Common pitfalls in the evaluation of gynecologic frozen sections

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Common gynecologic intraoperative consults

• **Uterus**
  - Endometrial carcinoma
  - Myometrial mass
• **Ovary**
  - Benign versus borderline versus carcinoma
  - Primary versus metastasis
• **Vulva**
  - Margin evaluation
• **Others (cervix, peritoneum etc)**

Gynecologic intraoperative consults

• Accuracy rates variable
• Most errors result from sampling issues

Uterus

• Endometrial carcinoma
• Myometrial mass
Endometrial carcinoma

- **Treatment decisions based on FS**
  - Lymphadenectomy or not
  - Extent of lymphadenectomy
  - Omentectomy

Endometrial carcinoma

**Features to evaluate at FS**

- Tumor grade
- Myometrial invasion
- Lymphovascular invasion
- Cervical or adnexal involvement

Endometrial carcinoma: Treatment decisions?

1. **Hysterectomy alone:**
   - Grade 1 endometrioid, no myoinvasion or LVI

2. **Hysterectomy + pelvic LNs:**
   - Grade 1 endometrioid with myoinvasion

3. **Hysterectomy + pelvic LNs + para-aortic LNs:**
   - Grade 1-2 endometrioid, myoinvasive, with LVI or cervical invasion
   - Grade 3 endometrioid or clear cell

4. **Hysterectomy + pelvic and para-aortic LNs + omentum:**
   - Serous carcinoma or MMMT

Endometrial carcinoma

**How to approach specimen:**

- Bivalve uterus and serial section every 5 mm
- Gross tumor present: Submit areas of apparent deepest invasion
- No grossly evident tumor: Representative section
- If any suggestion of cervical or adnexal involvement: submit section
- Usually 1 representative section sufficient
Endometrial carcinoma

How to approach specimen:
• Is gross evaluation sufficient?
  - Maybe a good idea to submit at least one representative section even if no visible tumor

Endometrial carcinoma: Tumor grade
• Prior biopsy/curettage results
• Evaluate architecture and cytology
• Frozen artifact makes cytology look worse!
Myometrial invasion: Pitfalls

*Over-diagnosis:*
- Irregular endo-myometrial junction
- Tumor involving adenomyosis

*Under-diagnosis:*
- MELF invasion
- Adenoma malignum pattern of invasion
Irregular endomyometrial junction

- Common
- Leads to overdiagnosis of myometrial invasion

**Clues:**
- Well rounded contours
- Preserved stroma
- Marker glands
- No desmoplastic response
Involvement of adenomyosis

- Leads to overdiagnosis of myometrial invasion

Clues:
- Well rounded contours
- No stromal response
- Preserved endometrial stroma
- Marker glands
- Presence of uninvolved adenomyosis
MELF invasion

- Microcystic elongated and fragmented pattern of myometrial invasion
- Can be subtle and underdiagnosed
- Usually seen with well or moderately differentiated endometrioid adenocarcinoma
- Associated with lymphovascular invasion and lymph node metastases

Lymphovascular invasion

- Comment if present
- Look carefully in cases of MELF invasion
- Be aware of artifact during surgery (Laparoscopic, robotic)
Endometrial carcinoma

- Cervical or adnexal involvement: Submit section(s) only if grossly suspicious

Myometrial mass

- Rapidly enlarging “fibroid”
- Careful gross evaluation
- Representative section
- Any atypical feature: “smooth muscle tumor with atypical features” and defer classification to permanent sections
Myometrial mass: Leiomyoma

Smooth muscle tumor with atypical features

Smooth muscle tumor with atypical features

Ovary
Ovary: Common FS issues

- Benign versus borderline versus malignant
- Primary versus metastasis

Benign versus borderline versus carcinoma: Treatment decisions

1. Cystectomy:
   - Benign or borderline in young patient
2. Salpingo-oophorectomy:
   - Benign in older patient
3. Salpingo-oophorectomy with staging:
   - Borderline or carcinoma

Benign versus borderline versus carcinoma

*How to approach specimen:*
- Examine surface of intact specimen
- Ink any disrupted or ragged areas
- Examine cut surface and assess for solid or papillary areas
- Submit sections from non-necrotic solid or papillary areas

Benign versus borderline

- Sample any papillary areas
- Assess for presence and amount of epithelial proliferation
- 10% cut-off used to diagnose borderline tumor
Serous cystadenofibroma

Serous borderline tumor
Cystadenoma with focal epithelial proliferation

- Insufficient for diagnosis of borderline tumor
- Consider submitting additional sections
- If similar findings: Cystadenoma with focal borderline features or focal epithelial proliferation
- May or may not stage
Borderline tumor versus carcinoma

- Study the accuracy of a borderline diagnosis at the time of frozen section
- 120 patients
- 15 reclassified as carcinoma on permanent sections
- Varied by histology: more common with endometrioid and mucinous tumors
- 5 serous borderline tumors reclassified as carcinoma on final pathology: all 5 showed micropapillary features

Shih KK, et al. Gynecol Oncol 2011

Mucinous/Endometrioid borderline tumor versus carcinoma

- Typically sampling issue
- Often focal carcinoma by expansile invasion in a background of extensive borderline tumor
- Consider calling frozen “at least borderline”
- Most patients will be staged regardless
Mucinous borderline tumor

Mucinous carcinoma

Mucinous carcinoma

Endometrioid borderline tumor
Serous borderline tumor versus low grade serous carcinoma

- Destructive stromal invasion > 5mm
- Micropapillary or cribriform architecture: still borderline but note these features (higher risk for low grade carcinoma on final pathology and higher risk of invasive implants)

Clear cell carcinoma versus serous borderline tumor

- 13 cases of CCC misdiagnosed as serous borderline tumors or low grade serous carcinoma

Features that favor CCC:
- Unilateral
- Non-heirarchical branching
- Monomorphic cell population
- Other architectural patterns
- Endometriosis

Primary versus metastasis

- Rule out metastasis
- Not required to subtype at frozen

Primary ovarian carcinoma

Problem area particularly with mucinous tumors

Significance
- Prognosis
- Therapy

Primary versus metastasis: prognosis

5 year survival:

Survival analysis of ovarian mucinous tumors. There is a statistically significant difference in survival between atypical proliferative tumors (with and without microinvasion), primary mucinous carcinomas, and metastatic carcinomas ($p < 0.001$, log rank test).
Primary versus metastasis: therapy

- **Surgery**
  - Primary ovarian cancer: comprehensive surgical staging and debulking
  - Metastasis: No staging

- **Chemotherapy:** Different agents

Primary versus metastasis

*Practical approach:*
- Clinical history and intraoperative findings
- Gross evaluation
- Microscopic evaluation

Primary versus metastasis: Intraoperative assessment

- **Clinical history**
  - Prior history
- **Radiology**
  - Bilateral ovarian involvement
  - Extra-ovarian disease
  - Lesion in another organ
- **Operative findings**
  - Status of contralateral ovary
  - Ovarian surface involvement
  - Presence of mucin in peritoneal cavity
  - Abnormal appearing appendix
  - Presence of extra-ovarian disease

Primary versus metastasis

<table>
<thead>
<tr>
<th>Gross features</th>
<th>Primary</th>
<th>Metastasis</th>
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</thead>
<tbody>
<tr>
<td>Laterality</td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Size</td>
<td>&gt;10 cm</td>
<td>&lt;10 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;12 cm</td>
<td>&lt;12 cm</td>
</tr>
<tr>
<td>Surface involvement</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Stage</td>
<td>Usually stage I</td>
<td>Advanced stage</td>
</tr>
</tbody>
</table>

Lee et al, Am J Surg Pathol 2003
Primary versus metastasis: pitfalls

**Gross:**
Metastatic mucinous tumors can be
- Unilateral
- Large
- Grossly multicystic
- Smooth surface

<table>
<thead>
<tr>
<th>Microscopic features</th>
<th>Primary</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern of growth</td>
<td>Expansile</td>
<td>Nodular</td>
</tr>
<tr>
<td>Destructive stromal invasion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ovarian hilar involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Microscopic surface mucin</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Signet ring cells</td>
<td>No</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>
Primary versus metastasis: pitfalls

**Microscopic:**
“Maturation phenomenon”
Metastatic mucinous carcinomas can simulate
- Mucinous cystadenoma
- Borderline mucinous tumor
- Borderline mucinous tumor with intraepithelial carcinoma
- Borderline mucinous tumor with microinvasion
Low grade mucinous appendiceal neoplasm mimicking mucinous cystadenoma
Primary versus metastasis

Be wary of calling ovarian primary with the following (irrespective of other findings)
- Bilateral ovarian involvement
- Pseudomyxoma ovarii or pseudomyxoma peritonei
- If patient has a prior relevant history

Primary versus metastasis

- Difficult cases even after application of all the criteria
  "Mucinous neoplasm, cannot exclude metastasis, defer to permanent sections"

Vulva

- Margin assessment for squamous lesions
- Paget disease-discouraged-multifocal and positive margin status has no prognostic impact

Pregnancy/Postpartum
Ectopic pregnancy

- Endometrial curettage
- Assess grossly for villi (spongy) and submit suspicious area for frozen
- Preferable to handle as a rush specimen for permanent sections if possible

Pregnancy/Postpartum: Common scenarios

- Diffuse peritoneal studding at the time of cesarean section
- Ovarian mass at the time of cesarean section

Disseminated peritoneal leiomyomatosis (DPL)

- Can look like peritoneal carcinomatosis to the surgeon
- Multiple small granular nodules on the peritoneal surfaces
- Women of reproductive age particularly in pregnancy
- Do not mistake for metastatic sarcoma
- Small (<1 cm), no atypia, mitoses or necrosis
Disseminated peritoneal leiomyomatosis

Ectopic decidua
- Ovarian or abdominal
- Tan hemorrhagic nodules
- Resemble decidual cells
- Can have mild nuclear pleomorphism and hyperchromasia
- Can resemble signet ring cells

Ovarian mass during pregnancy/postpartum
- Pregnancy luteoma
- Hyperreactio Luteinalis
- Large solitary luteinized follicle cyst of pregnancy and puerperium
Pregnancy Luteoma

- 80% multiparous and black
- Incidental finding at C-section but occasionally symptomatic
- 25% - hirsutism or virilization
- Elevated androgen levels
- Regress within days after delivery
- Androgen level normal within 2 weeks

Pregnancy Luteoma: Gross

- Single or multiple, bilateral in one-third
- Microscopic to >20 cm
- Cut surface solid, fleshy, circumscribed, red-brown and hemorrhagic
- Cells with abundant eosinophilic cytoplasm, hyperchromatic nuclei with prominent nucleoli
- Follicle like spaces
- Mitotic figures including atypical mitoses can be seen
- Can be mistaken for a metastatic oxyphilic tumor
Hyperreactio Luteinalis

- Bilateral ovarian enlargement
- Usually associated with increased HCG levels
- Pelvic mass during pregnancy, at C-section or postpartum
- Can lead to torsion or rupture
- Regression may take up to 6 months post partum
- Can occur during ovulation induction

Hyperreactio Luteinalis

- Bilateral
- Multiple thin walled cysts
- Can be very large
- Luteinized cells forming cysts or present within edematous stroma
- Typically bland but luteinized granulosa cells can have bizarre nuclei

Large solitary luteinized follicle cyst of pregnancy and puerperium

- Unilocular thin-walled cyst with watery fluid
- Nests of luteinized cells in the fibrous cyst lining
- Cells with abundant eosinophilic to vacuolated cytoplasm and bizarre nuclei with nuclear pleomorphism and hyperchromasia
- No mitotic figures
Other interesting cases

67 year old with right adnexal mass
Diagnosis?
Struma ovarii
Thank you