Early Surface Epithelial Neoplasms of the Ovary

Diagnostic Challenges and Controversies

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Precursor Lesions

Tumors of Low Malignant Potential (LMP)

Peritoneal & Omental Implants
PRECURSOR LESIONS
Precursor Lesions

- **Surface epithelium & inclusion cysts**
  - Epithelium & cysts adjacent to cancer
  - Contralateral ovary to one with cancer/LMP
  - Prophylactic oophorectomy (for family hx of ovarian or breast CA, BRCA 1 or 2 mutation)
  - Positive or susp cul-de-sac aspirate screen

- **Benign & Borderline tumors**
  - Serous
  - Mucinous
  - Others: Endometrioid, clear cell
Dysplasia of Surface Epithelium

**Cell Stratification**  
**Loss of polarity**

**Hyperchromasia**  
**Coarse chromatin**

- Severe dysplasia rarely reported in association with small CA, but not in prophylactic cases.
- Mild dysplasia seen by morphometry in prophylactic resections more than controls.
- Few studies show mutation or upregulation of TP53, similar to high grade serous carcinoma.

*(Bell & Scully 1994, Boyd 2003)*
Metaplasia & Proliferative Lesions

Papillae and tufts
Stratification
Tubal metaplasia in cysts
Endosalpingiosis

- A few conflicting reports
- ? increased frequency of cysts
- Reported in inguinal endosalpingiosis

Microscopic SE Carcinoma

- Rare reports of incidental findings

- Scully (1994) reported 14 cases, all unilateral and measured 1-7 mm, 10 were serous, and most were grade 2 or 3. About half of pts. died of disease, some after 10 yrs.

- Studies of BRCA1 or 2 patients showed only a few early ovarian CA, but more early tubal CA (Colgan 2003 & others)
Benign → Borderline → Invasive

- Mean age 44, 48 & 56
- 5X increase in incidence of benign tumors in close relatives of cancer patients
- Ultrasound evidence of mass increasing in size over time
- Combinations of more than one “phase” are not uncommon
LG serous CA (invasive micropapillary) is frequently associated with borderline micropapillary tumors & shares similar levels of expression of mutations in a progressive fashion, such as K-ras.

HG serous CA is rarely associated with benign or borderline & has different expression levels of genetic mutations.

(Smith, Sehdev 2003)
**Gene Mutations**

- **WT-1** gene rescues cells from p53-apoptosis. It is expressed in serous tumors of ovary, tube & peritoneum, but not in serous tumors of endometrium, or in ovarian mucinous, clear cell or Brenner.

- **K-ras** mutations separate serous carcinomas into LG invasive micropapillary (+ in 54%) from HG conventional serous CA which shows only native gene.

(Hashi 2003, Singer 2003, Acs 2004)
<table>
<thead>
<tr>
<th>Mutation</th>
<th>Benign</th>
<th>LMP</th>
<th>LG Ca</th>
<th>HG Ca</th>
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<td>0-6%</td>
<td>uncom</td>
<td>uncom</td>
<td>60%</td>
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<td>BRAF</td>
<td>50%</td>
<td>50%</td>
<td>0%</td>
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<tr>
<td>K-ras</td>
<td>high</td>
<td>high</td>
<td>v rare</td>
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<td>LOH*</td>
<td>~10%</td>
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<td>higher</td>
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*6p,6q,7p,7q,9p,9q,11p,11q,17p,17q*
Tumors of Low Malignant Potential: Confusing Terminology; Uncertain Outcome

- Clinically “on the border of malignancy” (Pfannenstiel 1898)
- “On borderline between benign & malignant” (Abel 1901)
- Semi malignant & borderline (Taylor 1929)
- Carcinoma of LMP (WHO 1973)
- Tumor of LMP (WHO & ISGP 1999)
- Atypical Proliferative Tumor (1990s)
- Borderline Tumors (WHO 2003)
Tumors of LMP: General Criteria

**Significant change (at least 10% of tumor), with 2 or more of the following:**

- Epithelial proliferation as tufting buds
- Stratification in papillae or glands
- Increased mitosis or altered distribution
- Mild to moderate nuclear / nucleolar atypia
- No stromal invasion

**Microinvasion:** focal, <3mm, <10mm², has no impact on prognosis
Serous Tumors of Low Malignant Potential
ST- LMP: Clinical Features

- 12% of all serous neoplasms
- Age 10-15 yr younger than CA (mean 38)
- Mean size 10 cm, 30-50% bilateral
- Often asymptomatic, 2/3rds are stage I
- May recur 20 yrs after therapy
- Extraovarian spread in 17-30% of ST- LMP
- 10 year survival 75-98% (20% in frank CA)
Serous Tumors of Low Malignant Potential (LMP)

- Unilocular cyst with lush papillae
- 50% have surface papillae, and in 10% of cases, they are the only element
- 25% of stage I have surface papillae (Ic)
- Few have major solid fibrous component
- Variants include micropapillary, surface serous & adenofibroma
ST-LMP: Histologic Criteria

- Papillary tufting, w/ complex hierarchical branching
- Small papillae often detach from larger ones as clusters of round eosinophilic cells
- Stratification up to 3 layers, ciliated cells
- Nuclei more round, w/ mild to mod. atypia, small nucleoli, mitosis rare (<4/10 HPF)
- Absence of frank stromal invasion
- Dx based on ovarian histology regardless of stage, extraovarian spread or behavior
Micropapillary Serous Borderline Tr

- 5-15% of serous borderline tumors. It is usually part of otherwise classic tumor, but a minimum of 5mm focus in a slide is required.

- More bilaterality, surface lesions & implants

- Long thin papillae extend from broad cores in the cyst wall or surface → filigree or cribriform pattern, without hierarchical branching (Medusa)

- No HG nuclear atypia (unlike carcinoma)
ST-LMP: Treatment

- Stage I treated by surgery alone:
  - unilateral SO, especially in young age
  - TAH, BSO in advanced stage
- Even if incompletely resected, more than 50% survive (unlike frank CA)
- Combination of stage III & invasive implants predicts a significantly worse prognosis, ? adjuvant Rx (Gilks 2003)
- Patients who die usually do so years after Dx, and most have extraovarian spread
# 10 yr Survival Rate of Ovarian Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serous</th>
<th>Mucinous</th>
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<tr>
<td></td>
<td>LMP</td>
<td>Frank</td>
</tr>
<tr>
<td>I</td>
<td>96</td>
<td>54</td>
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<tr>
<td>I-IV</td>
<td>91</td>
<td>23</td>
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Peritoneal Implants
Histogenesis of Implants

Multicentric from peritoneum

Foci of endosalpingiosis

Metastatic ovarian borderline tumors
Peritoneal Implants

- 95% of patients with implants have exophytic surface serous tumors of ovary

- 60% of patients with surface tumors have implants (Segal, Hart 1992)

- Implants can be:
  - noninvasive epithelial or desmoplastic
  - invasive
Noninvasive Epithelial Implants

- Nests extend into fibrous septa between fat lobules, but maintain well defined contours
- Small submesothelial spaces filled with papillae
- Hierarchical branching of papillae
- Minimal nuclear atypia
- Psammoma bodies frequent
- No desmoplasia
- No effect on prognosis
Noninvasive Desmoplastic Implants

- Plastered on surface and lacks irregular destructive invasion of underlying stroma
- Over 50% of lesion is fibrous or granulation tissue; only a minor epithelial component
- Well defined deposits with a few glands, papillae & small epithelial nests
- Mild to moderate nuclear atypia
- No effect on prognosis
Invasive implants

- Destructive invasion of normal deep stromal tissues by glands & small nests that are disorderly distributed
- Implants have irregular tentacular contours
- Epithelial cells are dominant
- Marked nuclear atypia, similar to LG CA
- Mature or immature stromal desmoplasia
Invasive implants

- Uncommon, ~ 15% of late stage LMP trs.
- 50% recur, 10 y survival rate 35%
- Significant prognostic marker for FIGO II & III borderline trs
- Lesions should be sampled thoroughly, since implants are heterogeneous
- Biopsy must include deep tissues
<table>
<thead>
<tr>
<th>SP Implant</th>
<th>Invasive</th>
<th>Noninv epith</th>
<th>Noninv desm</th>
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<tr>
<td>Contour</td>
<td>irregular deep</td>
<td>well defined between fat</td>
<td>well defined on surface</td>
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<td>Pattern</td>
<td>glands small nests</td>
<td>small cysts full of papillae</td>
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<td>Epithelium</td>
<td>dominant</td>
<td>dominant</td>
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<td>N. Atypia</td>
<td>marked as present</td>
<td>minimal absent</td>
<td>mild to mod present</td>
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<tr>
<td>Inflammation</td>
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<td>Prognosis</td>
<td>50% recur 35% 10yr S.</td>
<td>no impact</td>
<td>no impact</td>
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Invasive Implants: Issues

- Fibrous adhesions between fat lobules simulating invasion
- 25% of biopsies lack normal tissue
- Criteria of what constitutes invading epithelium are poorly defined. Single cells, clusters, cribriform or micropapillary patterns (Hart)
Outcome of Implants

- **Stabilize or regress**, with no impact on prognosis in most noninvasive and some invasive implants

- **Progress or recur** in 50% of invasive implants. Unusual if noninvasive

- **Transform to low grade** serous carcinoma
Aggressive ST-LMP with Extraovarian Implants

A few patients develop recurrence with aggressive behavior due to:

1- Original tumor misdiagnosed
2- Some tumors proliferate slowly, thus respond poorly to adjuvant Rx
3- A clone of invasive cells may start to proliferate after several years
Implants: Diff. Dx. I

**Endometriosis:**
- No nuclear atypia, papillae or psammoma
- Blood and macrophages.

**Endosalpingiosis:**
- Papillary or tubular, 1 layer of ciliated low columnar cells. NO stromal cells
- Single cells rare, some psammoma bodies
- Nuclear atypia is mild, if any
Implants: Diff. Dx. II

Serous Ca Ovary & Serous Tumors of Peritoneum
- High grade nuclear atypia
- Necrosis

Mesothelial hyperplasia:
- Close to the surface
- Cells are low cuboidal or flat, with simple papillae
- Nuclei have smooth regular contours

Mesothelioma
- Unlikely in females. Hx of exposure
- Nuclear atypia
MUCINOUS TUMORS OF LMP
Mucinous Tumors of LMP: Issues

- Definition & criteria
- How much is an adequate sample?
- Tangential sectioning
- What constitutes invasion or microinvasion?
- Relation to pseudomyxoma peritonei
- Primary versus metastatic
Mucinous Tumors of LMP: Gross

- Described 30 yr ago (1973)
- Peak age is 30-40 yr (mean 35)
- Unilaterial 90%; if bilateral rule out mets.
- Large tumors (mean 17cm), multilocular
- Heterogeneous, with foci of benign, LMP, microinvasive & invasive areas in same tumor, thus thorough sampling (1 slide per 1 to 2 cm) is critical to rule out occult CA
Mucinous Neoplasms

Benign → Borderline → Carcinoma

- 74-90% of CA have benign mucinous epithelium
- CA-Intestinal type - 68% show borderline areas
- CA-müllerian type 75-100% have borderline müllerian mucinous
- K-ras mutations similar in benign, borderline & CA areas of the tumor
- P53 mutation 13% in borderline, 40% in CA
- Most CA are associated with changes in RAS-RAF-MEK-ERK-MAP kinase signaling pathway
Mucinous Tumor of LMP: Course

- Almost all are stage I
- Extraovarian involvement in 15%
  - pseudomyxoma in intestinal type
  - subperitoneal implants in endocervical
- 10 yr. survival rate 96% (35% for CA)
- 2-4% of stage I recur or metastasize
Mucinous Tumors of LMP: Histology

- Daughter cysts close to large cysts
- Tufting, bridging, filigree, associated with mild stratification
- **Low grade nuclear atypia.** If HG, classify as intraepithelial CA
- Mitotic figures with altered distribution
- Granulomas, macrophages & giant cells
- Lack of capsular invasion
- Implants in peritoneum, tube & LN
Mucinous Tumors of LMP: Intestinal Type

- Most common type (90%)
- Cysts have smooth but thick wall
- Only a few papillae
- Some solid foci
- Epithelium includes goblet, gastric, neuroendocrine & rarely Paneth cells
Mucinous Tumors of LMP: Endocervical Type

- Less common (10%)
- Clinically similar to, and often mixed with, serous component
- Finer honeycomb than benign
- More papillae inside cysts or exophytic
- Pelvic endometriosis in 30% of cases
- Tall mucinous müllerian cells
- Polys in epithelium
Mucinous Tumors: Microinvasive LMP

- Foci are <3mm, with <10mm$^2$ surface area
- Small nest(s) surrounded by mucin, macrophages
- Seen in ~10% of LMP mucinous tumors
- No microinvasive LMP cases metastasized

DDx: Microinvasive carcinoma has HG nuclear atypia, and involves larger areas.
Mucinous Cystadenocarcinoma

- Often starts as malignant change in 5-10% of adenomas. Suspect in solid areas.
- Bilateral in 25%, but then R/O metastatic trans.
- Cells multilayered (>4 layers) & crowded, with bridging & cribriform pattern.
- High grade nuclear atypia & mitosis.
- Micropapillae without stromal core.
- Pseudomyxoma is not a criterion.
Mucinous Cystadenocarcinoma

- **Intraepithelial Carcinoma**
  - <3mm/10mm²
  - aka noninvasive or intraglandular carcinoma

- **Frank Carcinoma**
  - Solid irregular nests invade stroma destructively, associated with fibrosis & necrosis
Peritoneal Adenomucinosis (PP)

- Benign or LMP glands & mucin that dissect between fibrous & omental tissues
- Only with intestinal type
- In 15% of cases of LMP, but also in adenoma & CA, so it does not indicate CA
- Not an indicator of ovarian malignancy
- Presence of glands worsens prognosis. All recurrent cases have glands & most have LG trs. of appendix
Most Peritoneal Adenomucinoses Originate from Appendix

- ~85% of recurrent cases are associated with mucinous adenoma, villous adenoma or low grade tumors of appendix

- Synchronous tumors (ovaries & appendix) are CK 20 pos. & CK7 neg., supporting that ovarian tumors originate from appendix

- Rupture of ovarian tumors pre or intraoperatively almost never result in pseudomyxoma (3-19 yr)

- Mucin gene overexpression
Mucinous Tumors: DDx.

- **Krukenberg**
  - isolated signet ring cells
  - Rare glands

- **Teratoma**
  - often seen with benign mucinous trs

- **Signet ring cell stromal tumor**
  - No nuclear atypia
  - Absence of mucin
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Modified from Prat J, 2004