Endocervical Adenocarcinoma
Challenges in Classification, Differential Diagnosis and Reporting

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Pathology Department

Outline of Talk

- Treatment Decisions for Endocervical Adenocarcinoma
- New 2014 WHO Classification system
- Update on Mucinous Adenocarcinoma variants
- Common Problems in Usual type Endocervical Adenocarcinoma

General Treatment Decisions for Adenocarcinoma of Cervix

- If specimen is a biopsy and tumor is not clinically visible:
  Cone procedure, regardless of AIS, early or deep invasion
- If specimen is a biopsy and tumor is clinically visible:
  Hysterectomy / radiation

- If specimen is a cone:
  
  Key Factors
  - Desire for fertility preservation
  - In situ versus invasive adenocarcinoma
  - Early versus >Early stromal invasion
    - Depth, horizontal spread
  - Lymphovascular invasion
  - Margin status

  Less Critical Factors
  - Histologic subtype of adenocarcinoma
  - Tumor grade
**General Treatment Decisions for Adenocarcinoma of Cervix**

If specimen is a cone:

<table>
<thead>
<tr>
<th>Invasion</th>
<th>Margins</th>
<th>LVI</th>
<th>Fertility</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>Negative</td>
<td>No</td>
<td>Yes</td>
<td>Observation, repeat Pap/ECC</td>
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<tr>
<td></td>
<td>Positive</td>
<td>No</td>
<td>Yes</td>
<td>Repeat cone</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>No</td>
<td>No</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Early</td>
<td>Negative</td>
<td>No</td>
<td>Yes</td>
<td>Observation, repeat Pap/ECC</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>No</td>
<td>No</td>
<td>Repeat cone</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>No</td>
<td>No</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>&gt;Early</td>
<td>Negative</td>
<td>No</td>
<td>Yes</td>
<td>Trachelectomy</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>No</td>
<td>No</td>
<td>Radical trachelectomy / nodes</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>No</td>
<td>Yes</td>
<td>Radical hysterectomy / nodes</td>
</tr>
</tbody>
</table>

Positive margins preclude definitive diagnosis of “early” invasion

**What is the definition of “early invasive” adenocarcinoma?**

Different definitions exist:

- **FIGO/AJCC IA1, pT1a1**
  - Depth <3 mm and spread <7 mm

- **IA2, pT1a2**
  - Depth 3 to 5 mm and spread <7 mm

- **SGO microinvasion**
  - Depth <3 mm and NO LVI

Positive margins preclude definitive diagnosis of “early” invasion

**UCSF Pathology Report Template**

- Invasive tumor type
- Invasive tumor grade
- Depth of invasion (mm)
- Horizontal spread of invasion (mm)
- LVI
- Margin for invasive tumor
- Margin for in situ tumor
- Margin for HSIL
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What has changed?

Eliminated as a distinct tumor “type”
  - Glandular dysplasia
  - Early invasive adenocarcinoma (a tumor stage, not a type)

Elevated to a distinct tumor “type”
  - Villoglandular type
  - Usual type

Re-classified within a larger “type”
  - Minimal deviation type = form of gastric type mucinous adenocarcinoma

Evolving understanding of “Mucinous” adenocarcinoma types

- Not commonly associated with high risk HPV
- Often cytologically bland
- No adenocarcinoma in situ of usual type
- Uncertain precursor lesion (? Atypical LEGH)
- Often p16 negative / patchy
- Worse prognosis
- Risk for Peutz Jeghers syndrome
Evolving understanding of “Mucinous” adenocarcinoma types

Screening Challenges
- High risk HPV testing may not be effective
- Precursors may be difficult to recognize in Pap test

Diagnostic Challenges
- Difficult to distinguish from benign proliferations
- Difficult to distinguish from metastasis of primary GI tumors

Treatment Challenges
- Should more aggressive or different options be considered

Genetic Counseling
- Which patients to evaluate for risk for Peutz Jeghers syndrome?

Prevention Challenges
- HPV vaccination may not be effective for these types

2014 WHO Classification of Adenocarcinoma of Cervix

Tumor Grading
- WHO does not provide specific criteria
- FIGO / AJCC does not provide specific criteria
  
  Mentions option of well / moderate / poorly differentiated

- Practical approach:
  1. Apply FIGO criteria of endometrial adenocarcinoma
  2. Certain histologies are tied to grade:
    - Villoglandular type = well differentiated
    - Minimal deviation type = well differentiated
    - Serous carcinoma = high grade

Tumor Staging
- WHO advocates FIGO / AJCC staging criteria
- New 2014 edition of FIGO staging: NO changes

Endocervical adenocarcinoma in situ, usual type
Endocervical adenocarcinoma, usual type
Mucinous carcinoma
  - NOS type
  - Gastric type (including minimal deviation type)
  - Intestinal type
  - Signet ring cell type
Villoglandular carcinoma
  - Endometrioid carcinoma
  - Clear cell carcinoma
  - Serous carcinoma
  - Mesonephric carcinoma
  - Adenocarcinoma admixed with neuroendocrine carcinoma
2014 WHO Classification of Adenocarcinoma of Cervix

Prognosis

- Mostly dependent on FIGO stage
  
<table>
<thead>
<tr>
<th>Stage</th>
<th>5 y survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>100 %</td>
</tr>
<tr>
<td>IA2</td>
<td>93 %</td>
</tr>
<tr>
<td>IB1</td>
<td>89 %</td>
</tr>
<tr>
<td>IB2</td>
<td>83 %</td>
</tr>
<tr>
<td>II</td>
<td>49 %</td>
</tr>
<tr>
<td>III</td>
<td>34 %</td>
</tr>
<tr>
<td>IV</td>
<td>3 %</td>
</tr>
</tbody>
</table>

- Worse than Usual type Adenocarcinoma
  
  Gastric type
  Adenocarcinoma with neuroendocrine carcinoma
  Serous carcinoma

- Better than Usual type Adenocarcinoma
  
  Villoglandular type

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What is meant by “mucinous”? 

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Mucins</th>
<th>H&amp;E</th>
<th>Stains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal endocervix</td>
<td>acid mucin</td>
<td>blue-grey</td>
<td></td>
</tr>
<tr>
<td></td>
<td>neutral mucin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual type Adenocarcinoma</td>
<td>mucin depleted</td>
<td>minimal</td>
<td>eosinophilic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric type Adenocarcinoma</td>
<td>neutral mucin</td>
<td>clear / pale</td>
<td>MUC6</td>
</tr>
<tr>
<td></td>
<td>(pyloric mucin)</td>
<td>eosinophilic</td>
<td>HIK1083</td>
</tr>
<tr>
<td>Intestinal type</td>
<td>intestinal mucin</td>
<td>goblet cells</td>
<td>CDX2</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal Endocervix

Usual Type Adenocarcinoma
Gastric differentiation / Pyloric metaplasia

- Pyloric Glands of Stomach
- Pyloric Mucin: HIK1083, MUC6

![Image showing Pyloric Glands of Stomach and Pyloric Mucin](image)

Courtesy Kay Park MD

Intestinal Differentiation

- CDX2

Mucinous Adenocarcinomas of the Cervix

- Mucinous carcinoma, gastric type
  - Minimal deviation type
  - Gastric type
- Mucinous carcinoma, intestinal type
- Mucinous carcinoma, signet ring cell type

Gastric type Adenocarcinoma of Cervix

Definition:

- Tumor cells with abundant clear to eosinophilic cytoplasm
- Distinct cell membranes
- Pyloric gland mucin markers (MUC6, HIK1083)
- Well-differentiated = Minimal deviation type ("adenoma malignum")
- All other grades = Gastric type

Epidemiology:

- In Japan, this is up to 25% of cervical adenocarcinomas
- Usually not associated with high risk HPV
- Some patients have Peutz Jeghers syndrome (STK11 mutation)
- Worse prognosis than usual type adenocarcinoma
**Gastric type Adenocarcinoma of Cervix**

**Microscopic features:**
- Simple glands that are irregularly dilated
- Haphazard growth in stroma
- Minimal to no desmoplastic stroma
- Abundant clear to eosinophilic cytoplasm
- Distinct cell membranes

**Immunohistochemistry:**
- P16: often negative or patchy positive
- CK7: positive
- CK20: negative or focal positive
- p53: can be positive
- ER: negative.

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**Gastric type Mucinous Adenocarcinoma of Cervix**

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**Gastric type Mucinous Adenocarcinoma of Cervix**

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**Gastric type Mucinous Adenocarcinoma of Cervix**
Gastric type Mucinous Adenocarcinoma of Cervix

Minimal Deviation Type Adenocarcinoma of Cervix

Minimal Deviation Type Adenocarcinoma of Cervix

Mostly well differentiated

Focal atypia

Courtesy Kay Park MD
Minimal Deviation Type Adenocarcinoma of Cervix
Oddly angled simple glands
Focal desmoplastic stroma

Gastric type Adenocarcinoma of Cervix
Precursor lesion:
- Not usual type AIS
- ? Atypical Lobular Endocervical Glandular Hyperplasia (LEGH)

LEGH
- Rare, benign proliferation of endocervical glands with gastric differentiation
- Asymptomatic incidental finding or watery discharge
- 3rd to 7th decade
- Gross: circumscribed collection of cysts near the os
- Well demarcated proliferation of glands centered around a central duct.
- Abundant clear to eosinophilic cytoplasm
- Bland nuclei

Lobular Endocervical Glandular Hyperplasia

Lobular Endocervical Glandular Hyperplasia

Courtesy of Glenn McCluggage MD

Courtesy of Glenn McCluggage MD
**Gastric type Adenocarcinoma of Cervix**

**Pathogenesis**

- **LEGH**
  - Atypical LEGH
  - Minimal deviation type Adenocarcinoma
  - Gastric Metaplasia
  - Gastric AIS

**Intestinal type Adenocarcinoma of Cervix**

**Definition:**
- Goblet cells in adenocarcinoma

**Epidemiology:**
- Slightly older age (4th decade) compared to usual type (3rd decade)
- About 1/3 not associated with high risk HPV

**Microscopic findings:**
- Same as for usual type except goblet cells are present
- p16: most are diffuse/strong positive; some not
- MIB1: most are patchy; some are diffuse
- CDX2: positive
- CK20: negative or focal

**Intestinal type endocervical adenocarcinoma**
Intestinal type endocervical adenocarcinoma

Intestinal type Adenocarcinoma of Cervix

Differential diagnosis:

- Metastasis from a primary intestinal adenocarcinoma
  - CDX2: not helpful
  - P16: not helpful
  - CK20: positive (strong/diffuse) in colonic cancer
  - CK7: can be positive in some colon / gastric / pancreaticobiliary
  - PAX8: needs further study of sensitivity in mucinous cervical adenocarcinoma

Signet ring cells
Intracytoplasmic mucin

Signet ring cells
Intracytoplasmic mucin

CK 7  CK 20  CDX 2, p16
Metastatic Gastric Carcinoma to Endocervix

Metastatic Colon Cancer to Cervix

CK7, PAX8

CDX2
Ovarian Metastasis of Endocervical Adenocarcinoma

A Potential Diagnostic Pitfall

- May occur even if only AIS or early invasive cancer
- May occur with well differentiated mucinous types
  - May negative for hr HPV
  - May be p16 negative
  - May be PAX8 negative
  - May be CDX2 positive
- Mimics
  - Primary mucinous borderline tumor / carcinoma
  - Metastatic GI-pancreaticobiliary cancer
Ovarian Metastasis of Endocervical Adenocarcinoma

Mimics of Ovarian Mucinous Borderline Tumor / Carcinoma

- Low grade appendiceal mucinous neoplasm
- Colorectal carcinoma
- Gastric carcinoma
- Pancreatobiliary adenocarcinoma
  
  **Endocervical Adenocarcinoma**

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Common Problems in Usual type Endocervical Adenocarcinoma

Common Problems with Usual type Endocervical Adenocarcinoma

**Common Problems**

- Benign glandular lesions versus AIS
- AIS versus early invasive adenocarcinoma
- Measuring invasive adenocarcinoma for staging purposes
- Endocervical versus endometrial primary origin of adenocarcinoma

**Less Common Problems**

- Poorly differentiated adenocarcinoma versus serous carcinoma or small cell cancer
- Primary endocervical adenocarcinoma versus metastatic colorectal adenocarcinoma
Benign lesions versus AIS

- Tubal metaplasia
- Endometriosis
- Arias Stella reaction
- HSV / CMV infection
- Radiation atypia
- Tunnel clusters
- Hyperplasias
  - Microglandular hyperplasia
  - Lobular endocervical glandular hyperplasia
  - Diffuse laminar endocervical glandular hyperplasia

Diagnostic Criteria for AIS, usual type

A "constellation" of features should be present

**Common features**
- Cell crowding, stratification
- Enlarged nuclei with variable size/shape
- Hyperchromasia / large nucleoli
- “Floating” mitoses (located in apical cytoplasm)
- Atypical mitoses
- Apoptotic debris

**Less common features**
- P16 diffuse/strong positive
- MIB-1 higher than adjacent normal endocervix
- PAX2 loss of nuclear expression
- Cribriform growth
- Intraglandular tufting, branching, papillary
- Goblet cells

Floating Mitoses

Apoptosis
AIS with stratification (versus HSIL)

Note mucin and apoptosis

Diagnostic Criteria for AIS, usual type

Are mitoses in endocervical glands pathognomonic of AIS?

No.

Rare mitoses (in absence of other abnormalities) can be seen in:

- Normal endocervix
- Endometriosis of cervix
- Hyperplasias

Rare mitotic figure in normal endocervix

Rare mitotic figures in normal endocervix
Are “atypical” nuclei in endocervical glands pathognomonic of AIS?

No.

Abnormal nuclear size/shape (in absence of other abnormalities) can be seen in:

- Radiation atypia
- HSV, CMV infection
- Arias Stella reaction
- Reactive inflammatory changes
Superficial Endometriosis of Cervix
Mitoses, crowding, stratification
Endometrial stroma

Microglandular endocervical hyperplasia

Diagnostic Criteria for AIS, usual type

A “constellation” of features should be present
Common features
- Cell crowding, stratification
- Enlarged nuclei with variable size/shape
- Hyperchromasia / large nucleoli
- “Floating” mitoses (located in apical cytoplasm)
- Atypical mitoses
- Apoptotic debris
- P16 diffuse/strong positive
- MIB-1 higher than adjacent normal endocervix
- PAX2 loss of nuclear expression

Less common features
- Cribriform growth
- Intraglandular tufting, branching, papillary
- Goblet cells
**Diagnostic Criteria for AIS, usual type**

**How to manage abnormalities in between benign and outright AIS?**

**Actions:**
- Deeper levels
- p16, MIB-1, PAX2
- Second observer

**Reporting:**
- “Atypical endocervical glands”; see comment.
- Repeat tissue sample / follow up ECC, Pap test
- “Glandular dysplasia” no longer advocated by WHO

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**Common Problems with Usual type Endocervical Adenocarcinoma**

- Benign glandular lesions versus AIS
- AIS versus early invasive adenocarcinoma
- Measuring invasive adenocarcinoma for staging purposes
- Endocervical versus endometrial primary origin of adenocarcinoma

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**Types of Invasion in Endocervical Adenocarcinoma**

- Destructive stromal invasion
- Expansile invasion

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**Types of Invasive endocervical adenocarcinoma**

- Destructive stromal invasion
  - Jagged contours of malignant glands
  - Desmoplastic stroma
  - Haphazard distribution
  - Deep location
  - Proximity to large, thick walled vessels
Destructive Stromal Invasion

Desmoplastic Stroma
- Reactive fibroblasts
- Edematous matrix
- +/- inflammation

Desmoplastic Stroma

Superficial location but desmoplastic stroma

5/22/2014
Desmoplastic stroma
Detached clusters within stroma

Reactive versus Desmoplastic Stroma

Proximity to Large, Thick-walled Vessels
*Invasive Adenocarcinoma*
Look for LVI Near Large Vessels

Lymph Node Metastasis

Types of Invasion in Endocervical Adenocarcinoma

- Expansile invasion
  - WHO: Architecture too complex compared to normal endocervix
  - Proliferation of small malignant glands
  - Complex tubulo-glandular, papillary formation
  - Pushing growth
  - Features of destructive stromal invasion may not be present
Expansile pattern of Invasive Adenocarcinoma
Expansile pattern of Invasive Adenocarcinoma

*Complex tubular growth*

Expansile pattern of Invasive Adenocarcinoma

*Complex branching growth*

Expansile pattern of Invasive Adenocarcinoma

*Complex cribriform growth*

**Findings at the Cusp between AIS and Invasive cancer**

- Deeper levels of all blocks with AIS
- Also hunt for LVI (strong clue for stromal invasion)
- Second observer
Common Problems with Usual type Endocervical Adenocarcinoma

- Benign glandular lesions versus AIS
- AIS versus early invasive adenocarcinoma
- Measuring invasive adenocarcinoma for staging purposes
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Measuring Invasive Adenocarcinoma

<table>
<thead>
<tr>
<th>FIGO/AJCC Stage</th>
<th>Clinically Visible</th>
<th>Depth of Invasion</th>
<th>Horizontal Spread of Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>No</td>
<td>( \leq 3 \text{ mm} ) and ( \leq 7 \text{ mm} )</td>
<td></td>
</tr>
<tr>
<td>IA2</td>
<td>No</td>
<td>( &gt; 3, \leq 5 \text{ mm} ) and ( \leq 7 \text{ mm} )</td>
<td></td>
</tr>
<tr>
<td>IB1</td>
<td>Yes</td>
<td>any dimension &gt;IA2 and ( \leq 4 \text{ cm} )</td>
<td></td>
</tr>
<tr>
<td>IB2</td>
<td>Yes</td>
<td>any dimension &gt; 4 cm</td>
<td></td>
</tr>
<tr>
<td>II-IV</td>
<td>Yes and spread beyond cervix</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Depth Measurement

Depth of Invasion

- From epithelial/stromal junction of adjacent most superficial papillae
- Use ocular micrometer for tumors under 1 cm
- Consider deeper levels for cases at stage cut-off points
- Difficult scenarios
  - If multiple foci of invasion, report the deepest
  - If margins positive, report as “at least” X mm deep
  - If too fragmented or poorly oriented, report best judgment of the depth and document limitations
How Should Exophytic / Polypoid Tumors Be Measured?

If cervical wall landmarks are not present in biopsy:

- Document that cervical wall is not present
- Discuss possibility that tumor could be either invading the wall or growing as exophytic tumor
No landmarks present. ? Exophytic or stromal invasive ?

Potential Pitfall: Endocervical sampling in elderly patients

Potential Pitfall: Endocervical sampling in elderly patients

p16

p53: High grade uterine serous carcinoma
Measuring Invasive Adenocarcinoma

**Horizontal spread of invasive tumor**

- Maximal distance between peripheral edges of invasive tumor
- Use ocular micrometer for tumors under 1 cm
- Consider deeper levels for cases at stage cut-off points
- No rules are provided for measuring:
  - Multiple contiguous slides with invasion
  - Multiple non-contiguous foci of invasion in a single slide

Horizontal spread likely more than seen on single slide

*Caution advised if near a cut-off between stages*

Horizontal Spread Measurement if non-contiguous foci of invasion

*Use best judgment*
Measuring Invasive Adenocarcinoma

**Proposed “Pattern Based” Classification**

- Does using depth/spread lead to unnecessary lymphadenectomy?
- Are growth patterns of invasion better predictors of risk of nodal metastasis than measuring depth/spread?

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Definition</th>
<th>Incidence of Positive Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Well demarcated glands</td>
<td>0 %</td>
</tr>
<tr>
<td>B</td>
<td>Pattern A with early destructive invasion</td>
<td>4.4 %</td>
</tr>
<tr>
<td>C</td>
<td>Diffuse destructive invasion</td>
<td>23.8 %</td>
</tr>
</tbody>
</table>

Diaz de Vivar, 2013 Int. J. Gynecol Pathol

Common Problems with Usual type Endocervical Adenocarcinoma

- Benign glandular lesions versus AIS
- AIS versus early invasive adenocarcinoma
- Measuring invasive adenocarcinoma for staging purposes

Endocervical versus endometrial primary origin of adenocarcinoma

What is the gold standard to define origin?

- Gross findings in the hysterectomy specimen?
- HPV status?
- Immunophenotype?
- Molecular definition: PTEN? ARID1A?

Endocervical vs endometrial primary origin of adenocarcinoma

Superficial adenocarcinoma in cervix
Endometrial adenocarcinoma in cervix

### Endocervical vs Endometrial Primary Origin of Adenocarcinoma

**Features Favoring Primary Endocervical Origin**
- Intracytoplasmic mucin, goblet cells
- Apoptotic debris
- Floating mitoses
- AIS in adjacent endocervical glands
- HSIL in adjacent glands or surface epithelium

**Features Favoring Primary Endometrial Origin**
- Squamous differentiation
- Stromal foamy histiocytes
- Components of a second tumor type
  - Serous carcinoma
  - Carcinosarcoma
  - Clear cell carcinoma

Endocervical vs Endometrial Primary Origin of Adenocarcinoma

<table>
<thead>
<tr>
<th>Stains</th>
<th>Diffuse/Strong</th>
<th>Not Diffuse/Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16</td>
<td>Favor Endocervical</td>
<td>Favor Endometrial</td>
</tr>
<tr>
<td>mCEA</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Stains alone should not trump clinical, radiologic, gross findings
P16: Diffuse and strong

mCEA: apical and/or cytoplasmic

Endocervical Adenocarcinoma

mCEA: usually focal distribution

p16
Vimentin
ER
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