Ovarian Cancer
An Update

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Questions

• What tests to order?
• Should I refer patient to Gyn Onc or not?
• Special cases
  Endometriosis
  Ovarian Mass in Pregnancy
  Germ cell Tumor
• What’s new on ovarian cancer targeted therapy?
2012 Estimated US Cancer Deaths

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>29%</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Lung & bronchus
Breast
Colon & rectum
Pancreas
Ovary
Leukemia
Non-Hodgkin lymphoma
Uterine corpus
Liver & intrahepatic bile duct
Brain/other nervous system
All other sites
Unique aspects of newly diagnosed advanced ovarian cancer

• Upfront surgical management is standard of care: allows access to tissue

• OC is very chemotherapy sensitive at diagnosis; >80% of cancers will respond to platinum- and taxane-based chemotherapy upfront at dx.

• Cancer becomes more treatment-refractory following recurrence.

• Outcomes for newly diagnosed ovarian cancer have reached a plateau with platinum / taxane combination
Ovarian Cancer

• Improved survival outcome when treated by gyn oncologists
• Less than half of women with OVCA are treated by gyn oncologists
Screening – PLCO Trial

- TVUS + CA 125 versus annual exam
- N = 39,000 in each arm
- Age 55-74yo
- Asymptomatic
- Follow for 6 years
- Abnormal TVUS or CA125 led to further work up and sometimes surgeries

Buys, JAMA 2011
Screening – PLCO Trial

- RR 1.21, 95% CI [0.99-1.48]
- 212 vs 176 cases of cancer
- Same distribution of advanced ovarian cancer in each group
- No survival benefit
- Total false positive = 3,285
- 33% had surgery

Buys, JAMA 2011
CA125

• CA125 is an imperfect tool
• About 50% of women with stage I ovarian cancers will have a normal CA125
• Other benign conditions could also lead to elevated CA125
OVA1

- 5 serum protein markers – transthyretin, apolipoprotein, A-1, B2-microglobulin, transferrin, and CA125
- Multivariate index assay
- Single digit score of 0-10
- “as an adjunct” to clinical decision-making for women who are planning surgery for an adnexal mass
- Cost $650
OVA1

It is NOT for:

• Not approved for screening
• Not intended to replace clinical judgment as a stand-alone test
OVA1

• 09/2009 - FDA-approved as a dx test
• 7/30/2012 - Vermillion announced positive results from the OVA500 trial, ahead of publication of the abstract or manuscript
• OVA500 – total N = 1000, 259 malignancies, 84 in stage I/II
• OVA1 test identified 78 / 84 cases of early stage ovarian cancer (sensitivity 93%)
OVA1 Data

- Prospective study
- N = 590
- Women scheduled for surgery for a pelvic mass
- All enrolling physicians reported their preop assessment of mass (malignant vs benign), excluding OVA1 test
- 151 cases of cancer

Ueland, Obstet Gynecol 2011
# OVA1 Data

<table>
<thead>
<tr>
<th></th>
<th>OVA1 (N=590)</th>
<th>OVA500 (N=1000)</th>
<th>CA125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>94%</td>
<td>96%</td>
<td>77%</td>
</tr>
<tr>
<td>Specificity</td>
<td>35%</td>
<td>51%</td>
<td>68%</td>
</tr>
<tr>
<td>PPV</td>
<td>40%</td>
<td>N/A</td>
<td>52%</td>
</tr>
<tr>
<td>NPV</td>
<td>93%</td>
<td>98%</td>
<td>87%</td>
</tr>
</tbody>
</table>
OVA1 – Results Released by Company

- Overall: NPV 98%, Sens 96%, Spec 51%
- In Premenopausal women: sens 94%
- In stage I/II ovarian cancer patients: sens 91%
How does these translate into daily practice and referral to gyn oncologists?
• OVA1 does not replace clinical judgment.
• If you think the patient needs to be referred to gyn onc based on history / exam / imaging, it does not matter what her OVA1 result is.
• High sensitivity suggests that if OVA1+, referral to gyn onc should be made.
• Concern of low specificity may imply that a greater proportion of women with non-malignant tumors would be referred to gyn oncologists.
• An improved NPV may imply decrease referral to gyn oncologists.
• Does OVA1 really alter your referral pattern?
2011 ACOG/SGO Guidelines

Post-menopausal:

- Elevated CA125 (>35)
- Ascites
- Nodular or fixed pelvic mass
- Evidence of abdominal / distant metastasis
2011 ACOG/SGO Guidelines

Pre-menopausal:
• CA125 >50
• Ascites
• Evidence of abdominal / distant metastasis
Questions

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• Should I refer patient to Gyn Onc or not?
• Special cases
  Endometriosis
  Ovarian Mass in Pregnancy
  Germ cell Tumor
• What’s new on ovarian cancer targeted therapy?
Endometriosis
Endometriosis

Note homogenous appearance of ovarian cyst(s), no solid components, consistent with old blood
Endometriosis
## Endometriosis

<table>
<thead>
<tr>
<th></th>
<th>Endometriosis</th>
<th>Ovarian CA</th>
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</thead>
<tbody>
<tr>
<td>Early menarche</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Genetic Predisposition</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Infertility</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Estrogen Exposure</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>BTL</td>
<td>Protective</td>
<td>Protective</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>Protective</td>
<td>Protective</td>
</tr>
<tr>
<td>Progesterone Exposure</td>
<td>Protective</td>
<td>Protective</td>
</tr>
</tbody>
</table>
Endometriosis and Cancer

- 195 cases of malignant tumors arising from endometriosis

- **Sites**
  - Ovary: 78.7%
  - Extragonadal sites: 21.3%

- **Types of malignancies**
  - Endometrioid carcinoma
  - Clear cell carcinoma
  - Carcinosarcoma
  - Adenosarcoma

*Heaps J, Nieberg R, Berek J*

*Malignant Neoplasms Arising in Endometriosis*

*Obstet Gynecol. 1990 Jun;74(6):1023-8*
Endometriosis and Cancer

- Correlation of Endometriosis and Ovarian Cancer

- Prevalence of endometriosis higher in pts with epithelial ovarian cancer than in the general population
  - 21-26% in pts with endometrioid and clear cell ovarian cancer
  - 3-5% in pts with serous and mucinous

- Ovarian cancer been found in 5-10% of ovarian endometriotic lesions

- RR for malignant transformation and ovarian malignancy
  - 2.4% for pts with endometriosis
  - 4.2% for pts with endometriosis AND infertility

*Nezhat F, Datta M, Hanson V, Pejovic T, Nezhat C, Nezhat C*

Ovarian Mass in Pregnancy

- OVCA in pregnancy: rare 1/8000 – 1/20,000
- Usually low grade, early stage
- Germ cell tumor predominant
- Expectant management is standard
- Ovarian mass usually does not affect neonatal outcome
Ovarian Mass in Pregnancy

Risk of Surgery
- Fetal loss
- PTL
- Infection
- Prefer to do in 2\textsuperscript{nd} Trimester

Risk of Observation
- Torsion
- Rupture
- Obstruct labor
- Risk of untreated CA
Germ Cell Tumor

• Approximately 10-15% of all ovarian cancers
• Principally in adolescent girls and young women
• Median age- 16-20 yrs of age
• Range- 6-46 yrs of age
• A number of cases described in post menopausal women
Germ Cell Tumor

- Dysgerminomas-50%
- Non-dysgerminomatous malignant ovarian germ cell tumors (NDMOGTD)-50%
  - Yolk sac tumors-22%
  - Immature teratomas-20%
  - Mixed primitive germ cell tumors-8%
  - Embryonal carcinomas
  - Choriocarcinomas
  - Polyembryomas
Serum Markers in Germ Cell Tumors

<table>
<thead>
<tr>
<th>Histology</th>
<th>AFP</th>
<th>hCG</th>
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<tbody>
<tr>
<td>Dysgerminoma</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Yolk Sac Tumor</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Immature Teratoma</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>Mixed Primitive GCT</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Polyembryoma</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>
Dysgerminoma

- Grossly bilateral in 10-15% of cases
- Involves contra-lateral ovary microscopically in 10% of cases
- Predilection for lymphatic spread
Dysgerminoma

• Comprehensive surgical staging (NCCN guidelines)
• ~ 60-70% stage I
• Reproductive age group approach
  – Fertility sparing surgery – USO, conservation of uterus and contra-lateral ovary – not to be bivalve if inspection reveals normal size, shape and consistency.
Dysgerminoma

• Advanced disease: cytoreductive surgery recommended – benefit not clearly defined.

• Support for cyto-reductive surgery
    • Higher chemotherapy response with optimal debulking
    • Improved PFS if clinically NED
Germ Cell Tumor - NCCN

- Completely stage IA dysgerminoma and stage IA, grade I, IT require no adjuvant treatment.
- All other GCT require adjuvant chemotherapy even if stage I
- EP (dysgerminoma)/BEP (non-dysgerminoma) is recommended
  - 3 cycles for completely resected
  - 4 cycles for incompletely resected
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Targeted Therapy

• One of the most prolific arenas of drug development

• Dozens are in development
  – Compounds: modeled for direct and/or indirect AA properties
  – Approaches: ligand, receptor, signal, and regulators
  – Targets: endothelial cells, tumor cells, pericytes, immune effectors

• Approved: 16 (at least 2 others with indirect effects)
  – Most recent Axitinib (1/27/12) in RCC
Bevacizumab – GOG 218 and ICON7 Progression-free Survival

Burger, NEJM (2011) 365:2473
Perren, NEJM (2011) 365:2484
Bevacizumab – GOG 218 and ICON 7 Overall Survival

Burger, NEJM (2011) 365:2473

Perren, NEJM (2011) 365:2484
OCEANS: Primary analysis of PFS

<table>
<thead>
<tr>
<th></th>
<th>CG + PL (n=242)</th>
<th>CG + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>187 (77)</td>
<td>151 (62)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>8.4 (8.3–9.7)</td>
<td>12.4 (11.4–12.7)</td>
</tr>
<tr>
<td>Stratified analysis HR (95% CI)</td>
<td>0.484</td>
<td>(0.388–0.605)</td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>&lt;0.0001</td>
<td></td>
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Proportion progression free

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>CG + PL</th>
<th>CG + BV</th>
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<tbody>
<tr>
<td>Months</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>242</td>
<td>242</td>
</tr>
<tr>
<td>0</td>
<td>242</td>
<td>242</td>
</tr>
<tr>
<td>6</td>
<td>177</td>
<td>203</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
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<tr>
<td>18</td>
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<td>24</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
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OCEANS: Interim OS

Proportion alive

<table>
<thead>
<tr>
<th>Months</th>
<th>CG + PL (n=242)</th>
<th>CG + BV (n=242)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td>12</td>
<td>0.89</td>
<td>0.93</td>
</tr>
<tr>
<td>18</td>
<td>0.81</td>
<td>0.88</td>
</tr>
<tr>
<td>24</td>
<td>0.73</td>
<td>0.78</td>
</tr>
<tr>
<td>30</td>
<td>0.63</td>
<td>0.67</td>
</tr>
<tr>
<td>36</td>
<td>0.54</td>
<td>0.58</td>
</tr>
<tr>
<td>42</td>
<td>0.45</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Events, n (%)  
- CG + PL: 78 (32)  
- CG + BV: 63 (26)

Median OS, months (95% CI)  
- CG + PL: 29.9 (26.4–NE)  
- CG + BV: 35.5 (30.0–NE)

Stratified analysis  
HR (95% CI): 0.751 (0.537–1.052)  
Log-rank p-value: 0.094^a

No. at risk:  
- CG + PL: 242 235 195 131 77 26 8 0  
- CG + BV: 242 238 200 146 82 42 8 0
Bevacizumab

• Survival is the goal of primary therapy
• Bevacizumab was stopped prematurely in GOG 218
• Bevacizumab has no impact on overall survival in first-line or recurrent setting
Bevacizumab

- Recurrence is a lethal event in ovarian cancer
- Bevacizumab will have no impact on absolute survival in the recurrent setting
Gynecologic Oncology
Developmental Therapeutics

• Signaling/Angiogenesis
  – Bevacizumab/Aflibercept
  – RTKI’s:
    • Pazopanib
    • Cabozantinib
    • Sorafenib, etc
    • Cediranib
    • Nintedanib
  – AMG-386, MEDI-3617
  – PI3K/Akt/mTOR
  – MEK

• Folate:
  – EC-145
  – Farletuzumab
• NKTR-102
• Taxanes/epothilones
• Immunotherapy – vaccines and inducers
• PARPi