Current Status of Ultrasound Screening for Ovarian Cancer

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The problem of ovarian Cancer

- Ovarian CA is the 2nd most common GYN malignancy (endometrial is #1) and the most deadly (5-year survival of 45%).
- Familial predisposition accounts for only 5–10% of cases and is typically associated with BRCA1 and BRCA2 gene mutations.
- OV CA most commonly occurs in postmenopausal women with no family history.

Why screen?

- OV CA presents late due to vague symptoms such as distension, bloatedness or mass.
- Serous ovarian cancer is the most common subtype and has the poorest outcome.
- 60% of ovarian CA are diagnosed at an advanced stage, with a 5-year survival of 10%.
- When the disease is diagnosed at Stage 1 the 5-year survival is > 90%. Hence, early dx affect long-term survival.

Epithelial cell types are the most common

- Serous cystadenocarcinoma (>50% of epithelial ca) is similar in cell type to the fallopian tubes.
- Endometrioid adenoca (15-20% of epithelials) and clear cell (6% of epithelials) are associated with pelvic endometriosis in younger women.
- Mucinous adenocarcinoma (5-10% of epithelials) resembles the intestinal or cervical cell types.

Ovarian cancer may originate from the tube

- The most common ovarian cancer may originate from the fallopian tube – a lesion called serous intraepithelial tubal CA (STIC), is very similar to high-grade ovarian serous carcinoma.
- The current theory is that most of these tumors arise from a STIC in the fimbriated end of the tube, then spread to the ovary.
- Even when the ovaries are removed, a pt can still develop primary peritoneal carcinoma - a very aggressive cancer.

Sonographic appearance of cyst

- Are the wall/septae thick or thin?
- Is there color Doppler flow in the solid portions? (tumor)
- Do the solid areas jiggle with motion? (clot)
Grey Scale Characteristics for Complex Masses

<table>
<thead>
<tr>
<th>Prob Malignant</th>
<th>Prob Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Thick septations</td>
<td>Thin septations</td>
</tr>
<tr>
<td>Thick irregular wall</td>
<td>Thin smooth wall</td>
</tr>
<tr>
<td>Nodularity/solid areas</td>
<td>No nodules</td>
</tr>
<tr>
<td>Ascites</td>
<td>No solid areas</td>
</tr>
</tbody>
</table>

How does Doppler fit in?

Serous cystadeno CA
The most common epithelial ovarian cancer

Hemorrhagic Cyst

Hem Cyst with Clot
**Tumor Vascularity**

- Ovarian Ca are very vascular.
- Abnormal tumor angiogenesis leads to the proliferation of abundant and disorganized tumor vessels.
- Doppler shows irregular branching, pooling and multiple foci.

*Very disorganized beaded vessels*
Two similar size cystic masses in ovary

Ovarian cancer

Borderline Ovarian Cancer

- 10-15% of ovarian tumors are borderline and occur in younger pts.
- Stage 1 at dx in ≥ 90% of pts, excellent prognosis. Unrelated to hereditary ca.
- Survivals for Stage I &III approach 100% and 80-90% respectively, even in patients who have peritoneal spread.
2 cases of borderline CA - use of Doppler and morphology

Granulosa cell tumor – may present with vag bleeding

2. Scoring Indexes with Grey Scale

- Lerner score: weighted index - revised a couple of times. 96.8% sensitivity 77% specificity, PPV 29.4%.
- Valentin tried Lerner score and got 92% sensitivity, 36% specificity, PPV 30%
- Timmerman score Sensitivity 96%, specificity 87%

Valentin L. Ultrasound Obstet Gynecol 1999;14:273
Timmerman et al. Am J OB GYN 1999;181:57

The Low PPV in determining whether a mass is benign or malignant is disappointing

This indicates that we are still hampered by complex and malignant appearing lesions that are benign ovarian masses.

3. 5 Simple Rules

Benign
- Unilocular
- Solid areas <7mm
- Acoustic shadow
- Smooth borders multinocular tumor <10cm
- No color flow

Malignant
- Irregular solid areas
- Ascites
- ≥ #4 papillary projections
- >10cm - irregular multinocular solid
- High color content (4)

Timmerman et al IOTA group. BMJ 2010;341
Using the simple rules

<table>
<thead>
<tr>
<th>Number</th>
<th>n</th>
<th>Rate of CA</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>3B 0M</td>
<td>175</td>
<td>0.6 %</td>
<td>Certainly benign</td>
</tr>
<tr>
<td>2B 0M</td>
<td>1047</td>
<td>1.1 %</td>
<td>Benign</td>
</tr>
<tr>
<td>1B 0M</td>
<td>1235</td>
<td>5.5 %</td>
<td>Probably benign</td>
</tr>
<tr>
<td>B &gt; M (M&gt;0)</td>
<td>21</td>
<td>4.8 %</td>
<td>Probably benign</td>
</tr>
<tr>
<td>B = M</td>
<td>1075</td>
<td>41.9 %</td>
<td>Malignant</td>
</tr>
<tr>
<td>M &gt; B</td>
<td>1295</td>
<td>87.5 %</td>
<td>Certainly malignant</td>
</tr>
</tbody>
</table>

Updated Simple Rules:
- If 2 or more B and no M, then Benign
- If 1 B and no M, then Probably benign
- If equal or if > 0 M, then Malignant

5 Simple Rules

- 1938 masses of which 1396 (72%) were benign, 373 (19.2%) were primary cancers, 111 (5.7%) were borderline, and 58 (3%) were mets.
- The M and B rules gave definitive results in 77% of masses. In the other 23% cases, pattern recognition by an expert was necessary to aid in the diagnosis.

International Ovarian Tumor Analysis

- These IOTA simple rules: sensitivity & specificity for predicting a malignancy of 92% and 96% respectively.
- Subjective assessment by a specialist: sensitivity & specificity of 91% and 96%.
- Either way, about 15% of benign and 10% of malignant masses will be misdiagnosed.
- CA 125 as a single cut off value did not add to the ultrasound Dx.

Timmerman et al IOTA group. BMJ 2010;341

Cystadenofibroma

Adhesions – peritoneal inclusion cyst
University of Kentucky Study

- Single site, 37,293 volunteers (22% with fam/hist) – yearly scan.
- Sens. 86.4%, spec. 98.8%, ppv 14.53%, npv 99.97%
- 6.9 operations for each CA detected
- Most (70%) of the invasive ovarian cancers were early stage (Stage 1-2)
- 5 yr survival 84.6% screened vs 48.4% unscreened.

Van Nagell et al. Obstet Gynecol 2011;118:1212

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)

- Randomized controlled trial of 78,216 pts at 10 screening centers in US 1993-2001 with ultrasound and CA 125 fixed value.
- 60/89 (68.2%) of ovarian CAs were found by screening; 13 surgeries per CA.
- A total of 72% of the screen-detected cancers were late stage (3-4)
- The screening and control arms included 118 and 100 deaths (NS).
- Morbidity of excess surgery 5%

Buys et al. JAMA 2011;305:2295

2015 - The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)- prelim result

- 202,638 postmenopausal pts were randomized to Ca 125 + ultrasound versus just ultrasound.
- CA 125 was followed over time and if rising (9%), had ultrasound and 0.2% surgery (2.9 surgeries per ovarian CA).
- Multimodal strategy for primary invasive ov. ca had superior sens. (89%), spec (99.8), PPV (43%) to ultrasound screening alone - sens 84%, spec 98%, PPV 5%

Menon et al. Gynecologic Oncology 2014;132:490

Rt ovary
Lt ovary

Stage 1A ovarian CA

Diffuse peritoneal cancer after oopherectomy for profilaxis
Decidualized Endometrioma

• Cystic masses mimicking an ovarian malignancy during pregnancy, due to areas of nodularity containing blood flow by color Doppler.
• A prospective diagnosis is possible when a pregnant women has a cyst with solid smoothly lobulated nodules and internal vascularity, stable over several weeks.

22 masses in 17 pregnant pts
• 8 pts went to surgery, 9 (14 masses), had f/u scans and surgery 3-34 weeks later
• 8 of these masses showed no change and one became smaller.
• There were no characteristic sono features identified to distinguish decidualized endometriomas from ovarian malignancy.
• Lesions showing no change over 4 weeks, or lacking solid components and vascularity are more likely to be benign.

Grosman et al. In press JUM
Similar study from Italy

- 18 cases from seven centers.
- 15 of the 18 decidualized endometriomas contained rounded papillary projections with a smooth contour.
- Suggesting that these rounded papillations were different from those associated with malignancy.

Mascilini et al. in press UOG
Bilateral Ovarian Masses

- Struma Ovarii – mimicks dermoids
- Solid adnexal masses

A very large abdominal solid mass.

- Large cystadenocarcinoma

- Fibroma

- Benign adenofibroma
12 wks for NT asymptomatic

Tubular masses
Sent in for ? Of hydrosalpinx

Tubal carcinoma
Could be either ovarian or tubal

Metastatic colon to ovary

Metastatic appendix CA to ovary
Renal cell metastasis to ovary

**Conclusions**

- Screening will not eradicate or cure the disease and is currently ineffective in low-risk pts.
- With current techniques, at best 15% of benign cysts and 10% of malignant masses will be miscategorized.
- There is no evidence that any other imaging techniques is contributory.
- The future likely will involve a combination of biochemical (trending) and ultrasound markers although protocols to be worked out.