale eosinophilic cytoplasm (Figure 4, A through C). What has become evident is that there can be a wide range of morphologic features within a single tumor, with well-differentiated MDA-like components adjacent to poorly differentiated carcinoma (Figure 4, D). In addition, there may not necessarily be abundant clear cytoplasm in much of the tumor, although it does usually tend to be found at least focally (Figure 4, E). p16 staining is usually focal or shows negativity in these tumors with a few exceptions, and studies have proven that indeed GEAs are negative for HPV by polymerase chain reaction and in situ hybridization. Clinically, GEA has worse outcomes than UEA, even at stage I, and also presents more frequently at high stage (II or higher) as compared to other subtypes of adenocarcinomas with unusual patterns of spread involving the omentum, peritoneum, and visceral organs. A study by the Sankai Group has also confirmed the chemoresistance of these aggressive tumors. The ovary and fallopian tube can also be involved by GEA and it should be particularly noted that this can mimic lesions that are primary to that site (eg, ovarian mucinous cystadenoma/borderline tumors or mucinous metaplasia/neoplasia of fallopian tube) (Figure 4, F through I). Cytologically, in addition to having abundant eosinophilic or clear cytoplasm, it has been observed that GEA often has a foamy cytoplasmic quality (Figure 4, J). As mentioned above, immunohistochemical studies of GEAs have shown that they are mostly p16 negative; however, diffuse p16 positivity has been described. Therefore, it is not 100% sensitive or specific in distinguishing HPV- versus non-HPV-associated endocervical adenocarcinoma.
carcinomas. In addition, a few cases of endocervical adenocarcinoma have been described that have mixed features of GEA and UEA. A recent study showed that most tumors with mixed GEA and UEA features were Immunophenotypically “GEA-like,” while the minority were “UEA-like”; no evidence of a true mixed immunophenotype was reported. As such, it may be prudent to perform HPV testing if available in uncertain cases. Aberrant (overexpressed and null) phenotypes for p53 have been reported in 40% to 50% of GEAs, suggesting underlying p53 mutations. HIK1083, a marker for gastric type mucin, is relatively specific but not available for widespread use in routine practice. In our experience, it tends to be the strongest and most diffuse at the well-differentiated end of the morphologic spectrum, including in precursor lesions like lobular endocervical glandular hyperplasia (LEGH), with expression decreasing as the tumor becomes more poorly differentiated. Other positive immunomarkers include cytokeratin (CK) 7, MUC6, and CEA. GEA is typically negative for ER and PR. PAX8 has shown positivity in about 68% of GEAs in one cohort, which may be useful in distinguishing GEA from tumors of gastrointestinal or pancreatobiliary origin. Although the name gastric type endocervical adenocarcinoma suggests homology with gastric tumors, GEAs actually have morphologic and immunohistochemical overlap with pancreatic adenocarcinoma. GEAs and pancreatobiliary adenocarcinomas are typically positive for CK7, CEA, CA 19-9, with or without CK20 and CDX2 positivity, while PAX8 typically shows negativity in adenocarcinomas of pancreatobiliary origin. Therefore, PAX8 positivity could potentially be very useful in this scenario, recognizing that negativity for PAX8 does not entirely rule out GEA. In addition to the morphologic and immunohistochemical similarities described above, molecular analysis has also shown some similarities in genetic alterations between GEA and pancreatic adenocarcinoma. Next-generation sequencing of GEAs has shown somatic mutations in TP53, CDKN2A, ERBB2/ERBB3, and STK11. In cases without TP53 mutations, KRAS, BRAF, and GNAQ were found to be altered. Less commonly, mutations in GNAS, SMAD4, and PIK3CA were identified. Minimal deviation adenocarcinoma is part of the tumor spectrum in patients with Peutz-Jeghers syndrome, an autosomal dominant inherited syndrome characterized by germline mutations in STK11, which encodes a serine/threonine kinase that is involved in the regulation of cell polarity and is associated with numerous malignancies.

Figure 3. Stratified mucin-producing intraepithelial lesion (SMILE) and invasive stratified mucin-producing carcinoma (iSMILE). A. Immature epithelium with conspicuous mucin stratified throughout. Overt gland formation is not seen. B. SMILE and associated high-grade squamous intraepithelial lesion. C. iSMILE: invasive carcinoma with nests of stratified columnar cells and peripheral palisading. D. Evident apical mitotic figures and apoptotic bodies with prominent neutrophilic infiltrate. E. iSMILE with mucin-rich and mucin-poor areas and (F) corresponding mucicarmine. G. p16 positive. H. p40 positive. I. human papillomavirus positive (hematoxylin-eosin, original magnifications ×100 [A through C] and ×200 [D and E]; original magnification ×100 [F through H]; in situ hybridization, original magnification ×100 [I]).
Figure 4. Gastric type endocervical adenocarcinoma. A and B, Diffusely infiltrative adenocarcinoma with well-formed but irregularly shaped glands. C, Cells with basally located nuclei, abundant foamy pale cytoplasm, and apical eosinophilic cytoplasm within same gland, distinct cellular borders, and a single mitotic figure without apoptotic bodies. D, Well-differentiated minimal deviation adenocarcinoma–like gland forming tumor on the right adjacent to poorly differentiated irregular clusters and single cells on the left. E, Glands with mixture of cells containing abundant, tall apical mucin, goblet cells and mucin-poor eosinophilic cytoplasm, with nuclear grade ranging from low to high. F and G, Ovary metastasis mimicking mucinous cystadenoma. H and I, Fallopian tube metastasis with mucosal spread and focal stromal invasion. J, Foamy nature of cytoplasm in tumor cells (hematoxylin-eosin, original magnifications ×20 [A and F], ×40 [B, D, and H], ×200 [E, G, and I], and ×400 [C and J]).
including those arising in the breast, lung, testes, pancreas, GI tract, and gynecologic tract.\textsuperscript{37–39} Typical GEA\textsuperscript{40} has also been reported to occur in patients with Peutz-Jeghers syndrome.

Parallel to our increased understanding of invasive gastric type endocervical adenocarcinoma, our understanding of preinvasive endocervical lesions with gastric phenotype has also evolved.\textsuperscript{41–47} Currently, it is postulated that GEA might develop from a series of precursor lesions that begin with gastric metaplasia at one end of the spectrum, and proceed through LEGH, atypical LEGH, gastric type adenocarcinoma in situ, and finally to invasive carcinoma. There are several previously described entities that now fall into the category of noninvasive gastric lesions in the cervix in addition to LEGH and atypical LEGH. Diffuse laminar endocervical hyperplasia is cytologically identical to LEGH and in its original description was noted to often be confused with MDA.\textsuperscript{42} Type A tunnel clusters, originally described by Fluhmann\textsuperscript{41} in 1961, are also morphologically similar to LEGH and express gastric mucin.\textsuperscript{41,48} LEGH and pyloric metaplasia were first described by Nucci et al\textsuperscript{43} and Mikami et al,\textsuperscript{44} respectively, in 1999 as distinct lobular proliferations of small to moderately sized rounded glands often centered on a larger central gland in an acinar pattern, lined by columnar mucinous cells with bland cytology, often mimicking MDA (Figure 5, A through C). Gastric AIS and atypical LEGH could be considered a form of “progression” whereby the lesions acquire cytologic atypia without invasion into stroma (Figure 5, D and E).
These gastric lesions can present with clinical symptoms, commonly as a mass or with watery vaginal discharge, and can also be visible on imaging such as computed tomography or magnetic resonance imaging. The rate of malignant transformation of precursor gastric lesions to invasive carcinoma is unknown and currently there are no standards for how to manage such lesions.

Mesonephric Carcinoma

Mesonephric carcinoma of the endocervix is a rare malignancy arising from remnants of the Wolffian duct system, in contrast to many other neoplasms of the gynecologic tract, which are Müllerian derived. The Wolffian duct system represents the anlage of the male reproductive tract, which gives rise to the seminal vesicles, vas deferens, ejaculatory ducts, and epididymis. In the normal female, this ductal system regresses and involutes; however, remnants may remain and can be seen deep in the lateral cervical walls, among other locations in the pelvis. A spectrum of benign (mesonephric hyperplasia) to malignant (mesonephric carcinoma) mesonephric proliferations is recognized. Morphologically, mesonephric carcinoma is characterized by heterogeneous architecture, with various patterns of growth that include glandular/tubular, papillary, retiform, sex cord–like, solid, and spindled/sarcomatoid (Figure 6, A and B). Characteristically, dense eosinophilic secretions are seen within glandular luminal spaces, similar to that seen within benign mesonephric remnants (Figure 6, C). Clinically, these tumors can be aggressive and show metastases to distant sites including the lungs, with outcome being stage dependent. To date, no specific treatment regimens for this tumor type exist.

As these tumors are not associated with HPV infection, p16 immunostaining is typically patchy or negative. ER and PR also tend to show flat negativity. Cervical mesonephric carcinomas are consistently positive for PAX8 and GATA3 with variable staining for HNF1-β, TTF-1, calretinin, and CD10.

A recent study focusing on the molecular genetics of mesonephric carcinomas has demonstrated several novel findings including canonical KRAS mutations in most tumors (81%) and a smaller number harboring activating NRAS mutations. Mutations in chromatin-remodeling genes ARID1A/B were also common (62% of cases). Unlike EEA, alterations in PIK3CA and phosphatase and tensin homolog (PTEN) were not identified, nor were any cases found to have microsatellite instability. Several chromosomal abnormalities have been identified in mesonephric carcinomas with copy number gains in 1q, loss of 1p, and gain of chromosomes 10 and 12 being the most common. In a follow-up study evaluating 10 cases of mesonephric hyperplasias, no activating mutations in KRAS or NRAS were detected.

Clear Cell Carcinoma

Clear cell carcinoma (CCC) of the endocervix, like clear cell carcinoma elsewhere in the gynecologic tract, displays heterogeneous morphology with tubulocystic, papillary, and solid architecture (Figure 7, A through C). Hobnail cells with moderate to marked nuclear atypia without pleomorphism...
are characteristic (Figure 7, D). Similar to vaginal clear cell carcinomas, these rare malignancies can be associated with in utero exposure to diethylstilbestrol (DES), a synthetic estrogen given to women in the 1940s–1970s to prevent pregnancy loss and/or complications.

Clear cell carcinoma of the cervix shows a bimodal age distribution (young adults versus postmenopausal women). In DES-exposed patients, the peak risk of disease is at 19 years of age, although the risk persists through later years. In those patients, the anterior upper third of the vagina and ectocervix are the most likely sites of disease. In contrast, the peak age risk of disease in non–DES-exposed patients is wide, and spans the pediatric to postmenopausal population with the endocervix predominantly involved. A recent 40-year follow-up study in DES-exposed patients shows that the cumulative risk for development of CCC is 1 in 750 exposed patients, and 1 in 520 when the risk was adjusted to include nonexposed patients within the same birth cohort and year of diagnosis.

Immunohistochemically, these tumors are positive for CK7, PAX8, HNF1-β, and napsin-A. p53 and p16 may show positivity or negativity, while ER and PR typically show negativity. CEA has consistently shown negativity in these tumors, which could make it a useful marker to distinguish CCC from GEA with abundant clear cytoplasm.

Not much is known regarding the molecular underpinnings of cervical CCC. One study by Boyd et al. showed that microsatellite instability (widespread mutations in microsatellite repeats) is detected in all DES-exposed and 50% of non–DES-exposed cases, while no mutations in KRAS, HRAS, WT1 (Wilms tumor 1), ER, or TP53 genes were found. Mills et al. evaluated several cases of endocervical adenocarcinoma including 1 case of CCC for DNA MMR deficiency; the CCC showed retained MMR proteins, and they found no association between Lynch syndrome and endocervical adenocarcinoma. One study examining various molecular pathways by immunohistochemistry showed that a proportion of cervical CCCs had loss of PTEN, positivity for pAKT, and positivity for p-mammalian target of rapamycin (mTOR) with 1 case showing human epidermal growth factor receptor 2 (HER2) amplification by fluorescence in situ hybridization. However, no molecular analysis was performed in these cases and therefore, the correlation of these results with actual mutations is unknown.

**Figure 7.** Clear cell carcinoma. A, Papillary and tubulocystic architecture. B, Tubulocystic architecture with eosinophilic stroma. C, Solid growth pattern with clear cytoplasm. D, Cuboidal tumor cells hobnail appearance, and uniform moderate nuclear atypia (hematoxylin-eosin, original magnifications ×200 [A and C], ×100 [B], and ×400 [D]).
Serous Carcinoma

“Papillary serous carcinoma” of the endocervix was described by Gilks and Clement\(^6^8\) in 1992, with a follow-up study evaluating the clinicopathologic features of 18 cases in 1998.\(^6^9\) These reports highlighted a bimodal age distribution in patients (<40 years, >65 years), similar outcomes compared to UEA in patients with stage I disease, and the importance of excluding serous carcinoma of endometrial origin. One study presented in abstract form demonstrated HPV positivity in all 6 cases that were tested by polymerase chain reaction, 2 of which also showed aberrant p53 staining by immunohistochemistry.\(^7^0\) Another study\(^7^1\) evaluating the clinicopathologic and immunohistochemical features of so-called cervical serous carcinomas showed a number of interesting findings: (1) a bimodal age distribution was again noted with 3 premenopausal and 10 postmenopausal patients; (2) significant clinical differences were found between the 2 groups where all of the premenopausal patients were essentially cured (alive without disease after >20 years), while half the postmenopausal patients were either alive with disease or dead of disease; and (3) histologic variations were seen, with evidence of combined UEA and serous morphology in the premenopausal group but only pure serous histology in the postmenopausal group. HPV in situ hybridization was positive in both the serous and usual type areas in the 1 case that was tested in the premenopausal group. WT1 immunohistochemistry was also informative in that all premenopausal cases were WT1 negative, while 9 of 10 postmenopausal cases showed WT1 positivity. Similarly, p53 was overexpressed in 1 premenopausal case and only in the morphologically serous component, compared to aberrant expression in all postmenopausal cases. Most interesting in this series was the presence of concurrent serous tubal intraepithelial carcinoma (STIC) in 5 cases with identical TP53 missense mutations in the STIC and cervical lesions in 2/3 cases from the postmenopausal group. The systematic sectioning of the fimbriated end of the fallopian tube (SEE-FIM) has become a routine part of practice only in the last decade, which has allowed for the detection of these occult lesions that previously would have gone undetected. Another recent study showed that WT1 was not immunohistochemically detected in 12 cases of cervical serous carcinoma, with HPV 16 or 18 being detected in 4 of those cases.\(^7^2\) Even micropapillary growth pattern of cervical adenocarcinoma that can mimic peritoneal serous carcinoma has been described, usually associated with a component of UEA and harboring HPV (Figure 8, A through C).\(^7^3\)–\(^7^7\)

The evidence suggests that “serous carcinoma” of the cervix most likely represents a high-grade variant of HPV-associated UEA with “serous-like” features and that a certain proportion of so-called cervical serous carcinomas are likely drop metastases from the adnexa (assuming there is no endometrial lesion). If one is considering the diagnosis of primary endocervical serous carcinoma, metastases from the uterine corpus and adnexa, including occult tubal primary lesions, must be rigorously excluded. As such, SEE-FIM is required in these cases.

Endometrioid Adenocarcinoma

Until recently, specific diagnostic criteria for primary endocervical endometrioid adenocarcinoma were lacking in the literature, leading to great variability in the reporting of its frequency with some authors suggesting that it is quite rare,\(^7^8\) while others suggested that it was one of the more common subtypes.\(^7^9\) Because of the lack of well-defined criteria for the endometrioid variant of endocervical adenocarcinoma, there are conflicting data regarding prevalence and association with HPV. In 2018, the IECC included specific diagnostic criteria for endocervical endometrioid adenocarcinoma.\(^8^0\) The group showed that when using WHO criteria, a large percentage of tumors in their cohort would have been diagnosed as endometrioid adenocarcinoma; however, when strict evaluation for HPV-related features was conducted, only a small minority (3 of 371, 1.1%) actually fell into this category. These 3 tumors were found to be negative for HPV by in situ hybridization. The IECC used “confirmatory endometrioid features” to make the diagnosis, that is, at least focally identified low-grade endometrioid glands lined by columnar cells, pseudostratified nuclei demonstrating no more than moderate atypia, squamous differentiation, and/or the presence of endometriosis. HPV-associated adenocarcinoma features were lacking. Of note, there have been reports of endometrioid adenocarcinoma arising in cervical endometriosis.\(^8^1\) Overall, endocervical endometrioid adenocarcinoma should not be reflexively diagnosed when evaluating a mucin-poor adenocarcinoma arising in the endocervix, as the other tumors in the differential diagnoses are much more likely, including UEA, mesonephric carcinoma, and endometrial endometrioid adenocarcinoma extending into the cervix (Figure 9, A and B).
Adenocarcinoma, NOS

According to the IECC, this designation should be used when a tumor cannot be classified by either WHO or IECC criteria. In the IECC study, 2.4% of the studied cases were classified by consensus review as adenocarcinoma, NOS. HPV in situ hybridization and p16 results indicate that both HPV-related and non–HPV-related tumors may fall into this category.

Table 2. Summary of Important Points for Human Papillomavirus (HPV)–Associated and Non–HPV-Associated Endocervical Adenocarcinomas

<table>
<thead>
<tr>
<th>HPV-Associated Endocervical Adenocarcinomas</th>
<th>Non–HPV-Associated Endocervical Adenocarcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easily identifiable apical mitotic figures and apoptotic bodies; subclassified by cytoplasmic features</td>
<td>Lacking easily identifiable apical mitotic figures or apoptotic bodies; subclassified by previously established criteria</td>
</tr>
<tr>
<td><strong>Usual type</strong></td>
<td><strong>Gastric type</strong></td>
</tr>
<tr>
<td>Most common subtype</td>
<td>Second most common subtype</td>
</tr>
<tr>
<td>Most cases are stage I</td>
<td>Adenoma malignum included in the spectrum</td>
</tr>
<tr>
<td>Positive for p16, CEA, and HPV ISH</td>
<td>Aggressive, with metastases to unusual sites</td>
</tr>
<tr>
<td>Usually negative for vimentin, ER, and PR, though there can be considerable expression in some cases</td>
<td>Knowledge of precursor lesions is evolving</td>
</tr>
<tr>
<td><strong>Mucinous, NOS</strong></td>
<td><strong>Mesonephric carcinoma</strong></td>
</tr>
<tr>
<td>&gt;50% of tumor cells with evident intracytoplasmic mucin</td>
<td>Rare neoplasm of Wolffian duct origin</td>
</tr>
<tr>
<td>Immunophenotype as per usual type</td>
<td>Positive for PAX8, GATA3, and HNF1-β</td>
</tr>
<tr>
<td><strong>Mucinous, intestinal type</strong></td>
<td><strong>KRAS, NRAS, and chromatin-remodeling gene mutations as well as copy number gains and losses</strong></td>
</tr>
<tr>
<td>50% goblet cells in a background of usual type morphology</td>
<td><strong>Clear cell carcinoma</strong></td>
</tr>
<tr>
<td>May show at least focal enteric immunophenotype</td>
<td>DES-associated and non–DES-associated cases</td>
</tr>
<tr>
<td><strong>Mucinous, signet ring cell type</strong></td>
<td><strong>Bimodal age distribution</strong></td>
</tr>
<tr>
<td>Rarely exists in pure form, often admixed with usual type</td>
<td>Architecture and immunophenotype as in ovary</td>
</tr>
<tr>
<td><strong>Villoglandular type</strong></td>
<td><strong>Microsatellite instability</strong></td>
</tr>
<tr>
<td>Rare, well-differentiated variant of usual type</td>
<td><strong>Serous carcinoma</strong></td>
</tr>
<tr>
<td>Good prognosis</td>
<td>Rare (controversial existence)</td>
</tr>
<tr>
<td><strong>iSMILE</strong></td>
<td>Diligently exclude corpus and tubo-ovarian primary tumors and other mimickers as source</td>
</tr>
<tr>
<td>Recently described entity</td>
<td><strong>Endometrioid adenocarcinoma</strong></td>
</tr>
<tr>
<td>Along with its precursor SMILE, likely represents a marker of phenotypic instability</td>
<td>Rare</td>
</tr>
<tr>
<td>Variety of morphologic patterns</td>
<td>Confirmatory endometrioid features helpful in making the diagnosis</td>
</tr>
<tr>
<td></td>
<td>May arise in endometriosis</td>
</tr>
<tr>
<td></td>
<td>Exclude extension from corpus</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma, NOS</td>
</tr>
<tr>
<td></td>
<td>Used when the tumor cannot be specifically subclassified</td>
</tr>
<tr>
<td></td>
<td>HPV ISH helpful in diagnostically challenging cases</td>
</tr>
</tbody>
</table>

Abbreviations: CEA, carcinoembryonic antigen; DES, diethylstilbestrol; ER, estrogen receptor; HNF1-β, hepatocyte nuclear factor 1 β; ISH, in situ hybridization; iSMILE, invasive stratified mucin-producing carcinoma; NOS, not otherwise specified; PR, progesterone receptor; SMILE, stratified mucin-producing intraepithelial lesion.
CONCLUSIONS

Endocervical adenocarcinomas are a heterogeneous group of tumors, most of which are etiologically related to infection by high-risk HPV. However, it is now evident that a significant proportion of cervical adenocarcinomas are not driven by HPV and in the current era of HPV vaccination, it is likely that the relative incidence of HPV-unassociated tumors will increase. Importantly, endocervical adenocarcinomas can be difficult to recognize during routine cervical cytologic examination and will not be detected by HPV-only screening programs. Available evidence suggests that at least a subset of HPV-unrelated tumors behave aggressively, respond differently to standard chemotherapy regimens, and have different molecular drivers from HPV-associated carcinomas. Classification schemes like the IECC emphasize our current understanding of cervical glandular neoplasia and are supported by p16 and HPV in situ hybridization results. Essential take-home points for the endocervical adenocarcinoma subtypes are summarized in Table 2. Ongoing genomic and outcome studies will continue to further our understanding of this group of neoplasms.

References


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