The Role of the Gynecologic Oncologist in Ovarian Cancer Care

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University of Kentucky
Disclosure

Member of the Vermillion’s Speakers Bureau

- OVA1 blood test for ovarian cancer
Objectives

1. Understand the importance of specialists in the care of women with ovarian cancer
2. Understand the role of imaging tests, biomarkers, and algorithms in the evaluation of an ovarian tumor
3. Educate providers on contemporary referral strategies
Presentation Outline

1. Background and Relevance
2. Tools for Referral Decisions
   - Imaging
   - Biomarkers
   - Algorithms
3. UK Investigator Clinical Trials
4. Conclusions
Background and Relevance

Cancer Mortality Rates
NIH Consensus
Endorsement of Specialists
NCCN guidelines
Cancer Mortality Rates

National Center for Health Statistics, Center for Disease Control and Prevention, 2006
Ovarian Cancer Survival

Figure 3  Note: Estimated five year survival rates of patients treated at UK Markey Cancer Center, figures from patients treated in Kentucky and from the National SEER Database.
“Adequate and complete surgical intervention is mandatory primary therapy for ovarian carcinoma, permitting precise staging, accurate diagnosis, and optimal cytoreduction. The procedure is best conducted by a qualified gynecologic oncologist when there is a high probability of ovarian carcinoma.”

JAMA 273: 491-7, 1995
Value of Specialists

• Meta-analysis (18 studies) concluded survival benefit with gynecologic oncologist
  – Complete surgical staging with early stage disease
  – Optimal cytoreductive surgery with advanced disease
  – Improved median and overall survival

• Organizations supporting GO involvement
  – ACOG & SGO
  – GOC
  – London Medical Advisory statement
  – NIH consensus statement
  – NCCN guidelines

Are Women Receiving Optimal Surgery?

<table>
<thead>
<tr>
<th>Ovarian Cancer Surgeries</th>
<th>Gynecologic Oncologist</th>
<th>Gynecologist</th>
<th>General Surgeon</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=3067(^1)</td>
<td>33%</td>
<td>45%</td>
<td>22%</td>
</tr>
</tbody>
</table>

2M women in state of Kentucky
~400 ovarian cancers each year
213.5 active physicians per 100,000 population
(rank 32 of 50 states)
20 gynecologic oncologists

\(^1\)Earle et al. J Natl Cancer Inst. 98(3):172-180, 2006
Ovarian Cancer in the United States

Cancer Incidence

Death Rate

Incidence 11 per 100,000

Deaths 8 per 100,000
2012 NCCN Guidelines: Ovarian Cancer

Clinical Presentation
- Suspicious/palpable pelvic mass detected on abdominal/pelvic exam
- Ascites
- Abdominal distention
- Symptoms w/o other sources of malignancy
  - Bloating
  - Pelvic or abdominal pain
  - Difficulty eating or feeling full quickly
  - Urinary symptoms

Workup
- Consider FH evaluation
- Abdominal/pelvic exam
- GI evaluation if clinically indicated
- Ultrasound and/or CT of abdomen/pelvis
- Chest imaging
- CA-125 or other tumor markers
- CBC
- Chemistry profile with LFTs

Primary Treatment
- Laparotomy with comprehensive staging
- USO (clinical stage 1A or 1C, all grades) with comprehensive staging if patient desires fertility
- Cytoreductive surgery if clinical stage II, III, or IV
- Consider neoadjuvant chemotherapy with interval cytoreduction for very advanced disease or poor surgical candidates

Adherence to Treatment Guidelines for Ovarian Cancer as a Measure of Quality Care

- California Cancer Registry, 1999-2006
- N=13,321
- Recommended surgical procedures and chemotherapy
- 37% received NCCN-adherent care
  - High volume hospitals (20 or more per year)
  - High volume surgeons (10 or more per year)

**Fig. 2.** Ovarian cancer-specific survival for patients with International Federation of Gynecology and Obstetrics (FIGO) stage I and stage II disease (n=4,016).

Fig. 3. Ovarian cancer–specific survival for patients with International Federation of Gynecology and Obstetrics (FIGO) stage III and stage IV disease (n=9,305).

Imaging

Ultrasound
CT scan
MR imaging
# Ovarian Detection

<table>
<thead>
<tr>
<th></th>
<th>Bimanual examination</th>
<th>Ultrasound</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> ≥ 55 yr</td>
<td>0.30</td>
<td>0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Patient wt</strong> ≥ 200 lb</td>
<td>0.09</td>
<td>0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Uterine wt</strong> ≥ 200 g</td>
<td>0.16</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ueland et al. Gynecol Oncol 99: 400-403, 2005
Kentucky Morphology Index

Ueland et al. Gynecol Oncol. 91: 46-50, 2003
Kentucky Morphology Index

N=442 ovarian tumors

- MI ≥ 5
- Sensitivity: 0.981
- Specificity: 0.807
- PPV: 0.409
- NPV: 0.997
- Accuracy: 0.828

Serial Ultrasound

UK Morphology Index

Annual Meeting on Women’s Cancer, Los Angeles CA. March, 2013
Management of Adnexal Mass- AHRQ

• Evidence Report/Technology Assessment, Number 130
  – 530 pages
  – Prepared for the Agency for Healthcare Research and Quality
  – Prepared by Duke Evidence-based Practice Center

• “All diagnostic modalities showed trade-offs between sensitivity and specificity, but the literature does not provide sufficient detail to allow confident estimation of alternative diagnostic strategies”

### Predicting Malignancy - pooled analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bimanual exam</td>
<td>0.45</td>
<td>0.90</td>
<td>$</td>
</tr>
<tr>
<td>CA-125</td>
<td>0.78</td>
<td>0.78</td>
<td>$</td>
</tr>
<tr>
<td>US morphology</td>
<td>0.86</td>
<td>0.91</td>
<td>$$$</td>
</tr>
<tr>
<td>CT scan of pelvis</td>
<td>0.90</td>
<td>0.78</td>
<td>$$$$$$$$$$$</td>
</tr>
<tr>
<td>MRI of pelvis</td>
<td>0.91</td>
<td>0.88</td>
<td>$$$$$$$$$$$$</td>
</tr>
</tbody>
</table>

$ = $200

Biomarkers

General biomarkers
CA125
HE4
OVA1
## General Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Relevant Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>Mucinous neoplasms</td>
</tr>
<tr>
<td>CA19-9</td>
<td>Gastrointestinal (pancreatic)</td>
</tr>
<tr>
<td>LDH*</td>
<td>Germ cell tumors (Dysgerminoma)</td>
</tr>
<tr>
<td>β-hCG*</td>
<td>Pregnancy, Trophoblastic disease, Germ cell tumors (choriocarcinoma)</td>
</tr>
<tr>
<td>AFP*</td>
<td>Hepatic neoplasms, Germ cell tumors (endodermal sinus tumors)</td>
</tr>
</tbody>
</table>

*Most beneficial in young women with solid tumors*
CA125

• Antigen derived from:
  – Coelomic epithelium (pericardium, pleura, peritoneum)
  – Mullerian epithelium (tubal, endometrial, endocervical)

• Two different assays
  – CA125 $\leq 35$ U/mL
  – CA125-II $< 20$ U/mL

• Expressed by 80% advanced ovarian cancers
  – Rarely expressed in mucinous, clear cell, undifferentiated, sarcomatoid ovarian malignancies

• Expressed by only 50% of early stage ovarian cancers

HE4

- FDA-cleared in 2008 to monitor cancer treatment
- Antigen derived from human epididymis protein
- Individual performance
  - 93% serous; 100% endometrioid; 50% clear cell
  - Not for use monitoring mucinous CA or germ cell tumors
- Better than CA125 (Moore et al Gynecol Oncol 2008)
- No better than CA125 (Allard J et al Clinical Oncol 2009; Karlsen et al Gynecol Oncol Oncol 2012)
OVA1

- FDA-cleared September, 2009
- Multivariate Index Assay
  - $\beta_2$ microglobulin, CA125-II, Apolipoprotein A1, Prealbumin, Transferrin

<table>
<thead>
<tr>
<th>Test Range 0-10</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>&lt; 5.0</td>
<td>&lt; 4.4</td>
</tr>
<tr>
<td>High Risk</td>
<td>$\geq$ 5.0</td>
<td>$\geq$ 4.4</td>
</tr>
</tbody>
</table>

- First preoperative test FDA-clearance to evaluate malignant risk of an ovarian tumor when combined with clinical assessment
  - Not to be used to determine if surgery is indicated

OVA1 Instructions for Use, Vermillion, Inc. Austin TX
Combined Algorithms

ACOG referral guidelines
RMI
ROMA
OVA1 with clinical assessment
OVA1 with ACOG
Kentucky recommendations
ACOG Referral Guidelines

Premenopausal (<50 yrs)
- Very Elevated CA125
- Ascites
- Evidence of abdominal/distant mets (by exam/imaging study)
- First degree family history of breast/ovarian cancer

Postmenopausal (>50 yrs)
- Elevated CA125
- Ascites
- Evidence of abdominal/distant mets (by exam/imaging study)
- First degree family history of breast/ovarian cancer
- Nodular/fixed pelvic mass

ACOG Validation

• Im et al. Obstet Gynecol, 2005
  – Retrospective chart review 1035 patients, 7 tertiary centers
  – Imaging- 95%, CA125- 68%, both- 24%
  – “SGO and ACOG referral guidelines effectively separate women with pelvic masses into two risk categories for malignancy”

• Dearking et al. Obstet Gynecol, 2007
  – Prospective, 837 patients, single-institution
  – ACOG guidelines performed well in predicting advanced-stage disease, but “poorly” in early-stage disease, premenopausal women
  – “Need a more sensitive biomarker”
  – Recommended modifications:
    • CA-125 >67 U/mL (pre)
    • Exclude FH of breast, ovarian cancer
## Risk of Malignancy Index

### U x M x CA125

<table>
<thead>
<tr>
<th>RMI</th>
<th>Authors</th>
<th>US</th>
<th>Meno</th>
<th>Size</th>
<th>CA125</th>
<th>HR Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jacobs 1990</td>
<td>0, 1, 3</td>
<td>1, 3</td>
<td>NA</td>
<td>U/mL</td>
<td>&gt;200</td>
</tr>
<tr>
<td>2</td>
<td>Tingulstad 1996</td>
<td>1, 4</td>
<td>1, 4</td>
<td>NA</td>
<td>U/mL</td>
<td>&gt;125</td>
</tr>
<tr>
<td>3</td>
<td>Tingulstad 1999</td>
<td>1, 3</td>
<td>1, 3</td>
<td>NA</td>
<td>U/mL</td>
<td>&gt;200</td>
</tr>
<tr>
<td>4</td>
<td>Yamamoto 2006</td>
<td>1, 4</td>
<td>1, 4</td>
<td>1, 2*</td>
<td>U/mL</td>
<td>&gt;450</td>
</tr>
</tbody>
</table>

*<7 cm or ≥7 cm
Risk of Malignancy Index

- N=402, retrospective, RMI 2
- Denmark, referral to centralized system
- Sensitivity 71%, specificity 88%
- Conclusions
  - A valuable, reliable, and applicable method in the primary evaluation of patients with pelvic masses
  - Has significant limitations in borderline ovarian tumors, stage I invasive cancers, and non-epithelial tumors
  - Other methods should be evaluated to increase diagnostic accuracy

Andersen et al. Gynecol Oncol 90;109-112, 2003
Risk of Ovarian Malignancy Algorithm

- FDA-cleared September, 2011
- Indicated for women with a pelvic mass who are planned for surgery
- ROMA combines results of HE4, CA125 II, menopausal status into numerical risk score
  - 75% sensitivity for early-stage EOC (I and II)
  - 100% sensitivity for late-stage EOC (III and IV)
  - 68.4% sensitivity for LMP tumors and others

Fujirebio Diagnostics Press Release, Sept 6, 2011. ROMA is a trademark of Fujirebio Diagnostics, Inc.
Risk of Ovarian Malignancy Algorithm

- **ROMA superior** to individual markers (prospective, NR)
  - Nolen, Gynecol Oncol 2010
  - Moore, Obstet Gynecol 2011
  - Karlesen, Gynecol Oncol 2012 (Danish pelvic mass study)
  - Kadija, Int J Gynecol Oncol 2012

- **ROMA not superior** to markers (prospective, NR)
  - Van Gorp, Br J Cancer 2011
  - Jacob, Gynecol Oncol 2011
  - Montagnana Clinic Lab Med 2011
  - Partheen J Gynecol Oncol 2011
  - Molina, Tumour Biol 2011
OVA1 and Clinical Impression

“Effectiveness of a Multivariate Index Assay in the Preoperative Assessment of Ovarian Tumors”

<table>
<thead>
<tr>
<th>Subjects</th>
<th>OVA1</th>
<th>CA125-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers (n=161)</td>
<td>92.5%</td>
<td>68.9%</td>
</tr>
<tr>
<td>All epithelial ovarian cancers (n=96)</td>
<td>99.0%</td>
<td>82.3%</td>
</tr>
<tr>
<td>Early stage EOC (n=41)</td>
<td>97.6%</td>
<td>65.9%</td>
</tr>
<tr>
<td>Premenopausal women w/ early stage EOC (n=14)</td>
<td>92.9%</td>
<td>35.7%</td>
</tr>
</tbody>
</table>

Performance of OVA1 with clinical impression

- OVA1 detected 76% of malignancies missed by CA125
- 70% (GYN) and 95% (GYO) missed by physician assessment

**OVA500 Study Results**

<table>
<thead>
<tr>
<th>n=494</th>
<th>Clinical Impression</th>
<th>CA125-II</th>
<th>OVA1</th>
<th>OVA1 + CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity %</td>
<td>73.9</td>
<td>73.9</td>
<td>92.4</td>
<td>95.7</td>
</tr>
<tr>
<td>Specificity %</td>
<td>92.5</td>
<td>94.5</td>
<td>53.5</td>
<td>50.7</td>
</tr>
<tr>
<td>PPV %</td>
<td>69.4</td>
<td>75.6</td>
<td>31.3</td>
<td>30.8</td>
</tr>
<tr>
<td>NPV %</td>
<td>93.9</td>
<td>94.1</td>
<td>96.8</td>
<td>98.1</td>
</tr>
<tr>
<td>Rate of cancers missed (%)</td>
<td>26.1</td>
<td>26.1</td>
<td>7.6</td>
<td>4.3</td>
</tr>
</tbody>
</table>

**Effectiveness of OVA1 in identifying ovarian malignancy by non-gynecologic oncology providers**

**Performance summary of OVA1 with clinical impression**

- 94% sensitivity in premenopausal women
- 91% sensitivity for early-stage ovarian cancer
- Identified 71% of cancers missed by CA125; 83% missed by clinical impression

### OVA1 and the College Guidelines

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal (n=235)</th>
<th>Postmenopausal (n=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACOG</td>
<td>ACOG w/ OVA1</td>
</tr>
<tr>
<td>Sensitivity %</td>
<td>58</td>
<td>91</td>
</tr>
<tr>
<td>Specificity %</td>
<td>77</td>
<td>43</td>
</tr>
<tr>
<td>PPV %</td>
<td>38</td>
<td>28</td>
</tr>
<tr>
<td>NPV %</td>
<td>89</td>
<td>95</td>
</tr>
</tbody>
</table>

- Replacing CA125 with OVA1 identified 90% of EOC including 80% of malignancies missed by the current guidelines
- For early stage cancers, ACOG w/OVA1 had higher sensitivity than ACOG
  - Premenopausal (88% vs 47%)
  - Postmenopausal (100% vs 88%)

Impact of OVA1 on Patient Referral

- N=770 patients enrolled by non-gynecologic oncologists
- OVA1 and OVA500 data merged
- OVA1 vs CA125 vs modified ACOG vs Clinical Assessment
- Despite lower specificity, OVA1 had comparable referral rates to actual clinical practice

Sensitivity
- OVA1 90.2%
- Modified ACOG 79.3%
- Clinical Assessment 73.2%
- CA125 68.3%

Patient Referral

Cancer prevalence 21.3%

Kentucky Recommendations

Ovarian tumor ultrasound*

Unilocular/septate

- Serial US every 6 months

Complex morphology¹

- Biomarker (CA125, OVA1, RMI, ROMA, ACOG guidelines)
- low risk
  - Surgery with gynecologist
- high risk²
  - Referral to gynecologic oncologist

¹Complex morphology: solid or papillary areas, ascites, metastases, or MI ≥ 5
²High risk: CA125 > 200 U/mL (pre), >35 U/mL (post), high risk OVA1, RMI > 200, high risk ROMA, or ACOG guidelines

*Perform tumor morphology indexing (MI)
UK Ovarian Cancer Investigator Trials

Ovarian Cancer Screening Program
Neoadjuvant chemotherapy
Ovarian tumor evaluation using Morphology Index
Trials in development
Clinical Trials at the University of Kentucky

• Ovarian Cancer Screening Program (88-00219)
  – 25 years (1987-current)
  – 41,500 women, 241,000 visits
  – 85 cancers detected

• Neoadjuvant chemotherapy (11-GYN-098)

• Evaluating the Performance of Morphology Index in Surgical Decision-Making for Ovarian Tumors (14-GYN-200)
  – Prospective ultrasound-based decision making
  – Biomarker discovery

• Trials in development
Conclusions
Conclusions

1. Ovarian cancer survival has not improved in 50 yrs
2. Most do not have surgery with a gynecologic oncologist despite better survival
3. Algorithms reliably identify late but not early stage cancers, and often fail in premenopausal women
4. Educating providers on contemporary referral strategies is a moral imperative
Markey Cancer Center Affiliate Network 2014

**Current Affiliates**
- Ashland: Our Lady of Bellefonte Hospital
- Cynthiana: Harrison Memorial Hospital
- Elizabethtown: Hardin Memorial Hospital
- Frankfort: Frankfort Regional Medical Center
- Georgetown: Georgetown Community Hospital
- Harlan: Appalachian Regional Healthcare
- Hazard: Appalachian Regional Healthcare
- Louisville: Norton Cancer Institute
- Morehead: St. Claire Regional Medical Center
- Mt. Vernon: Rockcastle Regional Hospital
- S. Williamson: Appalachian Regional Healthcare

**Potential Affiliates**
- Henderson
- Winchester
- Cincinnati OH
- Huntington WV

**Other Affiliates**
- Henderson Methodist Hospital
- Winchester Clark Regional Medical Center
- Cincinnati OH The Christ Hospital Health Network
- Huntington WV St. Mary’s Medical Center