Mixed Epithelial Endometrial Carcinoma
ISGyP Endometrial Cancer Project

Joe Rabban MD MPH
UCSF Pathology Department

Mixed Epithelial Endometrial Carcinoma
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Sub-Group Members:

- Glenn McCluggage
- George Mutter
- Joe Rabban

Review by Full Working Group

- Seattle, March 2016

mixed epithelial endometrial carcinoma

Definitions

- Historical overview
- Current W.H.O. definition
- Controversies

ISGyP Recommendations

- Criteria and reporting
- Unresolved issues

Differential Diagnosis

Outline of Talk

- Historical overview
- Current W.H.O. definition
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Differential Diagnosis
Mixed Epithelial Endometrial Carcinoma

- History of Definitions
  - 2003 edition of W.H.O.
    - Admixture of type I and type II carcinomas
    - Each must make up at least 10% of the tumor
  - Rationale:
    - “25% or more of type II tumor implies a poor prognosis”

- 2014 edition of W.H.O.
  - Two or more different histological types of cancer
  - At least one Type II tumor
    - Most common mix: endometrioid + serous
    - Each must make up at least 5% of overall tumor
    - Advises p53, p16, PTEN staining for confirmation
  - Rationale:
    - “as little as 5% of a serous component adversely influences outcome”

Mixed Epithelial Endometrial Carcinoma

- Evidence behind 2014 W.H.O. Definition
  - Literature review of outcome studies using multivariate analysis:
    - Is there a prognostic difference between pure endometrioid adenocarcinoma versus endometrioid adenocarcinoma mixed with serous or clear cell carcinoma?

<table>
<thead>
<tr>
<th>Type II component</th>
<th># of Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous carcinoma</td>
<td>10</td>
<td>Yes, worse prognosis, even if as little as 5% present</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>1</td>
<td>Yes, worse prognosis, even if as little as 10% present</td>
</tr>
</tbody>
</table>

Mixed Epithelial Endometrial Carcinoma

- Limitations to Existing Evidence
  - Rare tumor
  - No standardization of reporting % of tumor components
  - Classification of endometrial cancer has evolved over time

The Cancer Genome Atlas (TCGA) Genomic Characterization of Endometrial Cancer

From TCGA: Nature 2013; 497: 67
Translation of TCGA-based Classification to Individual Diagnoses

Emerging Research

- Li&Gado/Transporter molecular classification
- Protein/Tissue and Protein/Genome molecular classification

Limitations to Existing Evidence

- Rare tumor
- No standardization of reporting % of tumor components
- Classification of endometrial cancer has evolved over time
- Observer reproducibility for tumor typing is problematic

ISGyP Recommendations

- Definition:
  Endometrioid adenocarcinoma with a component of serous or clear carcinoma

- Criteria:
  Each tumor type should be a spatially distinct component on H&E stain
  - Serous carcinoma: aberrant p53 and diffuse p16
  - Clear cell carcinoma: positive Naps2A and/or HNF-1

  No minimum amount of serous / clear cell carcinoma needed as long as it can be confidently recognized on H&E stain

ISGyP Recommendations

- Reporting:
  Each tumor type should be reported in final diagnosis
  - Percent composition of overall tumor
  - Grade

  Overall grade is 3 regardless of the percent of serous or clear cell type

Tumors that should NOT be classified as mixed epithelial carcinoma:

- Endometrioid adenocarcinoma with variant morphology
- Cancers that are difficult to classify (“ambiguous” morphology)
- Dedifferentiated endometrial carcinoma
- Carcinosarcoma

ISGyP Recommendations

- Han et al. Mod Pathol. 2015; 28: 1094
- Thomas et al. Arch Pathol Lab Med. 2010; 140: 836
- McConechy et al. J Pathol. 2012; 228: 20
2 Spatially Distinct Patterns of Tumor

Mixed Endometrioid and Serous Carcinoma

- Low grade Endometrioid Adenocarcinoma
- High grade Serous carcinoma

p53
- Wild-type
- Aberrant

p16
- Wild-type
- Aberrant

Endometrioid Adenocarcinoma
- High grade Serous carcinoma

Endometrioid Adenocarcinoma
- p53
- High grade Serous carcinoma
Endometrioid Adenocarcinoma

High grade Serous carcinoma

2 Spatially Distinct Patterns of Tumor

Pattern 1: Low grade Endometrioid Adenocarcinoma

Pattern 2: Clear Cell Carcinoma

Mixed Epithelial Endometrial Carcinoma

NapsinA NapsinA

ISGyP Recommendations

Unresolved Issues:
- What is the minimum component of type II cancer that portends poor outcome in otherwise low grade endometrioid adenocarcinoma
- More research needed:
  - multi-institutional collaboration
  - well sampled cases
  - clearly defined diagnostic criteria
Mixed Epithelial Endometrial Carcinoma

**Pathogenesis?**

- Two genetically independent tumors: "Collision tumor"
- Single tumor with progression from one type to a second type
- Common origin with divergence to different tumor types

**Molecular Analysis of Mixed Endometrial Carcinomas Shows Conallity in Most Cases**

- Marta Julve, MD, PhD; Hong, Ping, MD; Lee, N.; Hsiung, SH; MBD, J. Am. J. Obstet. Gynecol. 1989; 161:1104-1108

Mutation profile and clinical outcome of mixed endometrioid-serous endometrial carcinomas are different from that of pure endometrioid or serous carcinomas.

L. Campana, H. A. Garcia-Ríos, J. Pérez-de; et al.

Arch Gynecol Obstet 2004; 269:3-6

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Mixed Epithelial Endometrial Carcinoma

**Outline of Talk**

- Definition
  - History of evidence
  - Current WHO definition
  - Controversies
- ISGyP Recommendations
  - Criteria and reporting
  - Unresolved issues

**Differential Diagnosis**

Tumors that should not be classified as mixed cancers

**Tumors that Should Not be Classified as Mixed Endometrial Cancer**

- Pure endometrioid cancer with variant morphologic patterns

<table>
<thead>
<tr>
<th>Variation</th>
<th>Mimic</th>
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</thead>
<tbody>
<tr>
<td>Papillary patterns</td>
<td>Serous carcinoma</td>
</tr>
<tr>
<td>---Villoglandular</td>
<td>Small non-villous papillae</td>
</tr>
<tr>
<td>--Sloughing artifact</td>
<td></td>
</tr>
<tr>
<td>Clear cell change</td>
<td>Clear cell carcinoma</td>
</tr>
<tr>
<td>Corded, hyalinized pattern</td>
<td>Carcinosarcoma</td>
</tr>
</tbody>
</table>

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**Endometrioid adenocarcinoma with villoglandular growth**

- Papillary Grade 1 Endometrioid Adenocarcinoma
- Papillary High Grade Serous Carcinoma

<table>
<thead>
<tr>
<th>Architectural grade</th>
<th>Low</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear grade</td>
<td>Low</td>
<td>High</td>
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</tbody>
</table>
Endometrioid adenocarcinoma with villoglandular growth

Endometrioid adenocarcinoma with villoglandular growth

Endometrioid adenocarcinoma with villoglandular growth

Endometrioid adenocarcinoma with small non-villous papillae

Endometrioid adenocarcinoma with small non-villous papillae

Endometrioid adenocarcinoma with sloughing artifact
Glandular Pattern Serous Carcinoma

Endometrioid adenocarcinoma with clear cells

Endometrioid adenocarcinoma with mucinous features

Tumors that Should Not be Classified as Mixed Endometrial Cancer

- Pure endometrioid cancer with variant morphologic patterns
- Cancer that is difficult to classify

*Endometrial carcinomas with ambiguous features*

Robert J. Sestan, MD

Endometrial cancer with “ambiguous” features

Overlapping features

Poorly differentiated

Tumors that Should NOT be Classified as Mixed Endometrial Cancer

- Pure endometrioid cancer with variant morphologic pattern
- Cancer that is difficult to classify

Unique tumors with “biphasic” pattern
- Carcinosarcoma
- Dedifferentiated endometrial carcinoma

Carcinosarcoma

Dedifferentiated Endometrial Carcinoma

- Definition
  Mix of Endometrioid adenocarcinoma (lower grades) Undifferentiated endometrial carcinoma (UEC)

- Behavior
  - Advanced stage at presentation
  - Rapid progression to death (6 month median survival)
  - Even if UEC is only 20% of entire tumor

Undifferentiated Endometrial Carcinoma

- Morphology
  - Geographic necrosis
  - Discohesive, sheet-like growth
  - Corded growth within myxoid stroma
  - Monomorphic, moderately atypical cells
  - Rhabdoid cytoplasm

- Immunophenotype
<p>| Epithelial markers | EMA, Keratin, CK7 | Negative / Focal positive |
|-------------------------------------------------|----------------------|
| Mullerian markers | PAX2, ER | Often Negative |
| Cell-cell adhesion | E-cadherin | Negative |
| SWI-SNF complex | BRG1 (SMARC-A4) | ~ 1/3 negative |</p>
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Undifferentiated Endometrial Carcinoma
Geographic Necrosis

Discohesive cells

Rhabdoid cytology

Myxoid stroma

Loss of Keratin
Loss of EMA

Loss of E-Cadherin

Loss of BRG1
Dedifferentiated Endometrial Carcinoma

Endometrioid

Undifferentiated Carcinoma

Low grade Endometrioid

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