Ovarian surface epithelial neoplasms: Strategies for subclassification

Robert A. Soslow, MD
Memorial Sloan-Kettering Cancer Center

Introduction

- WHO classification
  - Serous
  - Mucinous
  - Endometrioid
  - Clear cell
  - Transitional
  - Squamous
  - Mixed epithelial
  - Undifferentiated

Rationale for “histotyping”

- Distinct disease entities
- Diagnostic criteria for carcinoma
- Carcinoma grading
- Personal and family cancer risk
- Therapeutic relevance

Problems with the traditional approach

- Mucinous carcinoma
- Clear cell carcinoma
- Poorly differentiated endometrioid carcinoma
- Mixed epithelial carcinoma

Serous tumors: demographics

- 80-85% of ovarian carcinomas
- 95% of stage III-IV ovarian carcinoma
- Low stage serous carcinomas are rare
  - <5% of serous carcinomas are stage I
- Association with BRCA1 and 2
Serous carcinoma: problems

• Differential diagnosis
  – Serous vs endometrioid carcinoma
  – Serous vs clear cell carcinoma
  – Serous vs transitional cell carcinoma
  – Serous vs mucinous carcinoma
  – Serous carcinoma vs borderline tumor
• Grading
Serous carcinoma: pathogenesis

Familial  
Tubal fimbria/inclusion  
*BRCA-1* mutation

Sporadic  
"Dysplasia"  
*TP53* mutation

Surface Epithelium  
Borderline tumor (BT)

Micropapillary BT  
Low grade carcinoma

High grade carcinoma

Serous carcinoma: immunophenotype

• WT1 (>75%, all grades)
  – Histologic subtype assignment
  – Primary site

• P53 (>70%, high grade)
  – Grade

• ER/PR (>90% low grade; variable high grade)
  – Therapeutics
  – Differential diagnosis viz clear cell carcinoma

Serous carcinoma: immunophenotype

• WT1 (>75%, all grades)
  – Histologic subtype assignment
  – Primary site

• P53 (>70%, high grade)
  – Grade

• ER/PR (>90% low grade; variable high grade)
  – Therapeutics
  – Differential diagnosis viz clear cell carcinoma

• Other
  – P16
  – PAX8
Grading

- MD Anderson 2-tier grading scheme
  - High grade (Shimizu/Silverberg grades 2 and 3)
  - Low grade (Shimizu/Silverberg grade 1)
    - Uniform nuclear size (less than 3x variation)
    - Less than 12 mitotic figures/10 high power fields

Serous—WHO

- “Ovarian tumours characterized in their better-differentiated forms by cell types resembling those of the fallopian tube”

MD Anderson grading—serous carcinoma

Summary: serous carcinomas

- Usually high stage (Stage IIC or greater)
Summary: serous carcinomas

- Usually high stage
- Broad range of histologic features
  - Slit-like spaces, irregular luminal contours
- Frequent WT1
- Low-grade: serous borderline tumor, *BRAF/K-ras, ER/PR*
- High-grade: tubal intraepithelial carcinoma, *p53, p16*, loss of BRCA1, BRCA1 or 2 family
- Other entities are excluded

Summary: serous carcinomas

- Usually high stage
- Broad range of histologic features
  - Slit-like spaces, irregular luminal contours
- Frequent WT1
- Low-grade: serous borderline tumor, *BRAF/K-ras, ER/PR*
- High-grade: tubal intraepithelial carcinoma, *p53, p16*, loss of BRCA1, BRCA1 or 2 family

Endometrioid
Endometrioid tumors: demographics

- 10% of ovarian carcinomas
- Most common stage I carcinoma (~50%)
- High stage endometrioid carcinomas are rare


Endometrioid tumors: prevalence

- 10% of ovarian carcinomas
- Most common stage I carcinoma (40-50%)
- High stage endometrioid carcinomas are rare

Endometrioid tumors: problems

• Differential diagnosis:
  – Endometrioid vs mucinous
  – Endometrioid vs sex cord stromal tumor
  – Endometrioid vs carcinosarcoma
  – Endometrioid vs metastasis
  – Endometrioid vs clear cell carcinoma
  – Endometrioid vs serous carcinoma

• Borderline tumor versus carcinoma

• Grading
  – Shimizu/Silverberg
"High grade endometrioid carcinoma"

“High grade endometrioid carcinoma”


Endometrioid tumors: immunophenotype

• WT1 (<5%)
  – Histologic subtype assignment
  – Differential diagnosis viz serous carcinoma
• Nuclear β-catenin (~30%)
  – Histologic subtype assignment

Endometrioid tumors: immunophenotype

• WT1 (<5%)
  – Histologic subtype assignment
• ER/PR (>75%)
  – Therapeutic
  – Differential diagnoses viz clear cell carcinoma
**Endometrioid tumors: immunophenotype**

- WT1 (<5%)
  - Histologic subtype assignment
- Nuclear β-catenin (~30%)
  - Histologic subtype assignment
- ER/PR (>75%)
  - Therapeutic
  - Differential diagnoses viz clear cell carcinoma
- P53 in “high grade” examples

**Endometrioid carcinoma grading**

- Differentiation
- Broder
- FIGO endometrial (GOG)
- Shimizu/Silverberg

**Endometrioid carcinoma grading**

- Differentiation
- Broder
- FIGO endometrial (GOG)
- Shimizu/Silverberg

**Shimizu/Silverberg grading**

- Architecture
  - Glandular (1 point)
  - Papillary (2 points)
  - Solid (3 points)
- Nuclear pleomorphism
  - Slight (1 point)
  - Moderate (2 points)
  - Marked (3 points)
- Mitotic activity
  - 0-9 mf/10 hpf (1 point)
  - 10-24 (2 points)
  - >24 (3 points)

Shimizu/Silverberg grading

- **Architecture**
  - Glandular (1 point)
  - Papillary (2 points)
  - Solid (3 points)

- **Nuclear pleomorphism**
  - Slight (1 point)
  - Moderate (2 points)
  - Marked (3 points)

- **Mitotic activity**
  - 0-9 mf/10 hpf (1 point)
  - 10-24 (2 points)
  - >24 (3 points)

- Grade 1 (3-5 points)
- Grade 2 (6-7 points)
- Grade 3 (8-9 points)

- Correlates with survival
- Do NOT use with clear cell carcinoma


Endometrioid—WHO

- “Tumours of the ovary…that closely resemble the various types of endometrioid tumors…of the uterine corpus”

Summary: Endometrioid tumors

- Low stage, low grade
Summary: Endometrioid tumors

- Low stage, low grade
- Endometrial-like, metaplasias, secretory change, expansile invasion
- Endometriosis, endometrioid borderline tumor, endometrioid uterine carcinoma

Summary: Endometrioid tumors

- Low stage, low grade
- Endometrial-like, metaplasias, secretory change, expansile invasion
- Endometriosis, endometrioid borderline tumor, endometrioid uterine carcinoma
- ER/PR, nuclear β-catenin; not WT1
- CTNNB-1 (β-catenin), PTEN, PIK3CA, MSI-H

Quiz
Diagnosis: High grade serous carcinoma

Clear cell tumors: demographics

- 5% of ovarian carcinomas (in the West)
- Disproportionately low stage (and unilateral)
  - 25-30% of stage I and II carcinomas are clear cell
- High stage clear cell carcinomas are rare
- HNPCC/Lynch syndrome in ~20% of pts <50 yrs

Clear cell tumors: prevalence

- 5% of ovarian carcinomas (in the West)
- Disproportionately low stage (and unilateral)
  - 25-30% of stage I and II carcinomas are clear cell
- High stage clear cell carcinomas are rare
- HNPCC/Lynch syndrome in ~20% of pts <50 yrs

Clear cell tumors: problems

• Differential diagnosis:
  – Clear cell vs serous carcinoma
  – Mixed clear cell and serous carcinoma vs serous carcinoma
  – Clear cell vs endometrioid carcinoma
  – Clear cell borderline tumor

• Grading
  • No grading scheme

Clear cell tumors: diagnostic reproducibility, immunophenotype, lessons learned

• Clear cell carcinomas have a distinctive architectural repertoire and immunophenotype
  – Reproducibly diagnosed


Clear cell tumors: diagnostic reproducibility, immunophenotype, lessons learned

• Clear cell carcinomas have a distinctive architectural repertoire and immunophenotype
• Mixed epithelial carcinomas containing clear cells (MEP-C) are not reproducibly diagnosed

Clear cell tumors: diagnostic reproducibility, immunophenotype, lessons learned

- Clear cell carcinomas have a distinctive architectural repertoire and immunophenotype
- Mixed epithelial carcinomas containing clear cells (MEP-C) are not reproducibly diagnosed
- MEP-Cs are seldom clear cell carcinomas—most are serous carcinomas


### Clear cell immunophenotype

<table>
<thead>
<tr>
<th></th>
<th>WT1</th>
<th>ER</th>
<th>p53</th>
<th>HNF-1β*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCC (n=11)</td>
<td>10%</td>
<td>10%</td>
<td>0%</td>
<td>85%</td>
</tr>
<tr>
<td>SC (n=10)</td>
<td>90%</td>
<td>90%</td>
<td>70%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>MET-C CC (n=11)</td>
<td>90%</td>
<td>90%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>MET-C SC (n=11)</td>
<td>90%</td>
<td>90%</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

Clear cell carcinoma: immunophenotype

• ER/PR (<10%)
  – Histologic subtype assignment (viz serous and endometrioid)

• WT1 (<10%)
  – Histologic subtype assignment (viz serous)

• P53 (<10%)
  – Histologic subtype assignment (viz hi grade serous)
Clear cell carcinoma: immunophenotype

- ER/PR (<10%)
  - Histologic subtype assignment (viz serous and endometrioid)
- WT1 (<10%)
  - Histologic subtype assignment (viz serous)
- P53 (<10%)
  - Histologic subtype assignment (viz hi grade serous)
- HNF-1β (85%)
  - Histologic subtype assignment (viz serous and endometrioid)

Clear cell tumors with papillary architecture

- High nuclear grade
  - Clear cell vs serous carcinoma
- Low nuclear grade
  - Clear cell vs serous carcinoma vs endometrioid carcinoma vs mesothelioma vs serous borderline tumors


Papillary ovarian tumors

<table>
<thead>
<tr>
<th>Clear cell CA</th>
<th>Serous CA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unilateral, low stage</strong></td>
<td><strong>Bilateral, high stage</strong></td>
</tr>
<tr>
<td>Round papillae</td>
<td>Elongate, hierarchical branching</td>
</tr>
<tr>
<td>Hyaline, edematous stroma</td>
<td>Fibrous stroma</td>
</tr>
<tr>
<td>Hobnail cells, cuboidal</td>
<td>Columnar cells</td>
</tr>
<tr>
<td>Monolayer</td>
<td>Cellular tufting, micropapillae</td>
</tr>
<tr>
<td>Uniform nuclei</td>
<td>Pleomorphic nuclei</td>
</tr>
<tr>
<td>Decreased mitotic activity*</td>
<td>High mitotic rate</td>
</tr>
<tr>
<td>Other CCC patterns</td>
<td>Slit-like spaces</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>No endometriosis</td>
</tr>
<tr>
<td>WT1-/ER-/p53-</td>
<td>WT1+/ER variable/p53+</td>
</tr>
</tbody>
</table>
Quiz

Summary: Clear cell carcinomas
- Low stage and unilateral

Summary: Clear cell carcinomas
- Low stage and unilateral
- Papillary, tubulocystic, solid, hobnail, frequently clear cytoplasm
- Endometriosis, clear cell borderline tumor
Summary: Clear cell carcinomas

- Low stage and unilateral
- Papillary, tubulocystic, solid, hobnail, frequently clear cytoplasm
- Endometriosis, clear cell borderline tumor
- Low ER/PR, WT1, p53, mib-1
  - Positive HNF-1β

Summary: Clear cell carcinomas

- Low stage and unilateral
- Papillary, tubulocystic, solid, hobnail, frequently clear cytoplasm
- Endometriosis, clear cell borderline tumor
- Low ER/PR, WT1, p53, mib-1; HNF-1β+
- Lack of features that define other entities
  - Metaplasias, secretory changes
  - Multilayering, serrated luminal profiles

Summary: Clear cell carcinomas

- Low stage and unilateral
- Papillary, tubulocystic, solid, hobnail, frequently clear cytoplasm
- Endometriosis, clear cell borderline tumor
- Low ER/PR, WT1, p53, mib-1; HNF-1β+
- Lack of features that define other entities
  - Metaplasias, secretory changes
  - Multilayering, serrated luminal profiles
- Association with HNPCC in women <50 yrs

Mucinous

Ronnett B, http://borderlineovariantumors.pathology.uic.edu
Intestinal-type mucinous tumors: demographics

• Only <3% of all ovarian carcinomas
• 2/3 are stage I
• 10-15% of all stage I tumors


Intestinal-type mucinous tumors: problems

• Primary versus metastasis
• Borderline tumor versus carcinoma
  – Same as endometrioid tumors
• Grading
  – Shimizu/Silverberg
Intestinal-type mucinous tumors:
features favoring metastasis

• Bilateral disease


Intestinal-type mucinous tumors:
features favoring metastasis

• Bilateral disease
• Surface involvement


Intestinal-type mucinous tumors:
features favoring metastasis

• Bilateral disease
• Surface involvement
• Destructive stromal invasion


Intestinal-type mucinous tumors:
features favoring metastasis

• Bilateral disease
• Surface involvement
• Destructive stromal invasion
• Nodular growth pattern

Intestinal-type mucinous tumors: features favoring metastasis

- Bilateral disease
- Surface involvement
- Destructive stromal invasion
- Nodular growth pattern
- Single cells/signet ring cells


Intestinal-type mucinous tumors: features favoring metastasis

- Bilateral disease
- Surface involvement
- Destructive stromal invasion
- Nodular growth pattern
- Single cells/signet ring cells
- Vascular invasion

Algorithm for distinguishing primary and metastatic mucinous carcinoma

- Bilateral mucinous carcinomas: metastatic
- Unilateral mucinous carcinomas <12 cm: metastatic
- Unilateral mucinous carcinomas >12 cm: primary ovarian

Pseudomyxoma peritonei (PMP)

PMP associated with ovarian tumor(s) is almost never derived from the ovaries themselves

Pseudomyxoma—high grade

Pseudomyxoma peritonei—low grade

Primary ovarian mucinous carcinoma: immunophenotype

- CK7>20
- Retained SMAD4
- Negative:
  - Racemase (positive in colorectal)
  - β-catenin (positive in colorectal and endometrioid)
  - ER (positive in endometrioid and breast)
  - P16 (positive in endocervical and serous)
  - Mesothelin (positive in pancreatic, serous and mesothelial)
  - Fascin (positive in pancreatic)
Mucinous carcinoma immunohistochemistry

- Informative IHC pattern: CK7<CK20
  - NOT ovarian primary (if algorithm suggests metastasis)
  - Rule out colorectal and appendiceal primaries
  - Consider other possibilities

\[\begin{array}{c}
\text{CK7} \\
<
\text{CK20}
\end{array}\]

Mucinous carcinoma immunohistochemistry

- Uninformative IHC patterns (CK7=CK20; CK7>CK20)
  - Rule out pancreatobiliary, upper gastrointestinal primaries (if algorithm suggests metastasis)
  - Consider other possibilities

\[\begin{array}{c}
\text{CK7} \\
>
\text{CK20}
\end{array}\]

SMAD4

- Smad4 (DPC4) mediates TGFβ pathway suppressing epithelial cell growth
- Germline mutations \(\rightarrow\) FJP
- Somatic alterations \(\rightarrow\) Panc CA (55%) \(\rightarrow\) Colon CA (10-35%)
- Immunohistochemical loss of expression
  - Pancreatic CA (46%)
  - Colon CA (11%)
  - Ovarian mucinous CA (0%)
  - Endometrioid CA (?>0%)

*Biochem Biophys Res Commun* 2003; 306: 799-804
Mucinous carcinoma immunohistochemistry

Algorithm suggests metastasis
CK7>20 or CK7=CK20

- SMAD4 retained
- SMAD4 lost

Not informative
Pancreatic>colorectal

Summary: intestinal mucinous carcinomas of ovary

- Unilateral ovarian tumor; no pertinent medical history
- Intracytoplasmic mucin, expansile invasion
- Intestinal mucinous borderline tumor

Summary: intestinal mucinous carcinomas of ovary

- Unilateral ovarian tumor; no pertinent medical history
- Intracytoplasmic mucin, expansile invasion
- Intestinal mucinous borderline tumor
- CK7>20, retained SMAD4
- Negative racemase, β-catenin, ER, p16, mesothelin, fascin
- K-ras
Summary: intestinal mucinous carcinomas of ovary

- Unilateral ovarian tumor; no pertinent medical history
- Intracytoplasmic mucin, expansile invasion
- Intestinal mucinous borderline tumor
- CK7>20, retained SMAD4
- Negative racemase, β-catenin, ER, p16, mesothelin, fascin
- K-ras
- Other entities are excluded: exclude metastasis

Can we apply these criteria to practice?

- Trans-Canadian study of diagnostic reproducibility
  - Training:
    - 6 gynecological pathologists participated in a training session using 40 ovarian cancers (http://spectrum.med.ubc.ca/pathology/)
  - Testing:
    - First round: another 40 cancers selected to ensure a representative distribution of cell types
    - Second round: IHC data provided

Kobel M, et al. Mod Pathol vol 22, abstract 1007

Can we apply these criteria to practice?

- Results:
  - 92.3% concordance (remained essentially unchanged after 2nd round)
  - Conclusions:

Kobel M, et al. Mod Pathol vol 22, abstract 1007

DON’T blame Canada!
Endometrioid tumors: borderline versus carcinoma

- Low stage ovarian carcinomas (n=140)
  - Diagnosis changed to borderline (30%)
  - 70% were mucinous or endometrioid


Endometrioid tumors: borderline versus carcinoma

- Expansile invasion (CAH vs CA), greater than microinvasion
  - Large cribriform glands
  - Extensive gland fusion
  - Complex papillary architecture

- Destructive invasion, greater than microinvasion (5 mm or 10 mm²)
Expansile invasion = Carcinoma

No expansile invasion = Borderline tumor


Clear cell tumors with papillary architecture

- Clear cell tumors with papillary architecture are carcinomas, not borderline tumors

Papillary/low nuclear grade

<table>
<thead>
<tr>
<th>Clear cell CA</th>
<th>Serous LMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Non-hierarchical branching</td>
<td>Hierarchical branching</td>
</tr>
<tr>
<td>Monomorphous population</td>
<td>Mixed cell population</td>
</tr>
<tr>
<td>Hobnail cells</td>
<td>Pink cell tufts</td>
</tr>
<tr>
<td>At least focal atypia</td>
<td>Minimal atypia</td>
</tr>
<tr>
<td>Increased mitotic activity*</td>
<td>Low mitotic rate</td>
</tr>
<tr>
<td>Other CCC patterns</td>
<td>LMP patterns</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Serous cystadenoma</td>
</tr>
<tr>
<td>WT1-/ER-</td>
<td>WT1+/ER+</td>
</tr>
</tbody>
</table>