Intraoperative Consultation in Gynecological Pathology: The Adnexal Mass

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Or,

“How to render a foolproof diagnosis on 1 mediocre frozen section of a 32 cm complex adnexal mass in 6 minutes or less”
OVARIAN MASS “NYD”

- Non-neoplastic
- Neoplastic
  - Primary
  - Metastatic
    - Epithelial-Stromal
    - Germ Cell
    - Sex cord-Stromal
    - Other
      - Benign
      - Borderline
      - Malignant

\{ Subtype \}
## Informal survey

| What is your level of confidence in IOC dx of an adnexal mass? (Scale 1-10) | 9-10 for benign & straightforward cases  
6-7 or less for difficult cases |
|---|---|
| **What areas do you find the most (a) Challenging?** | Primary vs Metastatic  
Florid borderline vs carcinoma  
Subtype classification in carcinoma  
Rare tumors & anything in young women |
| **(b) Straightforward?** | Benign tumors, dermoid cysts |
| **What factors would improve your ability to render an accurate IOC dx?** | Clinical information  
Gyne path feedback on final pathology  
Technologist assistance |
Intraoperative Consultation of an Adnexal Mass

• Fine tune the approach to IOC

• Pitfalls and limitations in frozen section
  • Emphasis on ovarian tumors prone to discrepant final diagnosis

• Understand the clinical consequences of IOC diagnosis
Royal Jubilee Hospital
(Subspecialty AP)

Victoria General Hospital
(frozen section coverage - not so subspecialty AP)
IOC in Gyne Pathology

• ~10% of IOC overall
  – 50-75% adnexal mass
    • *Our center* >90%
      – (Others = Uterus, vulvovaginal, lymph nodes)

• IOC expectations have evolved with improved understanding and histotyping of ovarian carcinomas
IOC of the adnexal mass:
Surgeon’s perspective

- Needs a tissue diagnosis
- Impact on surgical staging
- Preservation of ovarian tissue
  - Fertility
  - Hormonal benefits to age 65
The surgeon’s perspective

1. **Known diagnosis of high grade serous ca**
   - Interval debulking after 3-4 cycles chemotherapy
   - Tumor banking
   - Generally little or no role for frozen section

2. **Adnexal mass “NYD”**
   - Usually no prior tissue diagnosis
   - Often sent for frozen section
<table>
<thead>
<tr>
<th>Intraoperative Diagnosis</th>
<th>Surgery</th>
<th>Young</th>
<th>Old(er)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Cystectomy</td>
<td>SO TAH-BSO</td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>SO +/- staging*</td>
<td>TAH-BSO + staging*</td>
<td></td>
</tr>
<tr>
<td>Malignant: Primary surface-epithelial</td>
<td>SO + staging*</td>
<td>TAH-BSO, debulking, staging*</td>
<td></td>
</tr>
<tr>
<td>Malignant: Sex cord stromal, germ cell</td>
<td>SO +/- staging</td>
<td>TAH-BSO, staging</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>Often conservative surgery Exploration of peritoneum and viscera Appendectomy if mucinous*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IOC dx of primary ovarian malignancy: *Potential Consequences*

- Patient has the necessary and appropriate surgery
  - Especially for *clinically stage I* tumors (extra-ovarian spread subclinical in 25%)

- Conversion to laparotomy, longer OR time, higher postoperative morbidity

- HGSC $\rightarrow$ +/- Intraperitoneal catheter
IOC dx of primary ovarian malignancy: Potential Consequences if final pathology = Metastatic

- Unnecessary radical surgery
- Surgeon may have performed more extensive exploration for primary, or called in general surgeon to assist
IOC dx of malignant ovarian tumors – *Realistic comments*

- General gynecologists unlikely to perform full staging surgery

- In young patients, conservative is the rule and can await final pathology (can do second surgery, but cannot put parts back)
IOC dx of malignant ovarian tumors – *Realistic comments*

- Maintain open dialogue with surgical colleagues
  - “Adnexal mass” sent for IOC may not yield the whole story unless you ask specific questions

- Presume that IOC is of value (to the surgeon and in best interest of the patient)
The pathologist’s perspective

• Huge range of ovarian tumor types
• Diversity within tumor categories
  – Benign, borderline, or malignant?
  – Experience with rarer germ cell and sex cord stromal tumors may be limited
• Primary or metastatic?
• Not every “adnexal mass” is a tumor
  – Non-neoplastic lesions can mimic clinically advanced malignancy
The pathologist’s perspective

• Clinical information often lacking

• Concern about immediate surgical consequences

• Professional and practical desire to make the right diagnosis
Frozen section diagnosis of ovarian tumors

• Diagnostic accuracy 59-96%
  – What are the most problematic tumors?
  – Can accuracy be improved?
Intraoperative assessment of ovarian tumors

- Retrospective 5-year review of 914 consecutive ovarian tumor frozen sections
  - 60% benign, 10% borderline, 30% malignant

- Overall accuracy = 95.3%
  - Borderline tumors: Serous - 90%; mucinous - 65%
  - Malignant: Primary - 86%; metastatic - 59%
Intraoperative assessment of ovarian tumors

- 43 cases (4.7%) significant diagnostic discrepancy
  - Pathologist misinterpretation (53%), sampling error (40%), poor quality slides (20%)
  - Under-diagnosis in 32 cases (75%), usually mucinous
  - Over-diagnosis in 11 cases (25%), usually serous

- **FS diagnosis in 1104 borderline tumors (data pooled from 7 studies)**
  - Overall accuracy 67.1% (741/1104)
  - Under-diagnosis in 20% (mucinous histology as a significant predictor)
  - Cautious surgical decision-making for BTs based on FS dx, especially in mucinous tumors
What’s the problem?

- **Under-diagnosis**
  - Large tumors, mucinous tumors (*sampling*)
  - Unilateral tumors, tumor confined to ovary (*clinical bias*)

- **Over-diagnosis**
  - Serous neoplasms (*interpretation*)
  - Extra-ovarian spread (*clinical bias*)

- **Metastatic tumors**
  - Morphologic overlap with primary tumors

### Pre-IOC homework

<table>
<thead>
<tr>
<th>Operating Room Slate (Final)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURGEON-1</td>
</tr>
<tr>
<td>ASSISTANT</td>
</tr>
</tbody>
</table>

| | GYN00425 - HYSTERECTOMY ABDOMINAL, BILATERAL SALPINGO OOPHORECTOMY, OMENTECTOMY, STAGING AND DEBULKING | 50Y |
| | GYN00425 - LAPAROTOMY, UNILATERAL SALPINGO OOPHORECTOMY, POSSIBLE CYSTECTOMY, POSSIBLE STAGING | 27Y |
Pre-IOC homework: Clinical synopsis

- Presentation, signs and symptoms
  - Any unusual flags eg. hirsutism
- Previous gyne history/surgery
- Previous history malignancy
- Physical examination findings
- Clinical impression and plan
Pre-IOC homework: Imaging

• Cystic, solid, solid-cystic
  • “Complex ovarian mass” → 25% malignant
  • “Benign” → 30% malignant

• Unilateral or bilateral

• Any extra-ovarian spread (omentum), ascites

• Status of uterus, and of abdominal organs
## Bilaterality of stage I* ovarian tumors

<table>
<thead>
<tr>
<th>Type</th>
<th>Subtype</th>
<th>Bilaterality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>Borderline</td>
<td>25-40%</td>
</tr>
<tr>
<td></td>
<td>Carcinoma</td>
<td>15%*</td>
</tr>
<tr>
<td>Mucinous</td>
<td>Borderline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Intestinal</td>
<td>5-10%</td>
</tr>
<tr>
<td></td>
<td>- Endocervical type</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Carcinomas</td>
<td>5-10%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>Benign/borderline</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Carcinomas</td>
<td>15%</td>
</tr>
<tr>
<td>Clear cell</td>
<td>Carcinomas</td>
<td>2%</td>
</tr>
</tbody>
</table>

Clement & Young 2008
<table>
<thead>
<tr>
<th>Germ cell tumors</th>
<th>Mature cystic teratoma 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dysgerminoma 20%</td>
</tr>
<tr>
<td></td>
<td>YST Rare</td>
</tr>
<tr>
<td></td>
<td>Immature teratoma Rare</td>
</tr>
<tr>
<td>Sex cord-stromal tumors</td>
<td>AGCT &lt;5%</td>
</tr>
<tr>
<td></td>
<td>JGCT 2%</td>
</tr>
<tr>
<td></td>
<td>Fibroma 8%</td>
</tr>
<tr>
<td></td>
<td>Thecoma 3%</td>
</tr>
<tr>
<td></td>
<td>SLCT Rare</td>
</tr>
<tr>
<td>Metastatic tumors</td>
<td>70%</td>
</tr>
</tbody>
</table>
Pre-IOC homework: Tumor markers

- CA 125
  - High levels (>500) often present in advanced stage HGSC
  - Normal in 25% of stage I ovarian ca
  - Can be ↑ in non-neoplastic lesions (e.g., endometriosis)
  - Can be ↑ in colorectal ca, mesothelioma, also breast, lung, pancreas, bladder ...
Pre-IOC homework: Tumor markers

- **CA 19-9** (GI, 1° ovarian mucinous tumors)
- **CA 15-3** (Breast, 1° ovarian serous tumors)
- **CEA** (GI, lung, breast, sometimes ovary)
- **Others**
  - AFP, LDH, hCG (germ cell panel)
  - Androgens
  - Serum calcium (hypercalcemic small cell ca)
Ovarian Carcinoma Subtypes Are Different Diseases: Implications for Biomarker Studies


Surface-epithelial ovarian carcinoma: 5 major histologic subtypes

<table>
<thead>
<tr>
<th>Histotype</th>
<th>Proportion of cases</th>
<th>Proportion of early stage ca (I-II)</th>
<th>Proportion of advanced stage ca (III-IV)</th>
<th>Advanced stage at dx (by subtype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade serous</td>
<td>68-71%</td>
<td>36%</td>
<td>88%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Clear cell</td>
<td>12-13%</td>
<td>27%</td>
<td>5%</td>
<td>Often stage I</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>9-11%</td>
<td>26%</td>
<td>3%</td>
<td>Often stage I</td>
</tr>
<tr>
<td>Mucinious</td>
<td>3%</td>
<td>8%</td>
<td>1%</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>Low grade serous</td>
<td>2.4%</td>
<td>-</td>
<td>-</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

Seidman JD, et al 2004; Kobel et al, 2010; Conkin & Gilks 2013
The postmenopausal patient …

• Abdominal discomfort/distension, urinary frequency, change in bowel habit, early satiety, +/- PMB
• High levels Ca-125
• Adnexal mass (bilateral or large irregular pelvic mass), omental cake, ascites

*High grade serous carcinoma*
The pre- to peri-menopausal patient...

- Irregular periods, pelvic pain
- History of endometriosis
- Mild to moderate elevation CA 125
- Unilateral solid-cystic adnexal mass on pelvic U/S
- No evidence of extra-ovarian disease

*Broad ddx but be alert to endometrioid or clear cell ca*
The adult young patient (18 - 30)...

• Benign:
  • Mature cystic teratoma!
  • Epithelial tumors less common (often mucinous)

• Malignant → 30-30-30 rule:
  • Germ cell (*dysgerminoma*) - sex cord-stromal (*JGCT, SLCT*) – Surface-epithelial (*mucinous BT*)
  • Other eg. hypercalcemic small cell ca
  • Mets are very uncommon but do occur

Crum PC et al, Intraoperative evaluation of ovarian tumors 2006;821-38.
The IOC: Gross evaluation of the “ovarian tumor NYD”

- Dimensions x 3 (and weight)
- Orient – what tissue is actually received?
  - Cystectomy, SO, TAH-BSO, wedge biopsy
  - Fallopian tube
  - Ovarian surface
    - Intact?
    - Excrences, nodules, adhesions?
Tumor sampling: Go for the money

- Sample the area that looks most worrisome
- If heterogeneous, try to include adjacent different areas
- Attempt to open most cyst locules
- Consider more than one section (mucinous)
- +/- Smears
Case 1

- 61-year-old woman
- Booked for TAH-BSO, omentectomy
- No clinical notes available
- CA 125 = 886
- Imaging – adnexal mass, omental cake, ascites

→ IOC - 10 cm solid-cystic adnexal mass
Case 1 - Surgical outcome

- Completion of TAH-BSO, omentectomy as booked
- Debulked to minimal residual disease
  - Residual small (<1 cm) sub-diaphragmatic tumor plaque not resected
- Final pathology = HGSC, pT3c
Case 2

- 60 year-old woman
- TAH-BSO +/- omentectomy
- Breast cancer 6 years ago, remote hysterectomy
- Normal tumor markers
- Imaging
  - 15 cm solid-cystic right ovarian mass
  - Nil else
FS Dx:
Final Dx:
DDx of HGSC on frozen section

• Other primary high grade ca
  – Clear cell carcinoma
  – Endometrioid carcinoma

• Metastasis – breast
  – Poorly differentiated ductal – check pre-IOC and OR findings; may have to defer
  – (Lobular → Krukenberg)
Case 3

• 51 year-old, “fullness”
• Booked for TAH-BSO, omentectomy
• 10 cm solid-cystic adnexal mass
• No ascites
• CA-125 = 297, CEA normal

⇒ IOC – 10 cm solid-cystic ovarian mass, normal tube. FSx1 and smears
Final Dx:
Case 4

- 58 year-old, lower abd pain, “heaviness” x 2 months
- TAH-BSO, omentectomy
- Imaging - 12.5 cm solid-cystic adnexal mass, no ascites
- CA-125 = 111; normal CEA, 15-3, 19-9

→ IOC – 14 cm solid-cystic tubo-ovarian mass
FS Dx:
Final Dx:
Case 4 - Surgical outcome

- Completion of TAH-BSO, omentectomy as booked
- Final pathology = HGSC, pT3c
- Operative report
  - Large pelvic mass, nodularity in cul-de-sac
  - 100 ml ascites
  - Plaque of tumor rectosigmoid colon, omental nodules 2-3 cm
FS looks primary epithelial ca, but ? subtype

→ Ask about the operative findings (other ovary/tube, omentum, ascites)

→ Is the quality of FS acceptable?

→ Use of smears depends on comfort level with cytology

→ Gross – fimbrial tumor?
## HGSC vs CCC - clues

<table>
<thead>
<tr>
<th>Feature</th>
<th>HGSC</th>
<th>CCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td>Advanced</td>
<td>Confined to ovary</td>
</tr>
<tr>
<td><strong>Gross</strong></td>
<td>Fimbrial/tubo-ovarian mass</td>
<td>Normal tube</td>
</tr>
<tr>
<td></td>
<td>Solid-cystic, papillary</td>
<td>Solid area or nodules within unilocular cyst</td>
</tr>
<tr>
<td><strong>Architecture</strong></td>
<td>Lush papillae with tufting, slit-like spaces, solid TCC-like, glandular</td>
<td>Rounded papillae with cores and minimal stratification; tubulocystic, solid, hyaline</td>
</tr>
<tr>
<td><strong>Nuclei</strong></td>
<td>Pleomorphic, grade 3</td>
<td>Grade 3 but scattered</td>
</tr>
<tr>
<td><strong>Mitoses</strong></td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>
Case 5

- 56 year-old woman, pelvic discomfort
- Booked for USO, possible TAH-BSO

IOC:
- 15 cm left ovarian cystic mass, normal tube
- Unilocular cyst with turbid brown fluid
- Smooth internal lining with foci of brown granularity and a 2.0 cm nodule with calcification
Intraoperative diagnosis:

Grossly benign and intact
(probable mature cystic teratoma)
The surgeon said

- Tumor markers normal
- No ascites
- Uterus normal, atrophic right ovary and tube
- No other visible disease in pelvis or abdomen
- Closed after USO
Clear cell carcinoma arising in endometriotic cyst
Unilocular AGCT

Cystic struma ovarii
Case 6

- 32 year-old woman
- 10 cm complex ovarian mass
- Booked for cystectomy, possible SO
- Normal tumor markers
- No ascites
Case 6 - Surgical outcome

- SO, peritoneal washings
- No evidence of extra-ovarian disease; omental biopsy and peritoneal biopsies
- Final pathology = SBT, stage pT1a
Serous borderline tumor in pregnancy – lush papillae
Dx = Micropapillary serous borderline tumor
Dx = HGSC
Serous tumors: IOC targets

• **Benign vs SBT**
  - Firm, bulbous papillae, vs velvety soft excrescences
  - Simple papillae with bland nuclei, vs hierarchical branching, tufting, exfoliation, with mild-moderate nuclear atypia

• **SBT vs HGSC**
  - Exuberant papillae can lead to misinterpretation of SBT as serous ca → nuclei are key (and mitoses)
Serous tumors: IOC targets

- **HGSC vs …..**
  - CCC: architectural patterns, endometriosis, low stage
  - EC: squamous diff, endometriosis, low stage
  - CCC/EC may be cystic with multiple small nodules
  - “High grade ovarian carcinoma, (favor ….)”
  - (LGSC: Nuclei, mitoses)
  - (Metastasis - breast)
Case 7

- 48 year-old woman
- Abnormal uterine bleeding
- Imaging: 9 cm solid-cystic ovarian mass
Final Dx:
53 year old with 8 cm solid ovarian mass
Case 8

- 87 year-old woman
- Not on regular OR slate
- “Pelvic mass” submitted for FS
- 19 cm right ovarian mass, solid-cystic tumor with surface involvement; attached normal tube
FS Dx:
Case 8: Surgical outcome

Pathologist: “Any history of colon cancer?”

Surgeon: “Yes, we’re doing the resection right now”
Ovarian endometrioid carcinoma: IOC targets

- Glandular architecture, low grade nuclei, squamous differentiation
  - High grade EC are difficult
- Endometriosis
- 15-20% have endometrioid ca of endometrium
- Be wary of:
  - Many histological variants of EC
  - Mimics eg. sex cord stromal (AGCT, SLCT)
  - Metastasis, especially colorectal ca
Mucinous tumors
Primary ovarian mucinous tumors

• **Benign**

• **Borderline**
  – Intestinal type
  – Endocervical-like type (seromucinous)

• **Malignant**
  – Expansile invasion
  – Infiltrative invasion
Mucinous ca, expansile
Mucinous neoplasms: Primary vs Metastatic

Simple algorithm:

Unilateral and ≥ 13 cm = Primary
All others (bilateral* or < 13 cm) = Metastatic

*5-10% of primary IMBT and mucinous ca are bilateral!

68 year old with 28 cm unilateral left ovarian mass
58 year old with 20 cm unilateral right ovarian mass
FS Dx =
Case 9

- 28 year old woman, G0P0
- 12 cm complex right ovarian cyst
- Right ovarian cystectomy
- Incised to drain cyst fluid, and removed in 3 fragments
- No frozen section
• 6 mths later, follow-up U/S: 10 cm right ovarian cyst
• Laparotomy #2: RSO, appendectomy, omental bx

Recurrent IMBT

Irving and Clement, *Int J Gynecol Pathol* 2014
• Median age 36 yrs
• 95/97 Stage I
• Recurrence rate 13.4% (48 months F/U)
  • 7 borderline, 7 invasive carcinoma
• Single prognostic indicator for recurrence = CYSTECTOMY
Mucinous tumors: IOC targets

- Primary - Benign vs borderline vs carcinoma
  - Tendency to undercall
  - Take more than 1 section
  - Mental check re: possibility of metastasis
  - Experience with typical appearance of primary mucinous neoplasia helps (follow-up with final path)
  - “At least borderline” is entirely acceptable
Mucinous neoplasms: Metastatic

- Colorectal*
- Appendix
- Stomach**, small bowel
- Pancreas**, gall bladder
- Endocervical*
- Lung, breast

*Most likely to violate the algorithm; **May be occult
Primary vs metastatic mucinous neoplasms

- Unilateral
- Smooth external surface
- Expansile invasion
- Complex papillary pattern
- Benign & borderline areas (or teratoma, Brenner)

- Bilateral
- Surface involvement
- Hilar involvement
- Multinodular
- Infiltrative invasion “with preservation”
- Single cells or signet-ring cells
- LVI

Lee and Young Am J Surg Pathol 2003;27:281-92
Krukenberg tumor
Metastatic adenocarcinoma (colorectal primary)

Metastatic adenocarcinoma (endocervical primary)
Case 10

- 27 year-old
- Pelvic mass on clinical examination
- CA 125 = 346, CA 19-9 = 638

→ IOC - 19 cm ovarian mass, intact, smooth surface; normal tube
  - Solid-cystic with copious mucin, necrosis
Final Dx =
Case 11

- 76 year-old woman
- 3-mth hx increasing girth
- TAH 30 years prior
- CA 125 = 120, Ca 19-9 = 126; CEA 5.3, normal CA 15-3
- Imaging = 25 cm cystic ovarian mass, no solid components

→ IOC = 25 cm cystic mass, smooth surface
Permanent sections
Final Dx = + CK7, CK20, CDX2; focal weak PAX8; - ER, TTF-1, GATA-3
Case 11: Follow-up

- Remains asymptomatic
- CA 19-9 stable elevation
- Post-op CT 2 months later – heterogeneous mass body/tail of pancreas 19 x 13 mm, communicates with pancreatic duct
Case 12

- 82 year-old woman
- Left ovarian mass, NYD
- Operative findings – inspissated jelly-like fluid

→ IOC – 18 cm multiloculated cystic ovarian mass
FS Dx:
Well differentiated mucinous neoplasm,
? borderline mucinous tumor
Recommend appendectomy
Permanent sections

CK-20 and CDX-2 positive
CK-7 negative
Final Diagnosis:
Low grade appendiceal mucinous neoplasm metastatic to ovary
Mucinous tumors: IOC targets

• Algorithm one tool only, use with caution
  – Primary IMBT and mucinous ca can be bilateral
  – Mets can be large and unilateral
  – Mets can exhibit “maturation”

• Appendectomy?
  – “Low grade mucinous neoplasm, cannot exclude metastasis” OR if appendix is abnormal
Mucinous tumors: IOC targets

- Surface involvement and histology discordant with primary mucinous neoplasia ("odd-looking") can speak volumes
  - Deceptively bland glands and cysts of bizarre shape & sizes, small gland pattern, ++ signet rings → think metastasis
1. **Pre-IOC**

2. **IOC**

3. **Post-IOC:**
   - Follow-up with final pathology
   - Patient outcome
   - Formally track FS-Final correlation
Summary viewpoints

• Improved accuracy in subtyping of ovarian carcinoma can extend to FS

• With careful, considered approach, and awareness of pitfalls, improved accuracy is obtainable in IOC dx in mucinous, borderline, and metastatic tumors