Evaluating The Adnexal Mass

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Adnexal Mass
Clinical Implications
• Common clinical problem affecting women of all ages
• 5-10% lifetime risk of surgery in US
• 13-21% risk of having ovarian cancer
• Diagnostic and management dilemmas
• Most adnexal masses detected incidentally
• Accuracy of current technology limited
• Management complex

Adnexal Mass
Common Symptoms
• NONE
• Local
  • GI: nausea, vomiting, change in bowel habits, pelvic pressure, rectal bleeding
  • GU: Bleeding, change in voiding habits, dysparunia, pelvic pressure
• Systemic
  • Fever, change in girth or weight, pain, fatigue, decreased appetite, altered mental status

Adnexal Mass
Differential Diagnosis (Partial)
• Gynecologic
  • Benign
    • Functional cyst
    • Endometrioma
    • TOA
    • Ectopic pregnancy
    • Cystadenoma
    • Germ cell tumor
    • Hydrosalpinx
    • Leiomyomata
  • Malignant
    • Epithelial
    • Germ cell
    • Sex cord/stromal
    • Metastatic
• Non-Gynecologic
  • Benign
    • Abscesses
    • Pelvic kidney
    • Urinary diverticulum
  • Malignant
    • Breast
    • GI
    • Retroperitoneal sarcoma
    • Lymphoma
    • Metastatic

Adnexal Mass
Goals
• Determine etiology
  • Gynecologic from non-gynecologic
  • Benign from malignant
• Develop appropriate management plan
• Balance risks and benefits
• Conservative management vs. surgery
  • When, who, where, how
General Management

“It’s not so difficult…”

- Non-gynecologic
  - Appropriate referral as indicated
- Gynecologic
  - Probably benign: conservative unless symptomatic
  - Uncertain: often requires surgery for definitive diagnosis
  - Likely malignant: refer to gynecologic oncologist

Ovarian Cancer Overview

“The 800 lb gorilla…”

- Lifetime risk 1/70 (1.4%) for US women
  - Increased with genetic mutation (e.g., BRCA)
- Annually: 23,000 cases, 15,000 deaths

<table>
<thead>
<tr>
<th>Stage</th>
<th>Distribution</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>26%</td>
<td>92.7%</td>
</tr>
<tr>
<td>II</td>
<td>15%</td>
<td>71.1%</td>
</tr>
<tr>
<td>III</td>
<td>42%</td>
<td>30.6%</td>
</tr>
<tr>
<td>IV</td>
<td>17%</td>
<td>26.0%</td>
</tr>
<tr>
<td>Overall</td>
<td>100%</td>
<td>45.5%</td>
</tr>
</tbody>
</table>

De Novo Ovarian Cancer

- 14 microscopic malignancies (mean: 3.5 mm)
  - “…a subset of ovarian epithelial cancers develop de novo…without the intervening development of a benign tumor.”
- Outcome: DOD (3) AWR (2) NED (9)
  - “…question the assumption that early detection will result in a cure in most cases.”

Adnexal Mass

Diagnostic Modalities

- Physical examination
- Imaging studies
  - Ultrasound
  - CT, MRI, PET/CT
- Tumor markers
- Cyst aspiration
- Surgery
  - Laparoscopy
  - (Mini) laparotomy

Adnexal Mass

Accuracy Of Physical Examination

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts/Exams</th>
<th>Yrs.</th>
<th>Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garrett</td>
<td>23,635/74,868</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>McFarlane</td>
<td>1319/80,753</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Andolf</td>
<td>795/878</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
“In 74,000 examinations, we have found six cases of symptomless cancer of the ovary. Five of these patients are dead, and one survives. The conclusion is obvious. Vaginal examination as a means of early diagnosis of cancer of the ovary is a waste of time.”

Garrett, WJ

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**Adnexal Mass**

**Physical Examination**

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garrett PJ. Adnexal Mass: Transvaginal Ultrasound.

- Most widely used imaging modality
- No alternative imaging modality has sufficient superiority to justify its routine use
- Advantages
  - Widespread availability
  - Good tolerability
  - Reasonable cost-effectiveness
- Limitations
  - Lack of specificity, poor PPV for malignancy, especially in pre-menopausal women

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**Adnexal Mass**

**Imaging Modality Comparison**

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVUS</td>
<td>91%</td>
<td>81%</td>
</tr>
<tr>
<td>Doppler US</td>
<td>86%</td>
<td>91%</td>
</tr>
<tr>
<td>CT</td>
<td>90%</td>
<td>75%</td>
</tr>
<tr>
<td>MRI</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>PET</td>
<td>67%</td>
<td>79%</td>
</tr>
<tr>
<td>Pelvic exam</td>
<td>45%</td>
<td>90%</td>
</tr>
<tr>
<td>CA-125</td>
<td>78%</td>
<td>78%</td>
</tr>
</tbody>
</table>

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**Ultrasound Simple Adnexal Cyst**

- Largest prospective study published
  - 2,763 postmenopausal women, unilocular cysts ≤ 10 cm; serial transvaginal US every 4-6 months
  - Spontaneous resolution in 69.4%
  - No ovarian cancers detected after mean follow-up 6.3 years (>70,000 patient-years)
- Conclusion:
  - “The risk of malignancy in unilocular ovarian cystic tumors less than 10 cm in diameter in women 50 years old or older is extremely low. The majority will resolve spontaneously and can be followed conservatively with serial transvaginal ultrasonography.”

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**Ultrasound Unilocular Cysts**

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  - Spontaneous resolution in 69.4%
  - No ovarian cancers detected after mean follow-up 6.3 years (>70,000 patient-years)
- Conclusion:
  - “The risk of malignancy in unilocular ovarian cystic tumors less than 10 cm in diameter in women 50 years old or older is extremely low. The majority will resolve spontaneously and can be followed conservatively with serial transvaginal ultrasonography.”

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**Ultrasound Minimally Complex Adnexal Cyst**
Ultrasound Complex Adnexal Cyst

Adnexal Mass Color Doppler

• Hypoxic tissue recruits low-resistance, high-flow vessels
• Color Doppler measures blood flow indices
  • Resistive index, pulsatility index, maximum systolic velocity
• Goal is to increase specificity of TVUS
  • Controversial due to overlapping ranges of indices for benign and malignant adnexal masses

Ultrasound Highly Complex Adnexal Cyst

Adnexal Mass Color Doppler

TVUS Morphology Index

• Morphologic score (0-12) assigned by considering TVUS criteria
  • Ovarian tumor volume, cyst wall structure, septa structure
  • Each component assigned score from 0-4
    • Simple cyst, smooth-walled, 10 cm² = 0
    • Multiseptate cyst, irregular-wall, 100 cm² = 10
• Morphology score ≥ 5
  • Sensitivity 89%, PPV 46%, intraobserver variability high (K .41-.47)

Adnexal Mass Ultrasound Models

• Attempts to improve accuracy
• Variety of modalities
  • Logistic regression analysis using multiple variables
    • Age, maximum tumor volume, unilocularity, papillary projections, random echogenicity, highest peak systolic velocity, time-average maximum velocity, pulsatility index, resistance index
    • Sensitivity 93.3%, specificity 90.4%
  • Artificial neural network algorithm
    • Same variables
    • Sensitivity 100%, specificity 98.1%
• Prospective studies lacking
Adnexal Mass CT Scan

• Currently, main role is to assess the abdomen when malignancy is suspected
• Multi-detector CT (16-row)
  • Thin slices with high resolution
  • Reformating of images in any plane
  • 3-D reconstruction
• “…can be recommended as a reliable imaging modality to detect and characterize adnexal mass lesions…”

Adnexal Mass MRI

• Highly sensitive, more specific than TVUS
• Reserve for problem-solving when TVUS findings are non-diagnostic or equivocal
  • More accurate but more expensive
• Most likely to benefit:
  • Pregnant women
  • Premenopausal women with complex masses on TVUS but normal CA-125
• Visualizes entire pelvis (non-gynecologic organs)

Adnexal Mass PET/CT

“All in all, the suitability of FDG-PET in the assessment of malignancy in asymptomatic sonographically suspect adnexal masses is limited.”

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
<th>Accur.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>58%</td>
<td>76%</td>
<td>25%</td>
<td>93%</td>
<td>74%</td>
</tr>
<tr>
<td>TVUS</td>
<td>92%</td>
<td>60%</td>
<td>24%</td>
<td>98%</td>
<td>64%</td>
</tr>
<tr>
<td>MRI</td>
<td>83%</td>
<td>84%</td>
<td>42%</td>
<td>97%</td>
<td>84%</td>
</tr>
<tr>
<td>Combo</td>
<td>92%</td>
<td>85%</td>
<td>46%</td>
<td>99%</td>
<td>86%</td>
</tr>
</tbody>
</table>

CT Pelvis
Complex Right Adnexal Mass

Top Mag Reson Imaging 2006;17:379-397
**Adnexal Mass Tumor Markers**

- Order only if results affect management
- Specific markers
  - CA-125
  - βhCG, LDH,AFP
  - Serum inhibin A and B
- Serum-based (not yet validated)
  - OvaCheck™
  - OvaSure™

**Detection of CA-125 in Serum**

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>&gt;35 U/ml No. (%)</th>
<th>&gt;65 U/ml No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>888</td>
<td>9 (1.0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Males</td>
<td>537</td>
<td>4 (0.7)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Females</td>
<td>351</td>
<td>5 (1.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Benign disease</td>
<td>143</td>
<td>9 (6.3)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Non-gyn cancer</td>
<td>200</td>
<td>57 (28.5)</td>
<td>44 (22.0)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>29</td>
<td>17 (58.6)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Other</td>
<td>171</td>
<td>40 (23.4)</td>
<td>31 (18.1)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>101</td>
<td>83 (82.2)</td>
<td>75 (74.3)</td>
</tr>
</tbody>
</table>

**CA-125 Levels by Stage**

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;35 U/ml</th>
<th>≥35 U/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>72.0</td>
<td>28.0</td>
</tr>
<tr>
<td>II</td>
<td>16.6</td>
<td>83.4</td>
</tr>
<tr>
<td>III</td>
<td>4.3</td>
<td>95.7</td>
</tr>
<tr>
<td>IV</td>
<td>3.0</td>
<td>97.0</td>
</tr>
<tr>
<td>Total</td>
<td>20.0</td>
<td>80.0</td>
</tr>
</tbody>
</table>

**Adnexal Mass Non-Epithelial Ovarian Tumor Markers**

- Germ Cell Tumors: βhCG, AFP, LDH
- Granulosa Cell Tumors: Serum inhibin A and B

**SGO Position Statement Early Detection Markers**

The Society of Gynecologic Oncologists continues its surveillance and support of research directed toward the identification of accurate, effective and reliable early detection markers for ovarian cancer.

During the past year, researchers have continued to discover and validate new markers and techniques, and to replicate previous research.

SGO remains committed to actively following and contributing to this vitally important area of research. As physicians specially trained to care for women with gynecologic cancers, we eagerly await the day when all of these cancers can either be prevented or detected early. Because no test now exists to routinely detect ovarian cancer in its earliest and most curable stages, we urge that research aimed at identifying accurate early detection markers for ovarian cancer remain a high priority during the coming years.
### Adnexal Mass

Serum-Based Tumor Markers

- OvaCheck™
- OvaSure™

### OvaCheck™

- Serum-based diagnostic test
- Utilizes “N-dimensional” computational models developed through use of artificial intelligence
- Identifies patterns in the proteo-metabolome (protein, protein fragments, peptides and metabolites) that distinguish affected from unaffected patients

### Proteomic Pattern Analysis

A discriminating pattern formed by a small subset of proteins or peptides mathematically selected among the entire repertoire of thousands of proteins represented in the sample serum.

### Proteomic Testing Process

- **Pre-analytical preparation**
  - Sample is subjected to electrospray ionization
- **Testing**
  - Mass spectrometer generates spectrogram consisting of mass/charge ratio (m/z) features and their corresponding intensities
- **Analysis**
  - Results are subjected to pattern recognition analysis using previously developed computational models
  - The results are “scored” against previously created models to determine the probability that the individual is affected

### Proteomic Pattern Analysis

- The preliminary “training” population for comparison becomes enriched as the system learns over time from the accumulated cases
- In theory, the outcome will become more and more accurate over time

### Proteomic Pattern Analysis

- “Training set” consisted of 50 cancer samples and 50 negative controls
- Computational “model” developed by pattern discovery
- Analyzed 116 masked samples
  - 50 OvCa and 66 non-cancer
  - Sensitivity 100%
  - Specificity 95%
  - PPV 94%
- Identified all 18 Stage I cases

*Lancet* 2002; 359: 572-77
The Society of Gynecologic Oncologists recognizes the importance of accurate early detection biomarkers for ovarian cancer. For this reason, SGO reviewed the literature regarding OvaCheck, a serum-based diagnostic test for ovarian cancer.

In the opinion of SGO, more research is need to validate the test’s effectiveness before offering it to the public.

OvaSure™

- 6-marker panel composed of leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125, as well as a calculated Risk Index
- Multiplex, bead-based immunoassay
- "Components used in this test are labeled as research purposes only. The performance characteristics of this product have not been established by the assay manufacturer. Results should not be used as a diagnosis for ovarian cancer without confirmation of the diagnosis by another medically established diagnostic product or procedure."

Clin Cancer Res 2008;14:1065-72

Cyst Aspiration

- Contraindicated, esp. in post-menopausal women
- Sensitivity of cytology 25-82%
- Often not therapeutic
  - 25% cysts recur within one year
  - Spillage of cancer cells into peritoneal cavity or seeding along needle tract
  - Alters management, potentially decreases survival

Oncology 2003:65;29-36

Surgery

- “Gold standard” for diagnosis
- “Court of last resort”; Dr. George Morley
- Adequate preoperative preparation
- Prepare patient for possibility of malignancy
- Be honest about your skills
- Put patient’s best interests first
- Know when to refer
- Be willing to stop intra-operatively

OvaSure™

The Society of Gynecologic Oncologists recognizes the need for accurate early detection biomarkers for ovarian cancer. For this reason, SGO reviewed the literature regarding OvaSure, a serum-based diagnostic test for ovarian cancer.

After reviewing OvaSure’s materials, it is our opinion that additional research is needed to validate the test’s effectiveness before offering it to women outside of the context of a research study conducted with appropriate informed consent under the auspices of an institutional review board.
SGO Referral Guidelines

- Pre-menopausal (< 50 years)
  - CA-125 levels > 200 units/ml
  - Ascites
  - Evidence of abdominal or distant metastases
  - Family history of breast or ovarian cancer
- Post-menopausal (≥ 50 years)
  - Same as pre-menopausal, plus nodular or fixed pelvic mass

SGO Referral Guidelines

- Multicenter, retrospective validation trial
  - Six centers, 1,035 women undergoing surgery for an adnexal mass
  - Ovarian cancer prevalence 30.7% primary, 4.8% metastatic
  - PPV, NPV
  - Pre-menopausal 33.8%, 92%
  - Post-menopausal 59.5%, 91.1%

Conclusions

"The SGO and ACOG guidelines effectively separate women with pelvic masses into two risk categories for malignancy. This distinction permits a rational approach for referring high-risk patients to a gynecologic oncologist for management."

THANK YOU FOR YOUR ATTENTION