OVARIAN MASSES: MANAGEMENT CHALLENGE

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Thank you on behalf of the AIUM who convened this Consensus Panel on the Management of Suspicious Adnexal Masses.
AIUM convened a multi-disciplinary / international consensus panel to address the diagnosis and management of asymptomatic women with pelvic masses fall November 2014

- Chairs: Drs. Steven Goldstein & Phyllis Glanc

Agreed that the consensus statement published by SRU in 2009 entitled “Management of Asymptomatic Ovarian and Adnexal Cysts Imaged at Ultrasound” remains relevant and appropriate in 2015

*So why did we need another consensus statement? *
SRU Consensus Statement

- Agreed:
  - Pelvic US is still the primary imaging modality to evaluate adnexal masses
  - Based on morphologic features in combination with Doppler evaluation of vascularity an expert sonographer can correctly characterize most adnexal masses, especially if their appearance is classic for that entity

Why Another Consensus Conference?

1. **Too much surgery** done for benign masses
   - ACOG made this more likely when in 2013 stated that “with the exception of simple cysts on a TVS most pelvic masses in postmenopausal women will require surgical intervention.”
   - ~200,000 USA women undergo surgery for pelvic mass to find 22,000 women with ovarian cancer (0.1%)

2. **Too few referrals** to gynecology oncology for OC
   - Improved outcomes in OC when treated by a gynecology-oncologist

Panel mandate was to **address** the gap between current knowledge and the translation of this knowledge into practice
<table>
<thead>
<tr>
<th>Category</th>
<th>Management</th>
</tr>
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<tbody>
<tr>
<td>Almost certainly benign</td>
<td>Variable F/U depending on confidence clinician</td>
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<tr>
<td>Indeterminate*</td>
<td>Second stage testing</td>
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<tr>
<td>Suspicious for malignancy</td>
<td>Proceed to surgical evaluation involving gynecology-oncology</td>
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*Defined unable to unambiguously place into either the benign of malignant category after US*
Discussion Points

- High grades serous cancer (HGSC) often detected in FT with >85% Stage 2
- No documented relationship between serous cystadenomas & HGSC
  - All linkages are via retrospective data
  - Mutation evidence supports this statement
    - Molecular studies indicate that BRAF gene mutations are NOT found in cystadenomas, 86% polyclonal consistent with hyperplasia
    - P53 mutations have not been found in cystadenomas
    - < 5% stage I (borderline) serous tumors without more worrisome features (micropapillary architecture or complex growth) will recur
    - Some serous carcinomas are associated with ovarian lesions that closely resemble benign cystadenomas or cystadenofibromas, but high grade carcinomas are virtually never discovered as stage I tumors within these cystadenomas
Risk of encountering most lethal ovarian carcinoma i.e. HGSC in benign appearing US abnormality is low

- The long term risk of malignancy following a diagnosis of serous cystadenoma is similar to that of the general population.
- The risk of encountering the most lethal ovarian carcinoma (HGSC) in an otherwise benign appearing ultrasound abnormality or placing a patient at increased risk of this disease if the patient with a benign abnormality is managed conservatively is low.
 Definitions:

- Virtually all American publications have used the word unilocular to mean simple, in other words, no wall papillae, solid areas, complete or incomplete septae.

- The Europeans & IOTA mostly use unilocular cyst to include cysts with papillae < 3mm height ( < 4 in number) or with incomplete septa.

- IOTA & much of Europe do not include in the definition of unilocular the presence or absence of internal echoes.
Discussion Points - Trials
Risk Malignancy in Unilocular Cystic Tumors < 10 cm

- Ovarian Screen program – University of Kentucky Ovarian Screen Trial
- 15,106 women ≥ 50 years annual TVS
- 2,763 (18%) diagnosed with unilocular cysts
  - Repeat TVS @ 4-6 weeks with ~ 70% resolved spontaneously
    - 2/3 did within 3 months ( ? Some peri or premenopausal) – timing was not related to volume
    - Advised to undergo surgical excision if developed solid or wall abnormality, may also have undergone surgery if persistent or progression
  - 52% of 117 surgically excised unilocular cystic masses were serous cystadenomas and none were malignant or borderline
  - No cancers developed in simple cysts < 10 cm
  - 10 women were ultimately diagnosed with invasive cancer
    - 7 developed an additional morphological abnormality (gen solid or papill)
    - 2 cyst resolved prior to develop OC same ovary, 1 dev OC in other ovary
- Conclude: Risk malignancy in unilocular cysts < 10 cm in women ≥ 50 yrs is extremely low permitting conservative serial TVS (<.1%)

Greenlee et al: 4 years of TVS screening for the Prostate, Lung, Colorectal, and Ovarian cancer screening trial (PLCO)

- Simple cysts in 14% of women >55 years
- 1 year incidence of new cysts was 8%
- 1 year incidence persistence simple cysts 54%.
- If TVS showed ≥1 simple cysts no significantly increased risk for the subsequent development of invasive ovarian cancer (9/2217 women; 0.41%) compared with their counterparts with no cysts (55/12,638 women; 0.44%; P=.85).

Conclude: Simple cysts do not increase risk of subsequent invasive ovarian cancer.

Discussion Points - Trials
Malignant Potential Simple Cysts

- Sharma et al. UK Collaborative Trial of ovarian cancer screening (UKCTOCS) in post-menopausal women
  - 48,053 women of which 2,531 had unilocular cysts.
  - Within 3 years of first scan 5 of these patients developed a borderline tumour and 4 developed type 2 epithelial ovarian cancer
    - Authors did not report size but did comment that “there was a change in morphology in the few women with an initial unilocular cyst who went on to develop epithelial ovarian cancer”.
    - The data indicated that the absolute risk of malignancy was 0.4% or 4 in 1,000 cysts.
    - It is unclear if these were miscategorised initially as unilocular, whether they were truly “simple” or if they truly underwent some morphologic change.

- Study underscores two very important points:
  1) simple or unilocular cysts do not need immediate surgical intervention and
  2) follow up scans at some interval will be appropriate to detect the very small number of cysts (less than 0.4%) that were either difficult to evaluate initially or might undergo morphologic change.

Sharma et al. (UKCTOCS) in post-menopausal women

- **Overall risk of EOC within 3 years 1/22 if detect solid elements**
  - US abnormalities associated with > risk of slow growing borderline and type 1 EOC rather than the more aggressive Type 2 EOC
  - 25 (78.1%) of the borderline/Type I cancers had adnexal abnormalities with solid elements (unilocular solid/multilocular solid cysts or solid masses)

- In keeping with this the 11,982 women with normal scan annually had no BOT or Type 1 EOC but 8 developed Type 2 EOC or aggressive HGSC ie surveillance not helpful for Type 2

- Relative risk 22x for EOC if had **solid element** – most important

Discussion Points
Risk with Septations

- Ueland et al: A total of 2870 septated cystic ovarian tumors in 1,319 women were followed with repeat TVS US at 4- to 6-month intervals for an average of 77 months, and no patient developed ovarian cancer in the ovary with septal morphology but no solid elements.

- Consider multiseptated cysts with smooth inner walls malignancy unlikely, mucinous BOT of intestinal type typically > 10cm multilocular > 10 septations

Kentucky Group
- 1319 women were found to have multilocular cysts (no solid structures) in the Kentucky ovarian cancer screening study
- One was diagnosed with a borderline tumor
- One developed a papillary lesion 3.2 years after her first scan and was found to have an invasive EOC (Stage 3C)

PLCO trial
- Multicystic ovaries and unilocular ovarian cysts were not associated with an increased risk of OC compared to the women with no cysts
- Multilocular cysts were also more likely to be associated with borderline or Stage 1 primary invasive EOC than advanced ovarian cancer in a clinical series on 1066 women
Discussion Points - Trials
Other cystic Lesions

- Mucinous cysts
  - Require different index of suspicion for surveillance
Mature Cystic Teratomas – Malignant Potential

- Unknown but associations as follows:
  - Malignancy related to older age, larger tumor size (> 10cm), solid component (may enhance), rapid growth, cyst wall penetration, peritoneal spread
  - Malignant component in 0.17** - 0.8%
  - Typically SCC (SCC serum antigen unreliable)

If a woman is clearly post-menopausal then there is no physiological etiology for the presence of a hemorrhagic corpus luteum or cyst, thus hemorrhage is considered a worrisome feature in this subset of patients.

However, endometriomas (and associated hematosalpinx) can persist in post menopause, so careful assessment is needed.
Interrogate all septations or solid areas

- Meta-analysis of 46 publications concluded that the combination of US morphological assessment with CDS of tumor vascularity performed significantly better in ovarian mass characterization than either technique individually*.

- No discriminatory value of spectral Doppler to reliably distinguish malignant vs benign
  - > greater degree of vascularity > concern for potential malignancy
  - Central intratumoral vascularity > predictive value for malignancy whereas the absence of intratumoral vascularity has a high negative predictive value
    - although malignancy can occur with complete absence of flow

- THUS, Doppler cannot be used as an isolated feature to determine the risk of malignancy

Role General Gynecologist

- Front-line to decide monitor or surgery
- Foremost consideration risk malignancy
- Secondary considerations of impact on fertility, hormonal status and premature menopause, complications of surgery
Role Referral Gynecologic Oncology Consult

- Most important factor for survival is stage at diagnosis.
- After stage, appropriate referral to a center specialized in gynecological malignancy is an important prognostic factor in improving patient survival
  - Optimal surgical staging, surgical debulking, access to optimal adjuvant therapy and optimal employment of alternative treatment strategies (neoadjuvant chemotherapy, fertility sparing treatment)
  - Specialized pathology units affiliated with centers associated with gyne-malignancy less risk over and underdiagnoses of ovarian malignancies, in particular of borderline ovarian tumors on frozen section
Mass Characterization

- “Almost certainly benign”
  - Simple or unilocular cyst
  - Classic hemorrhagic cyst, including hemorrhagic corpora lutea
  - Classic endometriomas
  - Classic dermoids
  - Classic Ovarian fibromas

Mass Characterization

- **Indeterminate: Next Steps**

  - If the sonologist is unsure that a mass is a classic example of an “almost certainly benign” lesion, but it is not “probably malignant” then it can be characterized as “indeterminate.”
Next Steps: Indeterminate

- Serial ultrasound or referral to a specialized ultrasound consultant
- Application of established risk-prediction models
- Correlation with MRI imaging
- Referral to a gynecologic oncologist for further evaluation
- Correlation with serum biomarkers.
<table>
<thead>
<tr>
<th>Feature</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Solid component</td>
<td>In general solid component worrisome for malignancy, however typical hyperechoic shadowing of lesions with fat (mature cystic dermoids) or classic hypoechoic lesion with strong acoustic shadowing (fibromas) are solid benign lesions.</td>
</tr>
<tr>
<td>Blood Flow</td>
<td>Central vascularity &gt; concerning than peripheral. &gt; degree of vascularity &gt; concern.</td>
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<tr>
<td>Septations</td>
<td>Thin ≤ 2-3mm avascular incomplete septations are benign findings. vs thicker (≥3mm), multiple, irregular or vascular.</td>
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<tr>
<td>Papillary Projections</td>
<td>Papillary projection is solid protrusion height &gt; 3mm Multiple, ≥ 4 papillary projections, or involvement of more than half the wall with papillary projections of any size is worrisome</td>
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<tr>
<td>Ascites</td>
<td>Complex pelvic fluid extends beyond the pelvis is &gt; worrisome than simple fluid not extend beyond</td>
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<tr>
<td>Feature</td>
<td>Comment</td>
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<tr>
<td>Interim growth</td>
<td>No data determine amount of growth which is worrisome.</td>
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<tr>
<td>Change in Morphology</td>
<td>A change in sonomorphology, in particular the development of solid or vascular features is concerning.</td>
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<td>Hemorrhagic mass in a PMW</td>
<td>If clearly post-menopausal then no physiological etiology for hemorrhagic corpus luteum or cyst</td>
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<td></td>
<td>Note endometriomas (and hematosalpinx) can persist in post menopause, so careful assessment is needed.</td>
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<td>Bilateral Ovarian Masses</td>
<td>It is important to distinguish whether these represent primary tumor with metastases to the contralateral ovary or both represent metastatic deposits.</td>
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<td>Ovarian Mass with Known Malignancy</td>
<td>An ovarian mass in the setting of known malignancy requires the same detailed evaluation that a similar mass in the absence of known malignancy would receive, in order to determine whether this is a benign, indeterminate or suspicious mass.</td>
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Aims

- Panel mandate was to **address** the gap between current knowledge and the translation of this knowledge into practice
  - Aim to further decrease unnecessary surgery
  - Aim to improve referral rates to gynecology-oncologist when suspicious of malignancy
  - Aim to provide alternate next steps for indeterminate masses.
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<thead>
<tr>
<th>Name</th>
<th>Academic Affiliation</th>
<th>Society Affiliation</th>
<th>Country</th>
<th>Specialty</th>
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</thead>
<tbody>
<tr>
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Thank you for the opportunity to present preliminary work from this consensus conference