Uterine Cancer:
Practical Approach to Histologic Subtyping

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“Current” Approach to Diagnostic Pathology

1. Understanding how pathologic evaluation allows a surgeon to make the best decisions about current treatment options.

2. Understanding current criteria to classify tumors and navigate problematic cases.

Treatment Decisions for Uterine Carcinoma

1. Surgery versus Trial of Hormonal Therapy
2. Extent of Surgery
3. Type of Adjuvant Therapy
4. Candidacy for Lynch syndrome evaluation

UCSF Gyn Onc Division, 2013

High Risk Tumor Behavior

- Advanced stage at presentation
- Chemoresistance
- Local recurrence
- Distant metastasis
- Death

UCSF Gyn Onc Division, 2013
High Risk Tumor Behavior

- Advanced stage at presentation
- Chemoresistance
- Recurrence locally
- Distant metastasis
- Death

High Risk Tumor Criteria

- Any grade 3 sub-type (serous, clear cell, carcinosarcoma, endometrioid)
- Grade 1, 2 endometrioid type with any:
  - Lymphovascular invasion
  - Myometrial/cervical/adnexal involvement
  - Lymph node involvement

Decision 1. Surgery versus Trial of Hormonal Therapy

Surgery is the default unless:

- Grade 1 Endometrioid adenocarcinoma
- AND
- Fertility preservation
- Poor surgical candidate

Decision 2. Extent of Surgery

Biopsy / Frozen Section

Hysterectomy
- g1 Endometrioid, no Myoinvasion/LVI
- Plus pelvic lymph nodes
- g1 Endometrioid, +Myoinvasion
- Plus para-aortic lymph nodes:
- g1,2 Endometrioid, +Myo / LVI / CX invasion
- g3 Endometrioid
- Clear cell carcinoma
- Plus omentectomy:
  - Serous carcinoma
  - Carcinosarcoma

Decision 3. Type of Adjuvant Treatment

None
- grade 1, stage 1 endometrioid, no LVI

Chemotherapy considered
- grade 2 or 3 endometrioid / age / LVI / MM invasion
- serous, clear cell, carcinosarcoma

Radiation considered
- clear cell, serous, carcinosarcoma
- higher stage endometrioid

Ifosfamide considered
- carcinosarcoma with rhabomyosarcoma elements

Etoposide considered
- neuroendocrine carcinoma
Decision 4. Candidate for Lynch syndrome screening?

Any one criteria:

- Age < 50
- Bethesda Guidelines criteria
- Tumor Morphology
  - Tumor infiltrating lymphocytes
  - Peritumoral lymphocytes
  - Undifferentiated histology
  - Lower uterine segment origin
  - Concurrent ovarian cancer

WHO Classification of Uterine Carcinoma

- Endometrioid adenocarcinoma
- Serous carcinoma
- Clear cell carcinoma
- Transitional cell carcinoma
- Mucinous carcinoma
- Small cell carcinoma
- Squamous cell carcinoma
- Undifferentiated carcinoma
- Carcinosarcoma
- Mixed type (each type must be \( \geq 10\% \) overall tumor)

4 Pathology Variables Drive these Clinical Decisions

- Sub-typing
- Grading
- Staging
- Lynch syndrome tumor morphology and testing
The Cancer Genome Atlas Classification of Uterine Cancer

WHO Classification of Uterine Carcinoma
- Endometrioid adenocarcinoma
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- Transitional cell carcinoma
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- Small cell carcinoma
- Squamous cell carcinoma
- Undifferentiated carcinoma
- Carcinosarcoma
- Mixed type (each type must be $\geq 10\%$ overall tumor)

Outline of Talk

Practical issues:
- Problematic variations: A pattern-based approach
- Immunostain pearls and pitfalls
- Newer non-WHO definition of undifferentiated uterine carcinoma

Practical Approach to Classifying Uterine Carcinoma

Evaluate in order:
- **Clinical context:** Menopausal status / age
- **Low magnification:** Architecture
- **High magnification:** Cytology
- **Adjacent tissue:** Precursor lesion
- **If needed:** Immunohistochemistry
### Practical Approach to Classifying Uterine Carcinoma

<table>
<thead>
<tr>
<th>Pre-menopause</th>
<th>Precursor lesion</th>
<th>IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid,g1.2</td>
<td>yes</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>Endometrioid,g3</td>
<td>uncommon</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>Serous</td>
<td>uncommon</td>
<td>Serous EIC</td>
</tr>
<tr>
<td>Clear cell</td>
<td>uncommon</td>
<td>?</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>uncommon</td>
<td>?</td>
</tr>
</tbody>
</table>

### Problematic Patterns of Uterine Cancer

#### Pure glandular
- Grade 1 endometrioid carcinoma
- Papillary endometrioid carcinoma
- Serous carcinoma
- Clear cell carcinoma

#### Papillary
- Papillary endometrioid carcinoma
- Serous carcinoma
- Endocervical adenocarcinoma

#### Solid, with high grade nuclei
- Solid serous carcinoma
- Grade 3 endometrioid carcinoma
- Undifferentiated carcinoma
- Carcinosarcoma

#### Spindled
- Endometrioid carcinoma with spindled cells
- Endometrioid carcinoma with corded and hyalinized pattern
- Carcinosarcoma

#### Clear cell-rich
- Endometrioid carcinoma with clear cells
- Clear cell carcinoma

#### Mucin-rich
- Endometrioid carcinoma with mucinous cells
- Endocervical carcinoma

#### Necrosis, desmoplasia in a biopsy with low grade architecture
- Myoinvasive g1 endometrioid carcinoma or serous carcinoma
- Under-sampled dedifferentiated carcinoma / g3 endometrioid
### Problematic Patterns of Uterine Cancer

- **Pure glandular**
  - Papillary
  - Solid, with high grade nuclei
  - Spindled
  - Clear cell-rich
  - Hobnail, papillary, clear cell
  - Mucinous
  - Necrosis, desmoplasia in a biopsy with low grade architecture

- **Complex Atypical Hyperplasia**

- **Grade 1 Endometrioid Carcinoma**

- **Pseudoglandular Serous Carcinoma (grade 3)**

### Pure Glandular Pattern Uterine Cancer

- **@ low magnification:**
  - Simple gland shape
  - Columnar cells

- **Complex Atypical Hyperplasia**

- **Grade 1 Endometrioid Carcinoma**

- **Pseudoglandular Serous Carcinoma (grade 3)**
Grade 1 Pseudoglandular Endometrioid Serous Architectural Grade Low Nuclear Grade Low Discordant architecture versus nuclear grade

- Pleomorphic nuclei
- Cherry-red macronucleoli
- Smudge cells
- Atypical mitoses

Pure Glandular Pattern Uterine Cancer

Endometrioid carcinoma (upper end of size) irregular, large, cherry-red

Nucleoli

Serous carcinoma

Endometrioid carcinoma

Pseudoglandular Serous Carcinoma:

Atypical mitoses

Pseudoglandular Serous Carcinoma:

Smudged chromatin

Normal N/C ratio
Atrophy

Look for Precursor Lesion

“Early serous carcinoma”
“Serous EIC”

“Atrphy

Serous Carcinoma

Pure Glandular Pattern Uterine Cancer

<table>
<thead>
<tr>
<th>Adenomyosis</th>
<th>Myoinvasion by Pseudoglandular Serous cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architectural Grade</td>
<td>Low</td>
</tr>
<tr>
<td>Nuclear Grade</td>
<td>Low</td>
</tr>
</tbody>
</table>

Discordant architecture versus nuclear grade
- Pleomorphic nuclei
- Cherry-red macronucleoli
- Smudge cells
- Atypical mitoses

Pseudoglandular Serous Carcinoma

"Gaping" glands

Pseudoglandular Serous Carcinoma: Myoinvasion
Pseudoglandular Serous Carcinoma: Myoinvasion mimics adenomyosis

Glandular Pattern of Endometrial Cancer

<table>
<thead>
<tr>
<th></th>
<th>Grade 1 Endometrioid</th>
<th>Pseudoglandular Serous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architectural Grade</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Nuclear Grade</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>p16, p53</td>
<td>Wild type</td>
<td>Aberrant</td>
</tr>
<tr>
<td>ER</td>
<td>Diffuse, strong</td>
<td>Variable</td>
</tr>
</tbody>
</table>
**p53 IHC Interpretation in GYN Serous Carcinoma**

<table>
<thead>
<tr>
<th>Pattern of p53 IHC staining</th>
<th>p53 gene mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong/diffuse (&gt;60% cells)</td>
<td>90 %</td>
</tr>
<tr>
<td>Completely negative</td>
<td>88 %</td>
</tr>
<tr>
<td>Weak/patchy (rare to 50%)</td>
<td>20 %</td>
</tr>
</tbody>
</table>

**p53 gene mutation and meaning**

- **Aberrant p53**: Favor serous carcinoma
- **Wild type p53**: Not serous carcinoma

**Check for internal control**

**p53 interpretation in GYN Serous Carcinoma**

- **Aberrant p53**: Favor serous carcinoma
- **Wild type p53**: Not serous carcinoma

**Diffuse / strong p16**

- Favor serous carcinoma
- Not in favor of serous carcinoma

**Patchy p16**

- Favor serous carcinoma
- Not in favor of serous carcinoma
Endometrioid Adenocarcinoma, grades 1 & 2

- **p53**: Wild type
- **p16**: Patchy

Pseudoglandular serous carcinoma

- **p53**: Diffuse, strong
- **p16**: Diffuse, strong

Pseudoglandular serous carcinoma

- **p53**: 
- **p16**: 

Mixed pseudoglandular serous carcinoma plus grade 1 endometrioid cancer

- **p53**: 
- **p16**: 

Arrow indicating the mixed component.
Mixed pseudoglandular serous carcinoma plus grade 1 endometrioid cancer

p53

Mixed pseudoglandular serous carcinoma plus grade 1 endometrioid cancer

p16

Mixed pseudoglandular serous carcinoma plus grade 1 endometrioid cancer

Estrogen Receptor

PTEN Mutation

Common in endometrioid carcinoma
Uncommon in non-endometrioid carcinoma

Matias-Guiu & Prat 2013 Histopathology
PTEN Mutation  
Common in endometrioid carcinoma  
Uncommon in non-endometrioid carcinoma

PTEN Loss by IHC

<table>
<thead>
<tr>
<th>Condition</th>
<th>PTEN Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal endometrium</td>
<td>Rare</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>~30%</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>~75%</td>
</tr>
<tr>
<td>Endometrioid cancer</td>
<td>~60-75%</td>
</tr>
<tr>
<td>Non-endometrioid cancer</td>
<td>~25-35%</td>
</tr>
</tbody>
</table>

Cell proliferation and survival

Matias-Guiu & Prat 2013 HistoPathology
Djordjevic 2013 Mod Pathol
Darvishian 2004 AJSPP
Mutter 2000 JNCI

PTEN IHC in uterine cancer subtypes

Endometrioid cancer  
PTEN complete negative  
Serous carcinoma  
PTEN present  
Clear cell carcinoma  
PTEN present

PTEN IHC in uterine cancer subtypes

Problematic Patterns of Uterine Cancer

Glandular

- Papillary
  - Solid, with high grade nuclei
  - Spindled
  - Clear cell-rich
  - Mucin-rich
  - Necrosis, desmoplasia in a biopsy with low grade architecture
Papillary Pattern of Uterine Cancer

- Serous Carcinoma
- Papillary variants of Endometrioid Adenocarcinoma (grade 1 or 2)
  - Villoglandular variant
  - Small non-villous papillary variant
- Villoglandular Endocervical Adenocarcinoma

<table>
<thead>
<tr>
<th>Architectural Grade</th>
<th>Nuclear Grade</th>
<th>p53, p16</th>
<th>ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>wild type</td>
<td>diffuse, strong</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>aberrant</td>
<td>variable</td>
</tr>
</tbody>
</table>

Papillary Serous Carcinoma

- Architectural Grade: Low
- Nuclear Grade: High

Discordant architecture versus nuclear grade:
- Pleomorphic nuclei
- Cherry-red macronucleoli
- Smudge cells
- Atypical mitoses

Papillary Serous Carcinoma

 Discordant architecture versus nuclear grade

- Pleomorphic nuclei
- Cherry-red macronucleoli
- Smudge cells
- Atypical mitoses

Papillary Pattern Uterine Cancer

<table>
<thead>
<tr>
<th>Papillary variant Endometrioid Carcinoma</th>
<th>Papillary Serous Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architectural Grade: Low</td>
<td>Low</td>
</tr>
<tr>
<td>Nuclear Grade: Low</td>
<td>High</td>
</tr>
</tbody>
</table>

p53, p16: wild type, aberrant
Papillary Serous Carcinoma

- p16: diffuse / strong
- p53: diffuse / strong

Villoglandular endometrioid adenocarcinoma
Villoglandular endometrioid adenocarcinoma

Clues to raise concern:
- Young age (35-45)
- Clinical lesion in endocervix
- Apical: “Floating” mitoses
- Basal: Apoptotic debris
- Negative ER, Vimentin, p53
- Diffuse, strong p16
- mCEA can be positive
Villoglandular endocervical adenocarcinoma in “EMB”

Floating mitoses in apical cytoplasm

Endometrioid adenocarcinoma with small non-villous papillae
Mimics Serous Carcinoma
Endometrioid adenocarcinoma with small non-villous papillae

Endometrioid adenocarcinoma with small non-villous papillae

Endometrioid adenocarcinoma with sloughing papillary “buds”
*Mimics Serous Carcinoma*

**Problematic Patterns of Uterine Cancer**

- Glandular
- Papillary
  - **Solid, with high grade nuclei**
    - Spindled
    - Clear cell-rich
    - Mucin-rich
    - Necrosis, desmoplasia in a biopsy with low grade architecture
Solid Pattern Uterine Cancer with High Grade Nuclei

- Serous carcinoma
- Grade 3 endometrioid adenocarcinoma
- Undifferentiated uterine carcinoma
- Neuroendocrine carcinoma
- Undersampled carcinosarcoma
- Consider non-epithelial malignancies:
  - Leiomyosarcoma
  - Rhabdomyosarcoma
  - Lymphoma
  - Melanoma

<table>
<thead>
<tr>
<th>Grade 3 Endometrioid Carcinoma</th>
<th>Solid Serous Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columnar/polarized cells</td>
<td>Focal</td>
</tr>
<tr>
<td>Tubular, glandular</td>
<td>Focal</td>
</tr>
<tr>
<td>Squamous differentiation</td>
<td>Focal</td>
</tr>
<tr>
<td>Papillary, slit like spaces</td>
<td>No</td>
</tr>
<tr>
<td>LVI with papillary buds</td>
<td>No</td>
</tr>
<tr>
<td>Scattered bizarre nuclei</td>
<td>No</td>
</tr>
<tr>
<td>Precursor lesion</td>
<td>Hyperplasia</td>
</tr>
<tr>
<td>Aberrant p53/p16</td>
<td>Sometimes</td>
</tr>
<tr>
<td>PTEN</td>
<td>Lost</td>
</tr>
</tbody>
</table>

Solid Pattern Uterine Cancer

- Columnar/polarized cells: Focal
- Tubular, glandular: Focal
- Squamous differentiation: Focal
- Papillary, slit like spaces: No
- LVI with papillary buds: No
- Scattered bizarre nuclei: No
- Precursor lesion: Hyperplasia
- Aberrant p53/p16: Sometimes
- PTEN: Lost
Atrophy

Solid pattern serous carcinoma

Main tumor
p53

Junction between tumor and endometrium
p53

Consensus Diagnosis
p53 Staining

Endometrioid

Serous

p53 Normal

p53 Positive

Serous EIC

Atrophy

Solid pattern serous carcinoma

p53 Positive
### Solid Pattern Uterine Cancer with High Grade Nuclei

- Serous carcinoma
- Grade 3 endometrioid adenocarcinoma
- Undifferentiated uterine carcinoma
- Neuroendocrine carcinoma
- Undersampled carcinosarcoma

**Consider non-epithelial malignancies:**
- Leiomyosarcoma
- Rhabdomyosarcoma
- Lymphoma
- Melanoma

### Undifferentiated Uterine Carcinoma

#### Definition:
- Tumor without any morphologic or immunostain differentiation
- Two forms:
  - Pure undifferentiated uterine carcinoma (UUC)
  - Mixed UUC with low grade endometrioid carcinoma = Dedifferentiated (DDUC)

#### Significance:
- Highly aggressive / fatal
  - UUC worse than grade 3 endometrioid
  - DDUC worse than grade 2 endometrioid

### Undifferentiated Uterine Carcinoma

<table>
<thead>
<tr>
<th>Architecture:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sheets, rarely cords.</td>
</tr>
<tr>
<td>- Non-cohesive cells</td>
</tr>
<tr>
<td>- Geographic necrosis</td>
</tr>
<tr>
<td>- Myxoid stroma (sometimes)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytology:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Monotonous polygonal cells</td>
</tr>
<tr>
<td>- Moderate atypia</td>
</tr>
<tr>
<td>- Nucleoli, mitoses</td>
</tr>
<tr>
<td>- Rhabdoid cells (sometimes)</td>
</tr>
</tbody>
</table>

**Immunostains:**
- Keratin, EMA..............negative or focal (<10%)
- Neuroendocrine..............negative or focal (<10%)
- p16..........................Positive
- ER/PR.........................conflicting data
- p53..........................not studied
Undifferentiated Uterine Carcinoma

Non-cohesive tumor cells
Undifferentiated Uterine Carcinoma: Moderate atypia

Undifferentiated Uterine Carcinoma: Rhabdoid cells

Keratin: Undifferentiated Uterine Carcinoma

Dedifferentiated Uterine Carcinoma
Keratin: Dedifferentiated Uterine Carcinoma

Undifferentiated Uterine Carcinoma

Behavior:
- 40% to 60% die
- Median survival is 6 months
- Most deaths are within 5 years
- For dedifferentiated uterine carcinoma, prognosis is the same even if only 20% is undifferentiated carcinoma

Treatment:
- Same as for high grade cancer
- Often MSI-high so testing for Lynch syndrome is advised

Undifferentiated Uterine Carcinoma vs Endometrioid Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>UUC</th>
<th>Grade 3 Endometrioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubules, glands</td>
<td>No</td>
<td>Usually focally</td>
</tr>
<tr>
<td>Squamous differentiation</td>
<td>No</td>
<td>Focally</td>
</tr>
<tr>
<td>Geographic necrosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Non-cohesive cells</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rhabdoid cells</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Keratin/EMA</td>
<td>&lt;10% cells</td>
<td>Diffuse</td>
</tr>
</tbody>
</table>

Practical issues:
- A diagnosis of exclusion.
- Use formal diagnostic criteria, not WHO criteria.
- Do not report dedifferentiated carcinoma as grade 2 endometrioid carcinoma
  - Even a minor % of undifferentiated component is adverse
- Consider screening for Lynch syndrome
Undifferentiated Uterine Carcinoma vs Serous Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>UUC</th>
<th>Serous Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary growth</td>
<td>No</td>
<td>Usually focally</td>
</tr>
<tr>
<td>Slit like spaces</td>
<td>No</td>
<td>Focally</td>
</tr>
<tr>
<td>Nuclei</td>
<td>Monotonous</td>
<td>Pleomorphic</td>
</tr>
<tr>
<td>Geographic necrosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Non-cohesive cells</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rhabdoid cells</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Keratin/EMA</td>
<td>&lt;10% cells</td>
<td>Diffuse</td>
</tr>
</tbody>
</table>

Geographic necrosis is not pathognomonic for undifferentiated carcinoma

Serous carcinoma

Pleomorphism & cohesion

Biopsy with solid pattern high grade malignancy

How specific does the sub-typing need to be?

Reasonable to report as "high grade adenocarcinoma" with a comment if:

- The tumor is confirmed by IHC to be epithelial.
- The comment discusses differential diagnosis.

Problematic Patterns of Uterine Cancer

- Glandular
- Papillary
- Solid, with high grade nuclei
  - Spindled
    - Clear cell-rich
    - Hobnail, papillary, clear cell
    - Mucinous
    - Necrosis, desmoplasia in a biopsy with low grade architecture
Uterine Cancers with Spindle Cells

- Carcinosarcoma
- Endometrioid carcinoma with spindle cells, grade 1 or 2
  - Spindled/sarcomatoid type
  - Corded and hyalinized type
  - Progestin-treated type
  - Arising in atypical polypoid adenomyoma

<table>
<thead>
<tr>
<th>Spindled types</th>
<th>Endometrioid Carcinoma</th>
<th>Carcinosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypia</td>
<td>Lower grade</td>
<td>High grade</td>
</tr>
<tr>
<td>Spindle cells blend</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>with glandular cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterologous elements</td>
<td>No</td>
<td>Common</td>
</tr>
<tr>
<td>Aberrant p16, p53</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Carcinosarcoma: p53 (same for p16)

Carcinosarcoma with rhabdomyosarcomatous elements

Desmin Myogenin

Endometrioid carcinoma with spindle cells

Carcinosarcoma with rhabdomyosarcomatous elements
Endometrioid carcinoma with spindle cells

Endometrioid carcinoma with spindle cells

Endometrioid carcinoma with spindle cells

Endometrioid carcinoma, cored and hyalinized type
Endometrioid carcinoma, corded and hyalinized type

Endometrioid carcinoma, partial response to progestins
Endometrioid carcinoma arising in atypical polypoid adenomyoma

Problematic Patterns of Uterine Cancer

- Glandular
- Papillary
- Solid, with high grade nuclei
- Spindled

- Clear cell-rich
  - Mucin-rich
  - Necrosis, desmoplasia in a biopsy with low grade architecture

Clear cell-rich Endometrial Cancers

- Clear cell carcinoma
- Endometrioid carcinoma with clear cells / secretory change, any grade
- Serous carcinoma with clear cells

Clear Cell-rich Uterine Cancer

<table>
<thead>
<tr>
<th></th>
<th>Endometrioid Carcinoma With Clear Cells</th>
<th>Clear Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell shape</td>
<td>Columnar</td>
<td>Polygonal</td>
</tr>
<tr>
<td>Cell polarity</td>
<td>Preserved</td>
<td>Lost</td>
</tr>
<tr>
<td>Tubulocystic plus</td>
<td>Not common</td>
<td>Yes</td>
</tr>
<tr>
<td>Papillary growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaline globules</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyalinized stroma</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hobnail growth</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Open tumor rings</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Clear cell carcinoma: polygonal cells, central nuclei

Clear cell carcinoma: papillary & tubulocystic growth

Clear Cell Carcinoma

Hyalinized stroma

Hyaline droplets
Clear Cell Carcinoma

Free floating open rings

Endometrioid adenocarcinoma with clear cells

Endometrioid adenocarcinoma with clear cells

Endometrioid adenocarcinoma with clear cells
Serous carcinoma with clear cells

IHC of Uterine Clear Cell Carcinoma

<table>
<thead>
<tr>
<th>Positivity</th>
<th>HNF-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>p53</td>
<td>variable</td>
</tr>
<tr>
<td>p16</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>HNF-1</td>
<td>&gt;75%</td>
</tr>
</tbody>
</table>

HNF-1 Expression

<table>
<thead>
<tr>
<th></th>
<th>OVARY</th>
<th>UTERUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>94 - 98%</td>
<td>73 - 100%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>0 - 40%*</td>
<td>0 - 39%*</td>
</tr>
<tr>
<td>Serous</td>
<td>0 - 30%*</td>
<td>0 - 60%*</td>
</tr>
<tr>
<td>Secretory phase</td>
<td>Gestational phase</td>
<td>Arias Stella reaction</td>
</tr>
</tbody>
</table>

*weak/patchy staining

High grade solid cancer with clear cells

References:
- Kao 2012 Histopathol
- Delair 2011 AJP
- Fadare 2012 AIMM
- Delair 2009 AJP
- Kato 2006 Mod Pathol
- Yamamoto 2007 Hum Pathol
- Yamamoto 2007 Hum Pathol
IHC favors Serous Carcinoma with clear cells

- p53: Aberrant
- p16: Aberrant
- ER: Positive
- HNF: Negative

Lack of a distinct “separate” compartment is against a second tumor component

Lack of a distinct “separate” compartment is against a second tumor component

ARID1A Mutation

Common in Clear Cell Cancer
Endometrioid Cancer

TCGA 2013 Nature
Jones 2010 Science
Wiegand 2010 NEJM
ARID1A Mutation
ARID1A Loss by IHC

Common in Clear Cell Cancer
Endometrioid Cancer

- Endometrioid, grade 1 or 2: 29%
- Endometrioid, grade 3: 39%
- Clear cell carcinoma: 26%
- Serous carcinoma: 18%

TCGA 2013 Nature
Jones 2010 Science
Wiegand 2010 NEJM

Problematic Patterns of Uterine Cancer

- Glandular
- Papillary
- Solid, with high grade nuclei
- Spindled
- Clear cell-rich

- Mucin-rich
  - Necrosis, desmoplasia in a biopsy with low grade architecture

Moderate level of disagreement

Mucin-rich Endometrial Cancers

- Endometrioid carcinoma with mucinous features
- Endocervical adenocarcinoma
- Endometrioid carcinoma with microglandular hyperplasia-like features
Endometrioid adenocarcinoma with mucinous features

Endometrioid adenocarcinoma with mucinous features

Endometrial carcinoma with microglandular hyperplasia-like features

- Endocervical MGH-like changes at surface/periphery of endometrial cancer
- Low grade, low stage endometrioid / mucinous adenocarcinoma
- Older women

Benign endocervical MGH
Endometrial carcinoma with microglandular hyperplasia-like features

Problematic Patterns of Uterine Cancer

- Glandular
- Papillary
- Solid, with high grade nuclei
- Spindled
- Clear cell-rich
- Mucin-rich

- Necrosis, desmoplasia in a biopsy with low grade architecture

Necrosis or Desmoplasia in a Biopsy with Low Grade Tumor

- Degenerative changes
- Myoinvasive grade 1 endometrioid tumor
- Myoinvasive pseudo-glandular serous carcinoma
- Under-sampled higher grade tumor
  - Grade 2 or 3 endometrioid carcinoma
  - Dedifferentiated uterine carcinoma
  - Carcinosarcoma

Necrosis + low grade adenocarcinoma
Desmoplasia + low grade adenocarcinoma

Biopsy = Grade 1 Endometrioid cancer with necrosis

Hysterectomy = Grade 3 Endometrioid cancer

Necrosis or Desmoplasia in a Biopsy with Low Grade Tumor

- Degenerative changes
- Myoinvasive grade 1 endometrioid tumor
- Myoinvasive pseudo-glandular serous carcinoma
- Under-sampled higher grade tumor
  - Grade 2 or 3 endometrioid carcinoma
  - Dedifferentiated uterine carcinoma
  - Carcinosarcoma

Report as:

Adenocarcinoma with extensive necrosis; see comment.

Adenocarcinoma with desmoplastic stroma; see comment.

Discuss possibilities of higher grade or higher stage tumor.
Outline of Talk

**Practical issues:**
- Problematic variations: A pattern-based approach
- Immunostain pearls and pitfalls
- Newer non-WHO definition of undifferentiated uterine carcinoma