Common pitfalls in the evaluation of gynecologic frozen sections

Karuna Garg, MD
University of California San Francisco
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)**
Uterus: Endometrial carcinoma
Uterus: Endometrial carcinoma

- **Rationale for FS?**

  **To stage or not to stage**
  - All high risk patients are staged (FIGO grade 3 endometrioid, non endometrioid histologies)
  - What about apparent low risk endometrial cancer?

  **Staging in selective patients based on FS findings**
Endometrial carcinoma

Treatment decisions based on FS

- Lymphadenectomy or not
- Extent of lymphadenectomy
- Omentectomy and/or pelvic biopsies

- Sentinel lymph nodes for endometrial cancer
Endometrial carcinoma

**Accuracy of frozen sections:**
- Variable (from very good to very poor)
Of 784 patients, 10 (1.3%) had a potential change in operative strategy because of a deviation in results from frozen sections to paraffin sections.

Sanjeev Kumar, Fabiola Medeiros, Sean C. Dowdy, Gary L. Keeney, Jamie N. Bakkum-Gamez, Karl C. Podratz, Will...

A prospective assessment of the reliability of frozen section to direct intraoperative decision making in endometrial cancer

Gynecologic Oncology, Volume 127, Issue 3, 2012, 525 - 531

http://dx.doi.org/10.1016/j.ygyno.2012.08.024
Endometrial carcinoma

Features to evaluate at FS

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

- Tumor size (2 cm)?
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 1-2 representative sections sufficient
Endometrial carcinoma

• 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 useful (but up to 20% tumors may be upgraded on hysterectomy)
• Evaluate architecture and cytology
• Frozen artifact makes cytology look worse!
FIGO grade 1 EEC
FIGO grade 2 EEC
FIGO grade 2 EEC
Serous carcinoma
Serous carcinoma
Serous carcinoma
High grade carcinoma
High grade carcinoma
Uterus: CAH versus carcinoma?

• Ideally should not affect management

However:

• Some surgeons may perform limited pelvic lymphadenectomy for carcinoma but not CAH

• Sentinel lymph nodes for grade 1 carcinoma but not CAH

• In difficult cases, okay to diagnose CAH, cannot exclude grade 1 carcinoma
Myometrial invasion

• Disease limited to endometrium: 1% of patients have lymph node metastasis
• Deep one-third myometrial invasion: 25% pelvic lymph node and 17% para-aortic lymph node metastasis
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
- Can lead to overdiagnosis of myometrial invasion

**Clues:**
- Rounded contours
- Preserved stroma
- Marker glands
- No desmoplastic response
Irregular endomyometrial junction
Irregular endomyometrial junction
Irregular endomyometrial junction
Stroma and marker glands
Involvement of adenomyosis

• Can lead to overdiagnosis of myometrial invasion

Clues:
- Rounded contours
- Preserved stroma
- Marker glands
- No desmoplastic response
- Presence of uninvolved adenomyosis
Uterus: tumor involving adenomyosis
Uterus: tumor involving adenomyosis
Uterus: tumor involving adenomyosis
Uterus: tumor involving adenomyosis
Uterus: tumor involving adenomyosis
Uterus: tumor involving adenomyosis
Uterus: Myometrial invasion
Uterus: Myometrial invasion
Uterus: Myometrial invasion
Uterus: Myometrial invasion
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

MELF invasion
MELF invasion
MELF invasion: LVI
MELF invasion: Occult lymph node metastasis
Lymphovascular invasion

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

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

• 55 year old female
• Endometrial biopsy showed atypical mucinous proliferation suspicious for carcinoma
• Underwent hysterectomy and staging
• Intra-operatively surgeon noticed “yellow nodules” on the peritoneal, tubal and ovarian surfaces
Hysterectomy: tumor in fundus
Hysterectomy: tumor in fundus
Peritoneal nodule
Peritoneal nodule
Diagnosis?

- Endometrioid adenocarcinoma with extensive squamous differentiation
- Keratin granuloma
Keratin granulomas

- Endometrioid carcinoma with squamous differentiation
- Peritoneal cavity
- Foreign body response to desquamated keratin
- No viable neoplastic cells
- Should not be considered metastatic tumor
- No affect on patient outcome

Chen KT et al, Arch Pathol Lab Med 1978
Keratin granuloma
Uterus: Myometrial mass
Myometrial mass

• Common clinical scenario: 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
Ovary
Ovary: Common FS issues

- Benign versus borderline versus malignant
- Primary versus metastasis
Ovary

- **Rationale for frozen sections?**

  To stage or not to stage
  - All borderline tumors and primary ovarian carcinomas are staged
Ovary: Benign versus borderline versus carcinoma
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 or solid areas
- Assess for presence and amount of epithelial proliferation
- 10% cut-off used to diagnose borderline tumor
Diagnosis can vary based on the sampled area.
Mucinous cystadenoma
Diagnosis can vary based on the sampled area.
Mucinous borderline tumor
Serous borderline tumor
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
Cystadenoma with focal epithelial proliferation
Cystadenoma with focal epithelial proliferation
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
- 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
Left ovary
Mucinous borderline tumor
Mucinous carcinoma
Endometrioid borderline tumor
Endometrioid borderline tumor
Endometrioid carcinoma
Serous borderline tumor versus low grade serous carcinoma

- Destructive stromal invasion > 5 mm
- 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)
Micropapillary serous borderline tumor
Micropapillary serous borderline tumor
Low grade serous carcinoma arising in a serous borderline tumor
Low grade serous carcinoma
Clear cell carcinoma versus serous borderline tumor

• Potential pitfall particularly at FS
• 13 cases of CCC misdiagnosed as serous borderline tumors or low grade serous carcinoma

Features that favor CCC:
- Unilateral
- Non-heirarchical branching
- Lack of stratification and tufting
- Monomorphic cell population
- Other growth patterns
- Endometriosis

Clear cell carcinoma can resemble serous borderline tumor
Clear cell carcinoma
Clear cell carcinoma
Ovary: Primary versus metastasis
Primary ovarian carcinoma

• Do we need to subtype at FS?

• May have some implications:
  - Mucinous carcinoma: Surgeon may perform appendectomy and explore bowel
  - High grade serous carcinoma: May place port for IP chemotherapy in some patients
High grade serous carcinoma
Clear cell carcinoma
Primary versus metastasis

Significance

- Prognosis
- Therapy

- Particularly problematic with mucinous tumors
Primary versus metastasis: therapy

• *Surgery*
  - Primary ovarian cancer: comprehensive surgical staging and debulking
  - Metastasis: No staging
Primary versus metastatic: Intraoperative assessment

- Clinical history
  - Prior relevant history (another primary)
- 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

### Gross features

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>Metastasis</th>
</tr>
</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*
*Seidman et al, Am J Surg Pathol 2003*
*Yemelyanova et al, Am J Surg Pathol 2008*
Primary versus metastasis: Intraoperative assessment

Algorithm:
-Bilateral tumors of any size, unilateral <13 cm: Metastatic
-Unilateral > 13 cm: Primary

Application of this algorithm correctly identified 98% of primary tumors and 82% metastases

Exceptions: colorectal and endocervical carcinomas
Metastatic gastric carcinoma

Right ovary

Left ovary
Primary versus metastasis: pitfalls

**Gross:**
Metastatic mucinous tumors can be
- Unilateral
- Large
- Grossly multicystic
- Smooth surface
Left ovary: Low grade appendiceal mucinous neoplasm, right ovary: unremarkable
# Primary versus metastasis

**Microscopic features**

<table>
<thead>
<tr>
<th>Feature</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>Signet ring cells</td>
<td>No</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Pseudomyxoma ovarii</td>
<td>No (rare exceptions*)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pseudomyxoma peritonei</td>
<td>No (rare exceptions*)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Mucinous tumors arising in teratomas
Metastatic colon carcinoma: Nodular, infiltrative growth pattern with desmoplasia
Metastatic colonic mucinous carcinoma: Signet ring cells
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
Metastatic pancreatic carcinoma - mimicking mucinous cystadenoma
Low grade mucinous appendiceal neoplasm mimicking mucinous cystadenoma
Low grade mucinous appendiceal neoplasm mimicking mucinous cystadenoma
Low grade mucinous appendiceal neoplasm mimicking mucinous cystadenoma
Primary versus metastasis

- Difficult cases even after application of all the criteria

“Mucinous neoplasm, cannot exclude metastasis, defer to permanent sections”
Case

• 55 year old female with 15 cm left ovarian mass
Diagnosis?

• Metastatic colorectal carcinoma

• **Clues:**
  - Dirty necrosis
  - High grade cytology
  - History of colon cancer (NOT volunteered by surgeon!!)
1905: “I wish you pathologists could tell us if a tissue is cancer or not while the patient is on the table.”

Thank you!
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
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 masses 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

• 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
Pregnancy Luteoma
Pregnancy Luteoma
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 postpartum
• 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
Hyperreactio Luteinalis
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