Ovarian Borderline Tumors
(What’s in a name?)

Diagnosis and Management

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Conflict of Interest
Objectives

• Definition/Natural History
• Diagnostic Criteria
• Surgical options
• Post-operative Therapy
• Surveillance
Case #1

- 30 year old G0P0 with a tender, 7 cm. bilobed cystic mass in the left adnexa. CA-125 is 50 units. She wishes to attempt pregnancy in the next year. Laparoscopic left ovarian cystectomy with frozen section shows serous borderline tumor.

Now What?
Case #2

- 50 year old G2P2 with a tender, 8 cm. cystic mass in the right adnexa. CA-125 is normal. At the time of hysterectomy, BSO, multiple 5-7 mm. pink nodules are identified over the pelvic peritoneum.
- Final pathology shows serous BOT with non-invasive peritoneal implants.
Case #3

- 42 year old G2P2 with a bilateral adnexal masses, 6 cm. CA-125 is 60 units. Endometriosis is suspected. At the time of hysterectomy, BSO, multiple 5-7 mm. pink nodules are identified involving the peritoneum and omentum.

- Final pathology shows low-grade serous carcinoma.
Case #4

• 61 year old G2P2 with a 15 cm., right adnexal masses. CA-125 is normal. At the time of hysterectomy, BSO, the right ovary was drained of two liters of thick, viscous fluid. The appendix is normal in appearance.

• Final pathology shows mucinous borderline ovarian tumor.
Ovarian Borderline Tumors

History
Ovarian Borderline Tumors
Natural History

• 10-15% of all Ovarian Malignancies are LMP Tumors
• 75% are Stage I at diagnosis
• Bilateral
  – 30-60% in Serous Borderline Tumors
  – <5% in Mucinous Borderline Tumors
• Primarily cystic
Ovarian Borderline Tumors

History

“proliferative ovarian tumors without evidence of stromal invasion”

Malignant and Semimalignant Tumors of the Ovary
H.C. Taylor
Surg Gynecol Obstet 48:204-230, 1929
Ovarian LMP Tumors

History

“carcinoma of low malignant potential”

International Federation of Gynecology and Obstetrics: Classification and staging of malignant tumors in the female pelvis.
Ovarian Borderline Tumors

History

“borderline malignancies”

2014 WHO Classification of Tumours of the Female Genital Organs

“borderline tumor” is interchangeable with “atypical proliferative tumor”.

“tumor of low malignant potential” is no longer recommended.

## Evolution of our understanding of pelvic serous neoplasia

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>1961</td>
<td>FIGO. Serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth (low malignant potential)</td>
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<tr>
<td>1973</td>
<td>WHO. Tumours of borderline malignancy (carcinomas of low malignant potential) → borderline tumour. Extraovarian lesions designated ‘implants’ rather than metastasis</td>
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<tr>
<td>1980s</td>
<td>Implants divided into non-invasive and invasive as the latter more predictive of an adverse outcome</td>
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<tr>
<td>1990-2000</td>
<td>Serous borderline tumour (SBT) with micropapillary architecture identified: associated with a significantly worse outcome. SBT divided into atypical proliferative serous tumour and non-invasive micropapillary (low grade) serous carcinoma</td>
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<tr>
<td>2014</td>
<td>WHO. SBT/APST and SBT-micropapillary variant/non-invasive low grade serous carcinoma Invasive implants are low grade serous carcinoma</td>
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Serous Histology

• Serous borderline tumor (SBT) = Atypical proliferative serous tumor (APST)
• SBT with micropapillary pattern = non-invasive low grade serous carcinoma (niLGSC)
• Non-invasive vs. Invasive implants

Borderline Ovarian Tumors
Subtypes

- Serous
- Mucinous
- Endometrioid
- Clear Cell
- Seromucinous
- Brenner

95%
Diagnostic Criteria
Pathogenesis
Serous Tumors

- Benign, borderline, and malignant serous tumors account for about 30% of all ovarian tumors.
- About 70% are benign or borderline, 30% are malignant.
- Benign and borderline tumors – younger patients 20-45 yrs
- Malignant tumors – later in life unless genetically susceptible (BRCA 1 and 2).
- Risk factors for malignant serous tumors:
  - BRCA1/2 mutation – estimated risk 20-60% by the age of 70 years (these mutations are present in about 5% of women younger than 70 with ovarian cancer)
  - Nulliparity/low parity
  - Family history
- Reduced risk
  - OCP use
  - Tubal ligation
Ovarian serous carcinoma

Low-grade serous carcinoma (LGSC)
- Arise in serous borderline tumors
- Mutation: KRAS, BRAF, ERBB2
- Wild type: TP53

High-grade serous carcinoma (HGSC)
- Arise from STIC or inclusion cysts
- Mutation: TP53
- Amplification of oncogenes, deletions of tumor suppressor genes
- Present in BRCA1/2
- BRCA1/2 mutation rare in sporadic HGSC
Serous tumors

• Biologic behavior depends on degree of differentiation and peritoneal involvement (tumor present on ovarian surface vs spread to peritoneum)

• SBT & LGSC – slow progression even with peritoneal involvement, patient may survive for relatively long periods

• HGSC – often widely metastatic, rapid clinical deterioration

• Malignant tumors:
  – 5 yr survival if confined to ovary – 70%
  – 5 yr survival if involving peritoneum – 25%

• Borderline tumors:
  – 5 yr survival if confined to ovary – 100% - but may recur after many years
  – 5 yr survival if involving peritoneum – 90%
Atypical Proliferating Serous Tumor

Non-invasive, Low Grade Serous Carcinoma

Non-invasive Implants

Invasive Implants

• Gross examination:
  – May be cystic or solid
  – **Serous cystadenoma** (benign) – smooth cyst wall filled with fluid
    • 20% are bilateral
  – **Serous borderline tumors** – papillary projections on the cyst wall
    • 30% are bilateral
  – **Serous carcinoma** – cystic/solid, +/- papillary areas, +/- hemorrhage and necrosis
    • 66% are bilateral
Serous Cystadenoma

- Lined by a single layer of columnar epithelium with
- No increased cytologic atypia, stratification, or architectural complexity
- Underneath the epithelial lining, the wall of the cyst is generally thick/fibrous
SBT

- Increased complexity of the stromal papillae.
- Stratification of the epithelium.
- Mild nuclear atypia, but invasion of the stroma is not seen.
- Micropapillary pattern – papillae are long and thin (“medusa head”)
  Thought to be the precursor to low-grade serous carcinoma.
Mucinous tumors

- Mucinous tumors account for 20-25% of all ovarian neoplasms
- Occur in middle adult life
- Majority are benign or borderline tumors, most are unilateral
- KRAS proto-oncogene mutation found in benign, borderline, & malignant mucinous tumors
- Pseudomyxoma peritonei:
  - Characterized by extensive mucinous ascites, cystic epithelial implants on peritoneal surfaces, adhesions, and bilateral ovarian involvement
  - Most cases are due to an appendiceal mucinous neoplasm (not primary ovarian mucinous tumor), which is involving the bilateral ovaries
Mucinous cystadenoma
Mucinous Borderline Tumor

- Demonstrate epithelial stratification, tufting, and/or papillary intraglandular growth
Diagnosis of Borderline Tumors

Frozen Section Evaluation

- Only rarely is a frozen section diagnosis of Borderline tumor downgraded on permanent section.
- 27% of frozen section diagnoses of borderline tumor will be upgraded to invasive carcinoma on permanent section.


Stage of Borderline Tumors

- Stage I
- Stage II
- Stage III
- Stage IV

- Serous
- Mucinous

%
Diagnosis & Surgical Staging
Surgery & Staging of Borderline Tumors

- Based on FIGO specifications.

- Childbearing Completed:
  - TAH, BSO, Staging, Tumor Reduction if obvious metastatic tumor present.

- Childbearing Not Completed:
  - Unilateral salpingo-oophorectomy and staging
  - Ovarian cystectomy and staging

- If mucinous - perform an appendectomy.
Surgery & Staging of Borderline Tumors

• Sites of metastatic disease in decreasing order.
  – Peritoneum
  – Uterine Serosa / Fallopian Tube Serosa
  – Omentum
  – Retroperitoneal nodes
Surgery & Staging of Borderline Tumors

With minimal evidence to support cytotoxic chemotherapy or radiation therapy for treatment of metastatic LMP tumor, aggressive surgical cytoreduction of metastatic disease is the mainstay of therapy.
Mucinous Borderline Tumors

- Almost always unilateral
- If mucinous borderline tumor is bilateral, consider metastatic disease from GI tract.
- Advanced stage mucinous borderline with pseudomyxoma peritonei is probably appendiceal in origin.
Conservative Surgery for Borderline Tumors

• 108 patients treated conservatively for OBT
  – 89 treated with oophorectomy
  – 19 treated with ovarian cystectomy
• 3/89 (3.4%) treated with oophorectomy recurred.
• 3/19 (15.8%) treated with cystectomy recurred.
• 26/32 women attempting pregnancy conceived and carried.

Conservative Surgery for Borderline Tumors

• 38 patients with ovarian borderline tumors treated conservatively.
• 8% recurrence in the contralateral ovary.
• 15 patients with 22 subsequent pregnancies.

Advanced Stage Tumors

• 5-10% of patients with advanced stage borderline tumors will have **invasive** implants.

• 90-95% of patients with advanced stage borderline tumors will have **noninvasive** implants.
Ovarian Serous Borderline Tumors
Risk of developing serous carcinoma

- 1978-2002: 1026 women in Danish Patient Registry
- All slides reviewed by Johns Hopkins Pathologists
- Risk of developing serous carcinoma at 5 & 20 years
  - Atypical proliferative serous tumors: 0.9% & 3.7%
  - Non-invasive LGSC: 5% & 13.9%

Ovarian Borderline Tumors
Postoperative Therapy

- Stage I - None
- Stage II - IV with Noninvasive Implants - None
- Stage II - IV with Invasive Implants - Probably None
- Patients with residual or recurrent disease - Chemotherapy
- Primum Non Nocere
Postoperative Therapy

- Nothing
- Chemotherapy: For LGSC
- Antiestrogen therapy
Post Treatment Surveillance