Updates in HPV-Associated vs HPV-Independent Adenocarcinomas of the Endocervix

Park City Anatomic Pathology Update
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Disclosures

• I have no conflicts of interest to disclose.
Learning Objectives

• WHO Classification of Tumours-Female Genital Tumours (Uterine Cervix): Updates from the 5th Edition

• Utilizing a case-based approach, the following topics will be discussed:

  • HPV-associated adenocarcinomas of the endocervix: Pattern-based assessment of invasive carcinoma (Silva classification)
  
  • HPV-independent adenocarcinomas of the endocervix
    • International Endocervical Adenocarcinoma Criteria and Classification (IECC)
    • Proposed algorithmic workup
WHO Classification Update
WHO Classification of Tumours of Female Reproductive Organs (4th Ed.): Uterine Cervix

- Epithelial tumors
  - Squamous cell tumors and precursors (Squamous intraepithelial lesions (SILs), Squamous cell carcinoma (SCC) NOS, benign squamous lesions)
  - Glandular tumors and precursors (Adenocarcinoma in situ, Adenocarcinoma [usual type and variants])
  - Benign glandular tumors and tumor-like lesions
  - Other epithelial tumors (Adenosquamous carcinoma and other uncommon variants)
  - Neuroendocrine tumors (low-grade neuroendocrine tumor, high-grade neuroendocrine carcinoma)

- Mesenchymal tumors and tumor-like lesions
  - Benign (leiomyoma, rhabdomyoma, etc.)
  - Malignant (Leiomyosarcoma, rhabdomyosarcoma, alveolar soft part sarcoma, etc.)
  - Tumor-like lesions (Postoperative spindle-cell nodule, lymphoma-like lesion)

- Mixed epithelial and mesenchymal tumors
  - Adenomyoma, adenosarcoma, carcinosarcoma

- Melanocytic tumors
- Germ cell tumors
- Lymphoid and myeloid tumors
- Secondary tumors
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WHO Classification of Tumours-Female Genital Tumours (October 2020)

(5th Ed.): Uterine Cervix

• Squamous epithelial tumors
  • Mimics of squamous precursor lesions
  • Squamous cell tumors and precursors

• Glandular tumors and precursors
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  • Adenocarcinomas
  • Other epithelial tumors

• Mixed epithelial and mesenchymal tumors
  • Adenomyoma, adenosarcoma, carcinosarcoma

• Germ cell tumors

Differences from prior edition - major highlights

• Recognition of HPV-independent squamous cell carcinomas
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- Recognition of HPV-independent adenocarcinomas (clear cell, mesonephric, gastric-type, endometrioid carcinomas)
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• Recognition of HPV-independent squamous cell carcinomas and adenocarcinomas

• Recognition of HPV-independent adenocarcinomas (clear cell, mesonephric, gastric-type, endometrioid carcinomas)

• Staging updated to FIGO 2018 system
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• Neuroendocrine, hematolymphoid, mesenchymal, melanocytic and metastatic tumors are discussed in separate chapters
HPV-Associated Endocervical Adenocarcinomas
Case 1

• 63-year-old female initially presented with “Atypical glandular cells” on a screening Pap smear
• HPV status was not provided; a prior endocervical and endometrial biopsy showed “at least adenocarcinoma in situ”
• The patient underwent a cold knife conization
Case 1

- The sections showed invasive adenocarcinoma, 0.8 cm greatest dimension, with one focus of conventional stromal invasion measuring up to 0.35 cm depth of invasion, transected at the endocervical margin.

- The patient subsequently underwent a radical hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection; gross findings included a 2.4 cm mass centered in the cervix.
Radical hysterectomy:

- Invasive endocervical adenocarcinoma, usual type (HPV-associated)
- 2.4 cm in greatest dimension
- 0.4 cm depth of invasion
- Lymphovascular invasion present
- Negative margins, negative lymph nodes
- Stage pT1b2 (FIGO IB2)
Cervical Invasive Carcinoma: Revised FIGO Staging (2018):

1. Stage IA: lateral extension measurement removed
2. Stage IB divided into 3 subgroups
   • IB1: stromal invasion > 5 mm and < 2 cm greatest dimension
   • IB2: invasive carcinoma > 2 cm and < 4 cm greatest dimension
   • IB3: size > 4 cm greatest dimension
3. Imaging or pathology acceptable for evaluating retroperitoneal lymph nodes; if positive:
   • IIIC1: Positive pelvic lymph nodes
   • IIIC2: Positive paraaortic lymph nodes
Cervical Invasive Carcinoma - Revised FIGO Staging (2018), Fertility-Sparing Considerations:

1. Stage IA: lateral extension measurement removed
   - IA1: stromal invasion ≤ 3 mm in depth (CKC, LEEP)
   - IA2: stromal invasion > 3 mm and ≤ 5 mm in depth

2. Stage IB divided into 3 subgroups
   - IB1: stromal invasion > 5 mm and ≤ 2 cm in greatest dimension
   - IB2: invasive carcinoma > 2 and ≤ 4 cm in greatest dimension
   - IB3: invasive carcinoma > 4 cm

*For stage IB tumors treated with hysterectomy, additional factors such as size, LVI and stromal invasion may influence decision for additional adjuvant treatment
Problematic Growth Patterns in Assessment of Invasion

• Exophytic tumors (measure tumor thickness)
• Extensive adenocarcinoma in situ (AIS)
• Multifocal dispersed foci of superficial invasion in extensive AIS
Pattern-Based Classification of HPV-Associated Endocervical Adenocarcinoma: The Silva Classification

Pattern A: Non-destructive invasion

- Well demarcated glands with rounded contours
- Complex intraglandular growth permissible
- Relationship to large cervical vessels or depth of extension irrelevant
- No lymphovascular invasion
- Lack of solid growth, single cell infiltration or destructive stromal invasion
- Architecturally well to moderately differentiated, no high-grade cytology
Pattern-Based Classification of HPV-Associated Endocervical Adenocarcinoma: The Silva Classification

**Pattern B: Early/focally destructive invasion**

- Single cell or small group stromal invasion arising from well-demarcated glands
- Foci may be single, multiple or linear at base of tumor
- With or without lymphovascular invasion
- No solid growth (architecturally well to moderately differentiated)

WHO Classification of Tumors, Female Genital Tract, 5th ed., 2020; Diaz De Vivar et al., 2013
Pattern-Based Classification of HPV-Associated Endocervical Adenocarcinoma: The Silva Classification

Pattern C: Diffuse destructive invasion

• Diffusely infiltrative glands and/or extensive destructive invasion
• Associated desmoplastic response
• Confluent growth filling a 4x field (5 mm): glands, papillae or mucin lakes
• Solid growth pattern (architecturally poorly differentiated)
• With or without lymphovascular invasion

WHO Classification of Tumors, Female Genital Tract, 5th ed., 2020; Diaz De Vivar et al., 2013
Utility of the Pattern-Based Classification of Invasive Endocervical Adenocarcinoma

In a multi-institutional study of > 350 cases of HPV-associated invasive endocervical adenocarcinoma treated with excision and lymphadenectomy (at least 1 node excised), mean follow-up time of 52.8 months:

<table>
<thead>
<tr>
<th>Pattern</th>
<th>N (%)</th>
<th>DOI (x mm)</th>
<th>DOI &gt; 5 mm</th>
<th>LVI</th>
<th>Pts with LN met</th>
<th>Recurrences</th>
<th>DOD</th>
<th>Stage I</th>
<th>Stage II-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>352 (100%)</td>
<td>6.7</td>
<td></td>
<td></td>
<td>49 (13.9%)</td>
<td>39 (11.4%)</td>
<td>16 (4.6%)</td>
<td>311 (88.3%)</td>
<td>41 (11.7%)</td>
</tr>
<tr>
<td>A</td>
<td>73 (20.7%)</td>
<td>3.8</td>
<td>20 (27.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>73 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>B</td>
<td>90 (25.6%)</td>
<td>4.0</td>
<td>21 (23.3%)</td>
<td>24 (26.6%)</td>
<td>4 (4.4%)</td>
<td>1 (1.2%)</td>
<td>0 (0%)</td>
<td>86 (95.6%)</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>C</td>
<td>189 (53.7%)</td>
<td>9.2</td>
<td>140 (74.1%)</td>
<td>117 (61.9%)</td>
<td>45 (23.8%)</td>
<td>38 (22.1%)</td>
<td>16 (8.8%)</td>
<td>152 (80.4%)</td>
<td>37 (19.6%)</td>
</tr>
</tbody>
</table>

Diaz De Vivar et al., Int J Gynecol Pathol 2013; Roma et al. AJSP 2015
Case 2

- 56-year-old female initially presented with “Atypical glandular cells, favor neoplastic” on a screening Pap smear and abnormal pelvic exam
- HPV status was not provided and no prior biopsy was available for review
- A radical hysterectomy specimen was received which grossly showed a 3.3 cm mass in the endocervical canal extending to the lower uterine segment
Etiology of HPV Infection and p16 Immunohistochemistry

**Productive infection**

- E2
- E7
- E6

E2 regulates the expression of HPV oncoproteins E6 and E7 in low grade lesions that support episomal replication.

**HPV Integration (loss of E2)**

- E7
- Rb

Loss of E2 allows for upregulation of E6 and E7, resulting in cell cycle activation and progression to high grade dysplasia and cancer.

- p16

- p53

Thomison et al., Hum Pathol 2008
Histologic Features of HPV-Associated Lesions

- HPV 18, 16
- HPV 16, 18

Invasive squamous cell carcinoma (~70%)  
Invasive endocervical adenocarcinoma (10-25%)  
Adenocarcinoma in situ

Cytohistologic features of HPV-associated epithelial atypia in cervical lesions
Histologic Subtypes of HPV-Associated Endocervical Adenocarcinoma

• Usual type (70%), including villoglandular variant
• Mucinous type (10%; intracytoplasmic mucin in >50% of tumor)
  • Mucinous adenocarcinoma NOS
  • Intestinal
  • Signet-ring cell
  • Stratified mucin-producing carcinoma

WHO Classification of Tumors, Female Genital Tract, 5th ed., 2020
Typical Differential Diagnosis of Atypical Glandular Proliferations: Benign Mimics (mucin-poor)

- Tubal/tuboendometrioid metaplasia
- Endometriosis
- Microglandular hyperplasia
Typical Differential Diagnosis of Atypical Glandular Proliferations: Secondary Malignancies

- Metastatic endometrioid carcinoma
- Metastatic serous carcinoma
- Metastatic colorectal carcinoma
### Typical Differential Diagnosis of Atypical Glandular Proliferations: Secondary Malignancies

<table>
<thead>
<tr>
<th>Stains</th>
<th>Primary endocervical adenocarcinoma</th>
<th>Metastatic endometrioid carcinoma</th>
<th>Metastatic serous carcinoma</th>
<th>Metastatic colorectal carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16</td>
<td>Positive (strong, diffuse)</td>
<td>Negative or patchy positive</td>
<td>Positive (strong, diffuse***)</td>
<td>Negative</td>
</tr>
<tr>
<td>CEA</td>
<td>Positive</td>
<td>Negative</td>
<td>Typically negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>Typically negative</td>
<td>Positive or negative (grade dependent)</td>
<td>Positive or negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Other studies</td>
<td>HR HPV ISH positive</td>
<td>p53: wild type expression pattern (grade dependent)</td>
<td>p53: completely negative (null) or strongly positive</td>
<td>CK20, CDX2, positive (strong, diffuse), PAX8, ER negative</td>
</tr>
</tbody>
</table>

***Beware strong diffuse p16 positivity in a high grade carcinoma, could represent metastatic serous carcinoma (non-HPV-associated pathway)***
Case 1&2 - HPV-Associated Endocervical Adenocarcinoma: Take Home Points

• The pattern-based classification of HPV-associated invasive endocervical adenocarcinoma is prognostically relevant
• HPV-associated lesions are associated with characteristic cytomorphologic features
• The differential diagnosis of atypical glandular proliferations of the endocervix includes both benign and malignant (primary and secondary gynecologic and extra-gynecologic) entities
• Ancillary testing is helpful in the appropriate morphological context
Case 3

- 47-year-old female presented with copious mucoid vaginal discharge and abdominal pain
- Imaging workup disclosed a cervical mass, ascites and peritoneal nodules
- The patient underwent an exam under anesthesia with hysteroscopy and diagnostic laparoscopy
- Clinical findings included a cervical mass, pelvic sidewall and peritoneal nodularity
- Cervical and peritoneal biopsies were obtained
Case 3

- IHC panel applied:
  - CK7, PAX8: positive (strong, diffuse)
  - CK20, p16: positive (focal, weak)
  - ER, PR: negative
  - p53: positive, patchy (wild-type pattern)
  - HR HPV ISH: negative

- Additional studies: radiologically, no gastrointestinal mass or other dominant primary site identified
Gastric-type Primary Endocervical Adenocarcinoma

- HPV-independent
- Can be seen in Peutz-Jeghers syndrome
- Postulated to arise from atypical lobular endocervical glandular hyperplasia and gastric-type adenocarcinoma in situ
- Intracellular neutral mucin with absence of HPV-associated cytologic features
- Morphology varies from bland, very well-differentiated features (formerly adenoma malignum or minimal deviation adenocarcinoma) to cytoarchitecturally conventional high-grade adenocarcinoma
- Typically positive for PAX8, CK7, and CEA and negative for ER, PR and p16
- Aggressive tumors with higher propensity for destructive invasion, advanced stage at presentation compared with HPV-associated tumors
HPV-Independent Endocervical Adenocarcinomas
# Primary Endocervical Adenocarcinomas

### Gastric-type adenocarcinoma
- No HPV associated atypia
- PAX8 positive, ER negative

### Clear cell carcinoma
- Tubulocystic, papillary, solid patterns
- HNF1-beta, Napsin-A positive

### Mesonephric adenocarcinoma
- Lateral wall location when small
- GATA-3 positive

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**International Endocervical Adenocarcinoma and Criteria System**

- **HPVA (HPV Associated)**
  - Apical mitotic figures and apoptotic bodies at scanning magnification
  - If features not seen at scanning, cursory exam at 200x to detect additional cases

- **NHPVA (Non-HPV Associated)**
  - No easily identifiable mitotic activity and apoptotic bodies at scanning magnification
  - Focal or equivocal HPVA features at 200x – limited HPV, tentatively classified as NHPVA

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Park, KJ. Histopathol 2020
Primary Endocervical Clear Cell Carcinoma

- HPV-independent
- Two presentations: DES-associated (ectocervical); sporadic (endocervical)
- Tubulocystic, papillary, solid growth patterns
- Typically positive for HNF-1\(\beta\) and Napsin A (sensitive but not specific), and negative for ER and GATA3
- Likely better overall survival and lower recurrence rate in lower stage disease; lymph node status is important predictor of overall survival and recurrence
Mesonephric Adenocarcinoma

- HPV-independent
- Arise from mesonephric remnants in the lateral cervical wall
- Tubular growth pattern with PAS- and mucicarmine-positive eosinophilic luminal secretions
- Typically positive for PAX8 and GATA3, and negative for ER and Napsin A
- Very rare entity; about 1/3 of cases have been reported to recur, often after extended periods
Typical Differential Diagnosis of Atypical Glandular Proliferations: Benign Mimics (Non-mucinous)

- Tubal/tuboendometrioid metaplasia
- Tunnel clusters
- Microglandular hyperplasia
- Mesonephric remnants/hyperplasia
- Arias-Stella Reaction
Typical Differential Diagnosis of Atypical Glandular Proliferations: Benign Mimics (Mucinous)

Also:
• Lobular endocervical glandular hyperplasia
• Diffuse laminar endocervical hyperplasia
### Typical Differential Diagnosis of Atypical Glandular Proliferations: Secondary Malignancies (Mucinous)

<table>
<thead>
<tr>
<th>Stains</th>
<th>Primary endocervical adenocarcinoma, gastric-type</th>
<th>Metastatic endometrial endometrioid carcinoma with mucinous features</th>
<th>Metastatic gastric (or other GI) adenocarcinoma</th>
<th>Metastatic mammary lobular carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX8</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>ER</td>
<td>Negative</td>
<td>Positive (grade dependent)</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>CK7, CK20</td>
<td>Positive/negative</td>
<td>Positive/negative</td>
<td>Positive/positive or negative</td>
<td>Positive/negative</td>
</tr>
<tr>
<td>GATA3</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Other helpful findings</td>
<td>No uterine mass; no other known primary</td>
<td>Dominant uterine mass</td>
<td>Known primary</td>
<td>Known primary; targetoid inclusions</td>
</tr>
</tbody>
</table>

**Other helpful findings:**

- No uterine mass; no other known primary
- Dominant uterine mass
- Known primary
- Known primary; targetoid inclusions
Proposed Diagnostic Algorithm for Primary HPV-Independent Endocervical Adenocarcinoma

Stolnicu et al. AJSP 2018 42:989-1000
Case 3 – HPV-Independent Endocervical Adenocarcinoma: Take Home Points

• Non-HPV-associated endocervical adenocarcinomas include gastric-type, clear cell and mesonephric adenocarcinomas

• Distinction between gastric-type adenocarcinomas of the endocervix and metastatic adenocarcinomas of gastrointestinal origin can be challenging

• Judicious use of ancillary testing including HR HPV ISH will often assist in clarifying the diagnosis
Case 4

- Cervical biopsy in a 64-year-old female presenting with postmenopausal bleeding.

- IHC panel applied:
  - p16: positive (strong, diffuse)
  - CEA: positive (focal)
  - Estrogen: negative
  - Vimentin: negative
Case 4

- The patient was lost to follow-up and returned with marked anemia due to severe vaginal bleeding.
- She underwent a radical hysterectomy showing a deeply invasive dominant uterine mass extending into the cervix.
- IHC panel applied:
  - P16: positive (strong, diffuse)
  - CEA: positive (strong, diffuse)
  - P53: aberrant (strong, diffuse)
  - HR HPV ISH: Negative
# Endometrial Adenocarcinoma

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55-65 years</td>
<td>65-75 years</td>
</tr>
<tr>
<td>Clinical setting</td>
<td>Unopposed estrogen, obesity</td>
<td>Atrophy</td>
</tr>
<tr>
<td>Background endometrium</td>
<td>Hyperplastic</td>
<td>Atrophic</td>
</tr>
<tr>
<td>Tumor characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Histology</td>
<td>Endometrioid</td>
<td>Serous, clear cell, others</td>
</tr>
<tr>
<td>• Grade</td>
<td>1, 2&gt;3</td>
<td>3</td>
</tr>
<tr>
<td>• Depth of myometrial invasion</td>
<td>Often superficial</td>
<td>Deep</td>
</tr>
<tr>
<td>• Nodal involvement</td>
<td>Dependent on extent of invasion</td>
<td>Frequent</td>
</tr>
<tr>
<td>Stage</td>
<td>Typically early</td>
<td>Frequently advanced</td>
</tr>
<tr>
<td>Precursor lesion</td>
<td>Endometrial intraepithelial neoplasia/atypical hyperplasia</td>
<td>Serous endometrial intraepithelial carcinoma</td>
</tr>
<tr>
<td>Genetic basis</td>
<td>PTEN, ARID1A, PIK3CA, etc.</td>
<td>TP53, PIK3CA, PPP2R1A, etc.</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Favorable</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>

Adapted from Robbins and Cotran, 10th ed.
## Endometrial Adenocarcinoma

### Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Wild-type (can be aberrant in subset of grade 3 tumors)</th>
<th>Null or strongly positive</th>
<th>Typically wild-type</th>
<th>Wild-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>Wild-type</td>
<td>Null or strongly positive</td>
<td>Typically wild-type</td>
<td>Wild-type</td>
</tr>
<tr>
<td>ER</td>
<td>Positive</td>
<td>Positive or negative</td>
<td>Typically negative</td>
<td>Negative</td>
</tr>
<tr>
<td>p16</td>
<td>Positive (focal)</td>
<td>Positive (diffuse and strong)</td>
<td>Positive (focal)</td>
<td></td>
</tr>
</tbody>
</table>

### Genetic markers

- PTEN, ARID1A, PIK3CA, CTNNB1, TP53 (subset), POLE ultramutation
- TP53, PIK3CA, PPP2R1A, FBXW7, ERRB2 (HER2) amplification (30%)
- TP53, PPP2R1A, PIK3CA, PIK3R1, KRAS, ARID1A, SPOP

### Other helpful findings

- Often associated with EIN/AEH, metaplasias (mucinous, squamous)
- Can be superficial or involve an endometrial polyp, typically WT-1 negative
- Napsin-A, HNF1-beta positive
- Dedifferentiated carcinoma: grade 1 or 2 endometrioid component; both keratin positive

## Endocervical vs. endometrial adenocarcinoma: Classification in biopsies matters!

<table>
<thead>
<tr>
<th>Studies</th>
<th>Endocervical adenocarcinoma</th>
<th>Endometrial endometrioid carcinoma (type I)</th>
<th>Endometrial serous carcinoma (type II)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td>Cold knife cone, trachectomy, radical hysterectomy</td>
<td>Total hysterectomy with potential intraoperative frozen section evaluation</td>
<td>Total hysterectomy</td>
</tr>
<tr>
<td><strong>Lymph node sampling</strong></td>
<td>Dependent on tumor stage</td>
<td>Dependent on depth of myoinvasion or sentinel lymph node biopsy if gr 1-2</td>
<td>Regional lymph node sampling</td>
</tr>
<tr>
<td><strong>Systemic/radiation therapy</strong></td>
<td>Dependent on tumor stage</td>
<td>Dependent on stage and presence/extent of LVSİ</td>
<td>Dependent on stage; platinum-based regimens</td>
</tr>
</tbody>
</table>
Case 4 – Endometrial Adenocarcinoma: Take Home Points

• Distinction between primary endocervical and endometrial carcinomas is crucial from a clinical perspective and histologic assessment can be challenging
• While p16 is a surrogate marker of HPV infection, it can be strongly expressed in high grade endometrial carcinomas via a non-HPV-associated pathway
• Ancillary testing such as HR HPV ISH is definitive but not always available
• Ultimately the decision to apply ancillary testing must be anchored in histomorphology (HPV-associated cellular features, high grade vs. low grade cytology)
• Use of panels is strongly recommended