Frozen Section of Ovarian Tumors

Carmen Tornos MD
Stony Brook University Medical Center, SUNY, Stony Brook, NY
Frozen section of ovarian lesions:

**Indication**

- Establish a diagnosis that needs immediate additional surgery
Frozen section of ovarian lesions: Inappropriate requests

• to satisfy clinical curiosity
• desire solely to communicate results to the family
Frozen section of ovarian lesions:

**Indication**

- If the surgeon is not ready to perform definitive surgery when needed (staging, debulking) = the frozen section is not indicated and should not be performed
Surgeons performing ovarian surgery

- Only board certified Gynecological Oncologists are trained to perform definitive surgery for ovarian tumors including staging and/or debulking
- If the FS is requested by any other surgeon you should contact them before performing the FS
FS of ovarian lesions: Helpful Information

- Patient’s age
- Relevant clinical/family history
- Previous Hx of malignancy
- Previous pathology reports (slides)
- Serum markers (AFP, CEA, CA125, CA19.9, HCG), hormonal levels (estrogens, androgens)
- Imaging studies
Malignant Ovarian Tumors in Young Women (mean age)

- Germ cell tumors (18 years)
- Sex-cord stromal tumors
  - Juvenile granulosa cell tumor (13 y)
  - Retiform Sertoli-Leydig cell tumor (17y)
  - Sertoli-Leydig cell tumor NOS (28 y)
- Small cell carcinoma hypercalcemic type (23 y)
- Desmoplastic small round cell tumor of peritoneum (19 y)
- Metastases
- *Epithelial tumors are rare (most are LMP)*
Serum Alpha-fetoprotein (AFP)

- Normal in adults < 10µg/L
- Elevated:
  - Hepatocellular carcinoma
  - Non-seminomatous germ cell tumors (yolk sac tumor)
  - Pancreatic cancer
  - Colon cancer
  - Lung cancer
  - Granulosa cell tumors
  - Sertoli-Leydig cell tumor
  - Benign: pregnancy, hepatitis, cirrhosis
Serum Carcinoembryonic antigen (CEA)

- Normal: < 2.5 ng/ml in non-smoker, and < 5 ng/ml in smoker
- Elevated;
  - Colo-rectal cancer
  - Pancreatic cancer
  - Gastric cancer
  - Lung cancer
  - Breast cancer
  - Ovarian cancer
  - Benign: cirrhosis, chronic lung disease, pancreatitis
Elevated Serum CA 125

- Ovarian carcinoma (82%)
- Metastatic colo-rectal cancer to ovary (32%)
- Hepatocellular carcinoma
- Pancreatic adenocarcinoma
- Breast carcinoma
- Lung carcinoma
- Endometriosis
- Pericarditis
- Cirrhosis
- Pregnancy, menstruation.
Elevated serum CA 19.9

- Pancreatic cancer (71 to 93%)
- Gastric cancer (21 to 42%)
- Colon cancer (20 to 40%)
- Cholangiocarcinoma
- Hepatocellular carcinoma
- Obstructive jaundice
- Acute hepatitis
- Chronic liver disease
- Acute pancreatitis
Serum Human Chorionic Gonadotropin (HCG): Elevated

- Gestational trophoblastic tumors
- Some germ cell tumors
- Breast cancer
- Lung cancer
- GI cancer
- Bladder cancer
### Hormonally Active Ovarian Tumors

<table>
<thead>
<tr>
<th>Type</th>
<th>Estrogenic</th>
<th>Androgenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulosa cell t.</td>
<td>50%</td>
<td>rare</td>
</tr>
<tr>
<td>Stromal Luteoma</td>
<td>60%</td>
<td>12%</td>
</tr>
<tr>
<td>Thecoma</td>
<td>60%</td>
<td>0</td>
</tr>
<tr>
<td>SCTAT</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Sertoli-Leydig</td>
<td>rare</td>
<td>30%</td>
</tr>
<tr>
<td>Leydig cell tumor</td>
<td>rare</td>
<td>80%</td>
</tr>
<tr>
<td>Steroid cell t. NOS</td>
<td>15%</td>
<td>70%</td>
</tr>
<tr>
<td>Sertoli cell tumor</td>
<td>7%</td>
<td>20%</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other Hormonally Active Ovarian Tumors: Tumors with functioning ovarian stroma (androgenic or estrogenic)

- Struma ovarii
- Strumal carcinoid
- Trabecular carcinoid
- Dermoid cyst
- Dysgerminoma
- Metastatic carcinoid
- Mucinous tumors
- Rete ovarii cyst

Int J Gynecol Pathol 1986;5:319-337
Frozen sections in Ovarian Tumors: Gross examination

- Measure and weight

• Gross examination: rupture? lesions on external surface ? (ink)

• Clean cystic lesions thoroughly

• Selection of areas to sample: intramural nodules, papillary excrescences, solid component, benign cystic component

• Number of sections (mucinous tumors!)

• Goal: Identify the type of epithelium (mucinous, serous, etc)
Caution

• Not all ovarian tumors that are received open/deflated have undergone rupture (higher stage)

• Surgeons can empty the contents to facilitate the removal of the mass

• Ask the surgeon! (CAP template)
DD Ovarian tumors with a gross papillary growth

- Benign cystadenofibroma
- Serous LMP/borderline
- Seromucinous tumor
- Rarely serous carcinomas
Ovarian papillary nodules

- Hard consistency and white
  Benign

- Soft-friable, tan, translucent
  Borderline
Ovarian Tumors with Papillary Growth on the External Surface

- Benign Serous Cystadenofibromas
- Serous LMP tumors
- Ovarian carcinomas (serous)
- Metastases
Primary ovarian malignant tumors

- Heterogenous gross appearance
- Mixture of solid, cystic, with necrosis
- Clear cell carcinomas and endometrioid carcinomas can arise from benign cysts (endometriosis) and appear as small nodular areas on the cyst wall
Metastases

• Bilateral
• Multiple nodules preserving normal ovarian parenchyma in between
• Involving ovarian surface
Information that the surgeon needs at the time of the frozen section of an ovarian lesion?
Frozen Section of Ovarian Tumors

- Benign
- Borderline
- Malignant
  - Primary
    - Carcinoma
    - Sex-cord stromal tumor
    - Germ cell tumor
  - Metastasis (possible primary site)
Ovarian tumors

• Benign: no further surgery

• Borderline tumors:
  – TAH-BSO in postmenopausal + staging
  – Unilateral SO in young patients + staging
  – Staging? If comorbidity is high

• Ovarian carcinoma:
  – TAH-BSO + debulking/ staging

• Malignant sex-cord stromal tumors and germ cell tumors:
  – Unilateral SO in young patients + staging
Frozen section diagnosis of ovarian lesions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of cases</th>
</tr>
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<tbody>
<tr>
<td>Benign tumor</td>
<td>56 - 60%</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>20 - 30%</td>
</tr>
<tr>
<td>Non-neoplastic</td>
<td>15 - 20%</td>
</tr>
<tr>
<td>Borderline tumor</td>
<td>6 -10%</td>
</tr>
</tbody>
</table>
Sensitivity and specificity of ovarian frozen section diagnosis by final diagnosis

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>97 – 100%</td>
<td>81- 98%</td>
</tr>
<tr>
<td>Borderline tumor</td>
<td>57 – 99%</td>
<td>94- 98%</td>
</tr>
<tr>
<td>Malignant</td>
<td>86- 92%</td>
<td>97- 100%</td>
</tr>
</tbody>
</table>
Frozen sections of ovarian lesions: Discrepant diagnosis

- Sampling error (mostly mucinous tumors)
- Suboptimal quality of the FS
- Misinterpretation by pathologist
Dangerous Mucinous tumors!!

- Very heterogenous: same tumor can have benign, borderline and malignant areas
- Metastatic mucinous tumors can mimic primary tumors
Metastatic Tumors that Mimic Primary Ovarian Lesions

- **Mucinous**
  - Appendix
  - Colon
  - Pancreas
  - Gallbladder
  - Cervix
  - Bile ducts
  - Small intestine
  - Stomach
  - Lung

- **Endometrioid**
  - Colon
  - Endometrium
  - Gallbladder
  - Bile ducts
  - Cervix
  - Stomach
  - Appendix
  - Pancreas (rarely)
  - Breast (rarely)
  - Lung (rarely)
Mucinous Tumors in Ovary

• Ovarian mucinous tumors can lose most of their mucin when they become malignant

• Metastatic mucinous tumors to the ovary can have “maturation phenomenon”
Frozen sections of ovarian lesions: Most common diagnostic pitfalls

- Primary versus metastatic mucinous tumor
- Endometrioid carcinoma vs metastases
- Ovarian endometrioid carcinoma vs other primary ovarian tumors
- Serous tumors, benign, borderline vs malignant
- High grade ovarian cancer vs granulosa cell tumor
- Diagnosis of clear cell carcinoma of ovary
- Primary high grade ovarian cancer vs metastatic breast cancer
Features that Favor Ovarian Metastases in Mucinous Tumors

- Bilaterality
- Size < 13 cm
- Extensive intra-abdominal spread
- Ovarian surface involvement
- Hilar involvement
- Nodular invasive growth
- Abundant infiltrative pattern with desmoplastic stroma
- Extensive lymphovascular invasion
- Pseudomyxoma peritonei
- Extensive signet ring cell histology
- Colloid carcinoma pattern
- Small glands with bland cytology buy invasive pattern
Features that Favor Ovarian Primary in Mucinous Tumors

- Size > 13 cm
- Smooth external surface
- Benign/adenofibroma/borderline areas
- Endometriosis
- Complex papillary architecture
- Multiple histologic patterns
- Association with teratoma, Brenner, Sertoli-Leydig cell tumor
Case 1

- 67 year old woman with bilateral complex ovarian masses on CT scan.
- CA 125: 320 U/mL
- No Hx of malignancy
- A solid and cystic 13 cm ovarian mass was sent for frozen section
Elevated Serum CA 125

- Ovarian carcinoma (82%)
- Metastatic colo-rectal cancer to ovary (32%)
- Hepatocellular carcinoma
- Pancreatic adenocarcinoma
- Breast carcinoma
- Lung carcinoma
- Endometriosis
- Pericarditis
- Cirrhosis
- Pregnancy, menstruation.
Ovarian tumors with endometrioid glands/tubules

- Endometrioid carcinoma (ovary, uterus)
- Sertoli-Leydig cell tumor
- Endometrioid-variant of yolk sac tumor
- Carcinoid (primary or metastatic)
- Metastatic colo-rectal cancer
- Metastatic endocervical adenocarcinoma
Metastatic Tumors that Mimic Primary Endometrioid Ovarian Lesions

- Colon
- Endometrium
- Gallbladder
- Bile ducts
- Cervix
- Stomach
- Appendix
- Pancreas (rarely)
- Breast (rarely)
- Lung (rarely)
Features that Favor Ovarian Metastases in Non-Mucinous Tumors

- Bilateral multinodular solid masses
- Involvement of ovarian surface
- Nodular invasive growth
- Extensive LVI
- Extensive desmoplastic stroma
- Preservation of normal structures
- Uniform histology
- Extensive necrosis
- Segmental destruction of glands
- Garland/cribriform + dirty necrosis
- Low grade architecture with high nuclear grade
- Occasional goblet cells
- Metastases to mesentery and/or liver
Patterns of Spread

- Ovary
- Peritoneum
- Uterine serosa
- Omentum
- Colonic serosa

- Colo-rectal
- Mesenteric nodes
- Liver
Features that Favor Ovarian Primary in a Tumor with Endometrioid Features

- Variable histology
- Low grade areas
- Adenofibroma component
- Squamous metaplasia
- Morular metaplasia
- Sertoliform areas (sex-cord like areas)
- Spindle cell metaplasia
- Endometriosis
Sertoliform endometrioid carcinoma of ovary

- Cancer 1982; 50:1322-1331
- Int J Gynecol pathol 1989; 8:364-373
- Int J Gynecol Pathol 1998; 17:266-271
- Modern Pathol 1999; 12:933-940
- Arch Pathol Lab Med 2007; 131:979-981
Endometrioid carcinoma of the ovary with a prominent spindle cell component: A report of 14 cases

Metastatic Colo-rectal Carcinoma to Ovary

• 33% present with ovarian involvement first (before diagnosis of colon cancer)
• These patients are younger (mean 48 vs 63 years) and lack specific colo-rectal symptoms.
• Often have elevated CA 125
• Often mucinous and endometrioid differentiation
Metastatic Endocervical Adenocarcinoma to Ovary

• Cervical cancer can be minimally invasive (2 mm)
• Metastases can be seen concomitant or before Dx of cervical cancer
• Metastases can be very large and mimic primary ovarian tumor (range 2 – 30 cm, average 12 cm)
• Mostly unilateral (80%)
DD of Endometrioid carcinoma of Ovary vs Sertoli Leydig in FS is Important

- Endometrioid Carcinoma
- TAH-BSO
- staging
- Sertoli-Leydig
- Unilateral SO if well differentiated
- Unilateral SO and staging if higher grade
Sertoli-Leydig cell tumor

- Small uniform glands
- Clear cytoplasm
- Solid tubules
- Leydig cells
- Mixed with other patterns (sex-cords, trabecular, sarcomatoid, retiform, heterologous elements)
- Myxoid-like hypocellular areas
# Differential Diagnosis of Ovarian Tumors

<table>
<thead>
<tr>
<th></th>
<th>Endometrioid carcinoma</th>
<th>Sex-cord Stromal Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Postmenopaus.</td>
<td>&lt; 40 years</td>
</tr>
<tr>
<td><strong>Bilaterality</strong></td>
<td>30%</td>
<td>&lt; 2 %</td>
</tr>
<tr>
<td><strong>Mucin</strong></td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td><strong>Squamous met</strong></td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td><strong>Adenofibroma</strong></td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td><strong>Nuclei</strong></td>
<td>nucleoli</td>
<td>grooved, non atypical</td>
</tr>
<tr>
<td><strong>Endometriosis</strong></td>
<td>present</td>
<td>absent</td>
</tr>
</tbody>
</table>
Tumors with Sex-cord-like features

- Sertoli-Leydig
- Adult granulosa cell tumor
- Sertoliform endometrioid carcinoma
- Carcinoid
Favor Endometrioid Carcinoma

- Nuclei are round, hyperchromatic, with nucleoli
- Typical glands of endometrioid carcinoma
- Endometriosis
- Adenofibroma component
- Squamous/morular metaplasia
- Positive EMA, negative calretinin and inhibin
Carcinoid Tumor in Ovary

- **Primary**
- Other teratomatous components
- Sertoli-Leydig
- Mucinous tumor

- **Metastasis**
- Bilateral
- Spread outside ovary in 90% cases
- Carcinoid syndrome
- Vascular invasion
- Multinodular growth
- Prominent stromal hyalinization
Carcinoid Tumor in Ovary

• J cancer Res Clin Oncol 1984; 107:125-135
• Gynecol Oncol 2007; 106:65-68
Endometrioid Variant of Yolk Sac Tumor

- Age 11 – 34 years (mean 22 years)
- Increased serum levels of alpha-fetoprotein
- Other classic components of yolk sac tumor
- Primitive nuclei
- Secretory vacuoles
- Important to make correct diagnosis since it can be treated and cured
Case 1 Metastatic colonic carcinoma

- Bilateral
- Cribriform with central necrosis, uniform histology.
- High nuclear grade
- Nodular pattern
- Colonic mass found at the time of surgery
Case 2

- 45 year old with unilateral adnexal mass
- Normal Ca 125
- A 9 cm adnexal mass was sent for frozen section
Grossly hemorrhagic ovaries

- Torsion (infarcted ovary)
- Granulosa cell tumor, adult type
- Carcinosarcoma
- Choriocarcinoma
Solid ovarian tumor

- Fibroma
- Granulosa cell tumor
- Metastatic endometrial stromal sarcoma
- Spindle cell variant of endometrioid carcinoma
- Ovarian carcinoma: Undifferentiated or serous carcinoma
- Lymphoma
- Rarely metastatic carcinoma (breast, renal cell ca, etc)
Solid tumor with low grade cytology

- Fiboma/thecoma
- Granulosa cell tumor, adult type
- Endometrial stromal sarcoma
Solid ovarian tumor

- Cytology
- More sections: look for other areas more typical of GCT, Fibroma, carcinoma, etc
Patterns of Adult Granulosa Cell Tumor

- Microfollicular (Call-Exner bodies)
- Macrofollicular
- Trabecular
- Insular
- Hollow-tubular
- Solid tubular
- Solid
- Watered-silk
Solid ovarian tumor with low grade cytology

- Fibroma
- Collagen
- Spindle cells

- Granulosa cell tumor
- Richly vascularized
- Oval cells
- Nucleoli
- Grooves
- Other histologic patterns
- Staging?
Solid ovarian tumors with high grade cytology

- Spindle cell variant of endometrioid carcinoma
- Ovarian carcinoma: Undifferentiated or serous carcinoma
- Lymphoma
- Rarely metastatic carcinoma (breast, renal cell ca, etc)
Common problem at time of frozen section

• Primary solid ovarian cancer vs

• Metastatic solid carcinoma
Features enhanced by formalin fixation

- Papillary growth
- Micropapillary type of invasion
- Clear cytoplasm
Labs that fix FS with ethanol

• Higher incidence of solid primary ovarian tumors
Frozen sections fixed in formalin

- Tissue may become detached from glass slide
- Use slide warmer for few seconds before staining
Features that may help in the Dx of serous carcinoma on frozen section

Modern Pathology, 2008; 21 supplement 1, 224A
## Frozen Sections of Solid Ovarian Tumors

<table>
<thead>
<tr>
<th></th>
<th>Serous Ca. (56)</th>
<th>Metastases from Breast (31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large nuclei (15 microns)</td>
<td>96%</td>
<td>0</td>
</tr>
<tr>
<td>Multinucleated cells (28 microns)</td>
<td>89%</td>
<td>6%</td>
</tr>
<tr>
<td>Macronucleoli (&gt; 3 microns)</td>
<td>78%</td>
<td>45%</td>
</tr>
<tr>
<td>Psammom. Cals</td>
<td>21%</td>
<td>3%</td>
</tr>
<tr>
<td>Uniform nuclei</td>
<td>1.7%</td>
<td>80%</td>
</tr>
</tbody>
</table>
Features that favor serous carcinoma

- Large cells
- Multinucleated giant cells
- Areas of more typical serous carcinoma (papillary, micropapillary)
- Psammomomatous calcifications
- Squamoid morular-like areas
Case 2

Granulosa cell tumor, adult type
Conclusions:

1- If The FS is not indicated it should not be done
Conclusions, cont.

- Check the OR schedule the night before
- Clinical history
- Previous pathology reports
- Radiology studies
- Clinical laboratory tests
Frozen sections of ovarian lesions: My advice

• In doubt: never render a malignant diagnosis (is better to under-call)
  – Re-examine the gross specimen
  – Take additional sections
  – Do a touch prep
  – Get a second opinion
  – Talk to the surgeon
    - Get more history
    - Ask for his/her impression