Borderline ovarian tumours

Robert A. Soslow, MD  
soslwr@mskcc.org

Outline

• Orientation
• Ovarian tumor overview
• Serous and seromucinous borderline tumors
  – Clinical summary
  – Morphologic description
  – Prognostic indices
• Low grade serous carcinoma

Borderline tumors

• Synonyms:
  – Tumor of borderline malignancy
  – Borderline tumor (BT)
  – Tumor of low malignant potential (LMP)
  – Atypical proliferative tumor
Borderline tumors

- Borderline: Neither clinically benign nor malignant
  - Recurrence is common, but death is uncommon

- Borderline: Neither morphologically benign nor malignant
  - Architectural complexity without malignant cytologic features or invasion
Borderline tumors

• Serous BTs and seromucinous BTs are both histopathologically "borderline" and clinically "borderline."

• Intestinal mucinous, endometrioid and transitional BTs are only histopathologically "borderline"; they are not clinically borderline. They are instead clinically benign.
Serous carcinoma: pathogenesis

Familial
- Fimbria?
  - BRCA-1 mutation

Sporadic
- Serous Epithelium
  - BRAF, KRAS

Dysplasia
- TP53 mutation

High grade carcinoma
- Low grade carcinoma

Borderline tumor (BT)
- Micropapillary BT

Low grade serous carcinoma: pathogenesis

Putative precursor to SBT and LGSC: Papillary tubal hyperplasia (PTH)

Clinical

- Fifth decade
- Pelvic discomfort
- +/- elevated CA125
- 70% stage I (30% of total are bilateral)
- 30% have extraovarian, peritoneal disease
- 95% 5-year survival

Serous borderline tumor:
5/10 yr follow up

Serous borderline tumors:
10/20 yr follow up

** ~50% of patients died

Gershenson DM, Silva EG. Cancer 1990;65:578-85

Seromucinous borderline tumor

• Synonyms
  – Mullerian mucinous borderline tumor
  – Endocervical-type mucinous borderline tumor
  – Mixed epithelial borderline tumor
• “True” borderline tumor, akin to serous borderline tumor
Seromucinous borderline tumor

- Similarities with serous borderline tumor
  - Growth pattern
  - Association with implants
  - Possibility of malignant behavior (very rare!)


- Differences with serous borderline tumor
  - Association with endometriosis
  - Morphologic similarities to endometrial cancers with mucinous metaplasia
  - Malignant potential is lower
Seromucinous BT: further evidence supporting kinship to endometrioid neoplasia

- Lack or paucity of WT1 staining
- Presence of ARID1A mutation in approximately 1/3 of cases


Prognosis

- Confirmed
  - Stage
    - Success of debulking
    - Implant invasion
Prognosis

- Confirmed
  • Stage
    - Success of debulking
    - Implant invasion
  - Probable
    • Architecture i.e. micropapillarity
    • Microinvasion

- Probable
  • Architecture i.e. micropapillarity
  • Microinvasion

- Not
  • Lymph node involvement

Implant terminology (historical)

- Ovarian borderline tumor + peritoneal disease = *borderline tumor with implant*

- Ovarian carcinoma + peritoneal disease = *metastatic ovarian carcinoma*
Implant terminology (future)

- Ovarian borderline tumor + noninvasive peritoneal disease = \textit{borderline tumor with noninvasive implant}
- Ovarian borderline tumor + invasive peritoneal disease = \textit{metastatic low grade serous carcinoma (with associated serous borderline tumor)}
- Ovarian carcinoma + peritoneal disease = \textit{metastatic carcinoma}

Significance of implant type

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of implant</th>
<th>Stage III survival (10 yr)</th>
<th>Metastatic carcinoma survival (10-20 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive</td>
<td>~95%</td>
<td>~25-50%</td>
<td>33-50%</td>
</tr>
<tr>
<td>Invasive</td>
<td>33-50%</td>
<td>25-50%</td>
<td>33-50%</td>
</tr>
</tbody>
</table>

Implant morphology

- No invasion WITHOUT diffuse high grade cytologic atypia or micropapillary architecture: \textit{non-invasive}
- Tumor stroma prominent WITHOUT fat or muscle invasion, diffuse high grade cytologic atypia or micropapillary architecture: \textit{non-invasive}
Implant morphology

- No invasion WITHOUT diffuse high grade cytologic atypia or micropapillary architecture: non-invasive
- Tumor stroma prominent WITHOUT fat or muscle invasion, diffuse high grade cytologic atypia or micropapillary architecture: non-invasive
- Fat or muscle invasion: invasive
- Diffuse high grade cytologic atypia: carcinoma

No invasion AND no diffuse high grade cytologic atypia or micropapillary architecture: non-invasive epithelial implant
Exophytic micropapillary architecture WITHOUT fat or muscle invasion or diffuse high grade cytologic atypia: 
*controversial entity*

Tumor stroma prominent AND no fat or muscle invasion, diffuse high grade cytologic atypia or micropapillary architecture: 
*non-invasive “desmoplastic” implant*

Tumor stroma prominent AND no fat or muscle invasion, diffuse high grade cytologic atypia or micropapillary architecture: 
*non-invasive “desmoplastic”*
Fat or muscle invasion: invasive implant
Endophytic micropapillary architecture WITHOUT fat or muscle invasion or diffuse high grade cytologic atypia: indeterminate/probably invasive/may progress and then invade

Diffuse high grade cytologic atypia: high grade serous carcinoma

Implant assessment

<table>
<thead>
<tr>
<th>Fat invasion</th>
<th>Cytologic atypia</th>
<th>Carcinoma</th>
<th>Micropapillary</th>
<th>?Invasive</th>
<th>Non-invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>No</td>
<td>No</td>
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</tbody>
</table>
Significance of micropapillary (MP) architecture in a non-invasive ovarian tumor

• Established:
  – MP tumors are more frequently associated with invasive implants
  – MP tumors are more frequently bilateral (70% vs 20%)
  – MP tumors more frequently involve the ovarian surface (60% vs 30%)
  – MP tumors are more aggressive because of their association with invasive implants

• Probable:
  – MP tumors present at higher stage
  – MP tumor recur more frequently
Significance of micropapillary (MP) architecture in a non-invasive ovarian tumor

- Does this justify classification as "carcinoma?"

Significance of MP architecture in an ovarian tumor

Analogy: MP tumors are akin to low grade carcinomas in situ.

1) If they’re non-invasive, they behave like other low grade, non-invasive tumors.

2) If they’re invasive (anywhere), they behave like low grade carcinoma.
Significance of MP architecture in an ovarian tumor

Analogy: MP tumors are akin to low grade carcinomas in situ.

1) If they’re non-invasive, they behave like other low grade, non-invasive tumors.
2) If they’re invasive (anywhere), they behave like carcinoma.
3) If they’re incompletely excised, they can progress to carcinoma.
4) If you don’t know whether they’re invasive, you must investigate further.
5) Avoid unequivocal diagnosis of borderline tumor at FS when MP architecture is present.
Microinvasion

• Definition
  – One or more foci
  – <5mm in any one dimension or <10mm²

• Description
  – Pink cells in spaces
  – Micropapillary or cribriform nests

• Associations: pregnancy

• Significance (not pregnancy-associated)
  – Over-represented in high stage cases
  – Possible adverse outcome (Longacre)

Lymph nodes

• ~30% of stage III SBTs have involved LNs
• Prognostic implication: none
• Differential diagnosis:
  – Carcinoma
    • Nodular aggregates > 1mm
  – Benign Mullerian inclusions (endosalpingiosis)
  – Mesothelial hyperplasia

Therapy

• Surgical disease

• Hormonal therapy
• Cytotoxic chemotherapy
  – 4% complete response to platinum and taxol*
• Targeted therapy
  – MEK inhibitors for invasive implants/low grade serous carcinoma


Borderline tumors at frozen section

• When and why do gynecologists perform staging operations?
  – Detect extraovarian disease
    • Serous and seromucinous BT
  – Concern that BT diagnosis will be “upgraded” to carcinoma on permanent sections
    • Micropapillary serous, intestinal mucinous, endometrioid and clear cell
Borderline tumors at frozen section

• BTs at frozen section at MSKCC
  – Serous (67%)
  – Seromucinous (11%)
  – Gastrointestinal mucinous (17%)
  – Endometrioid (4%)
  – Clear cell (2%)
  – RED= mean size >10 cm


Borderline tumors at frozen section

• FS is 87% accurate for BT diagnosis at MSKCC
  • “Undercalls”
    – Serous (6%)
    – Seromucinous (0%)
    – Gastrointestinal mucinous (25%)
    – Endometrioid (80%)
    – Clear cell (50%)

  Small numbers
  – RED= mean size >10 cm


Borderline tumors at frozen section

• Serous tumors: importance of micropapillary architecture
  – Serous BT, no MP: 96% accuracy
  – Serous BT with MP: 57% accuracy

Serous carcinoma: pathogenesis

Familial
- Fimbria?
- BRCA-1 mutation

Sporadic
- Dysplasia
- TP53 mutation

Serous epithelium
- High grade carcinoma

Borderline tumor (BT)

Micropapillary BT

Low grade carcinoma

MEK inhibitors

Managerial classification of SBT

- BENIGN:
  - Ovary-confined SBT (with or without MP)
Managerial classification of SBT

• BENIGN:
  – Ovary-confined SBT (with or without MP)

• UNCERTAIN MALIGNANT POTENTIAL:
  – Unstaged SBT-MP

• (S)LOW MALIGNANT POTENTIAL:
  – SBT (with or without MP) with noninvasive implants

• MALIGNANT
  – SBT (with or without MP) with invasive implants
Summary (1)

- Serous and seromucinous BTs as a group are neither benign nor overtly malignant
- Prognosis depends on stage, debulking, implant type, microinvasion and, probably, micropapillary/cribriform architecture
Summary (1)

- Serous BTs as a group are neither benign nor overtly malignant
- Prognosis depends on stage, debulking, implant type, microinvasion and, possibly, micropapillary architecture
- Tumors with non-invasive implants may recur as invasive implants/low grade serous carcinoma
- Tumors with invasive implants are similar to low grade serous carcinoma

Summary (2)

- Low-grade serous carcinomas (LGSC) are clinically, biologically and morphologically distinct from HGSC
Summary (2)

• Low-grade serous carcinomas (LGSC) are clinically, biologically and morphologically distinct from HGSC
• Many might represent progression from SBT and SBT with micropapillary features
• They rarely progress to a high-grade neoplasm