Practice of Medicine-1
Ovarian Cancer Clinical Correlation

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American Cancer Society Female Cancers 2000 Statistics

Breast 152,000
Lung & Bronchus 74,000
Colorectal 60,000
Uterine cervix 30,000
Naso-Pharyngeal 25,000
Ovary 23,000
Melanoma of skin 18,000
Urinary Bladder 14,000
Prostate 14,000
Thyroid 12,700
Cancer Cases by Site
All Sites 609,400

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American Cancer Society Female Cancers 2000 Statistics

- Lung & Bronchus: 52,000
- Colon & rectum: 15,000
- Breast: 40,500
- Cervix: 12,300
- Non-Hodgkin's lymphoma: 11,500
- Leukemia: 7,400
- Uterine corpus: 6,069
- Brain: 3,460
- Stomach: 3,383

Cancer Deaths by Site
Males: 309,100
Females: 302,100

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American Cancer Society Female Cancers 2007 Statistics

Ovarian Cancer

- Second most common gynecologic malignancy in the US
- Responsible for 25,000 cases annually
- 14,500 deaths annually
- Most lethal gynecologic malignancy
- 70% of patients present with advanced disease

American Cancer Society 2000
Ovarian Cancer: Histologic Distribution

- Epithelial: 65%
- Germ Cell: 25%
- Sex Cord Stroma: 8%

Ovarian Cancer: Stage Distribution and Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percent</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>24</td>
<td>95%</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>65%</td>
</tr>
<tr>
<td>III</td>
<td>55</td>
<td>15-30%</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
<td>0-20%</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>50%</td>
</tr>
</tbody>
</table>

American Cancer Society 2000

Relative Survival: Ovarian & Breast Cancers

<table>
<thead>
<tr>
<th>Five-Year Relative Survival Rates by Stage at Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Local</td>
</tr>
<tr>
<td>Regional</td>
</tr>
<tr>
<td>Distant</td>
</tr>
<tr>
<td>All Stages</td>
</tr>
</tbody>
</table>
Ovarian Cancer: Risk Factors

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>OCPs</td>
</tr>
<tr>
<td>Family history</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Infertility/low parity</td>
<td>Tubal ligation</td>
</tr>
<tr>
<td>Personal cancer history</td>
<td>Breast-feeding</td>
</tr>
</tbody>
</table>

Ovarian Cancer: Hereditary Risks

<table>
<thead>
<tr>
<th>Family History of Ovarian Cancer</th>
<th>Lifetime Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.5%</td>
</tr>
<tr>
<td>1 first-degree relative</td>
<td>5%</td>
</tr>
<tr>
<td>2 first-degree relatives</td>
<td>7%</td>
</tr>
<tr>
<td>Hereditary ovarian cancer syndrome</td>
<td>40%</td>
</tr>
<tr>
<td>Known BRCA1 or BRCA2 germline mutation</td>
<td>35-65%</td>
</tr>
</tbody>
</table>

Ovarian Cancer: Hereditary Syndromes

- Account for only 10% of EOC
- Autosomal dominant inheritance
- Incomplete penetrance
- Associated with breast, colon, prostate and endometrial cancers
- BRCA1, BRCA2, mismatch repair genes
Ovarian Cancer: Risk Reduction & Prevention

- OCP RR 0.5 after 5 or more years of use, reduction persists for 10 years
- First full-term pregnancy < age 25; number of pregnancies
- Breast-feeding
- BTL/Hysterectomy RR 0.33/0.67
- Prophylactic Oophorectomy (risk of primary peritoneal cancer remains)

Ovarian Cancer: Screening Recommendations

- Comprehensive family history on all patients
- None or 1 family member
  - Annual rectovaginal pelvic exam
- 2 or more family members
  - Genetic counseling,
  - Annual rectovaginal pelvic exam, CA125, transvaginal ultrasound
- Consider clinical trial participation

Ovarian Cancer: CA125 Testing

- CA125
  - Is elevated in greater than 80% of advanced EOCs
  - Is elevated in 25-50% of Stage I cancers
  - Has poor specificity, especially in premenopausal women
  - NOT a screening test for the general population
Ovarian Cancer: Ultrasound Screening Studies

- Screening of 5,000 women
  - 65 exploratory surgeries for every case of ovarian cancer
- Screening of 1,600 women with a family history
  - 12 exploratory surgeries for every case of ovarian cancer
- Survival benefit unproven

Ovarian Cancer: Symptoms

- 95% of women DO report symptoms.
- Symptoms can be vague and not gynecologic:
  - Abdominal bloating, increased girth
  - Fatigue
  - Gastrointestinal disturbances
  - Urinary symptoms
  - Abdominal/pelvic pain
  - Menstrual irregularities

Ovarian Cancer: Diagnostic Modalities

- Rectovaginal pelvic exam
- TVS and/or CT scan or MRI
- CA125
- If diagnosis uncertain, laparoscopy may be useful diagnostic tool
- Surgical exploration
Ovarian Cancer: Surgical Treatment for Advanced Disease

- Significant survival advantage for women optimally cytoreduced
- Procedures may include:
  - En bloc resection of uterus, ovaries and pelvic tumor
  - Omentectomy
  - Bowel resection
  - Removal of diaphragmatic and peritoneal implants
  - Splenectomy, appendectomy

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Ovarian Cancer: Survival by Residual Disease

- PR 52, microscopic
- PR 52, <1 cm
- PR 97, <2 cm
- PR 97, >2 cm

GOG Protocols (PR) 52 and 97
Ovarian Cancer: Surgical Rx for Early Stage Disease

- Optimal therapy: TAH BSO + staging (including pelvic and PALN)
- In younger women, reproductive conservation may be appropriate
- Approximately 30% will have histologic evidence of metastatic disease

Ovarian Cancer: Chemotherapy

- All patients should receive a taxane and a platinum
- 73% response rate
- Median survival: 38 months for Stage III/IV
- Many new agents being tested
- Encourage clinical trial participation

Ovarian Cancer: Follow-up Healthcare

- RV pelvic exam and CA125 q 3-4 mo x 2 years, q 6 mo for years 3-5
- CT scan for symptoms
- General health maintenance (mammography, Pap smear, bone density, colon-rectal screening, cholesterol, etc.)
- Discuss HRT, diet, exercise
Ovarian Cancer: Recurrence

- 75% of patients relapse
- Treatment options include:
  - Secondary cytoreduction
  - Retreatment with platinum/taxane
  - Second-line therapies, including chemo, radiation, immunologic, gene therapies
  - Encourage clinical trials

Ovarian Cancer: Future Directions

- Cost-effective screening
- Early detection
- Prevention
- Reversing chemoresistance
- Immunotherapy
- Gene therapy

Ovarian Cancer: Evolution of Molecular-based Therapies
TARGETS AND INHIBITORS

The Angiogenesis Hypothesis

Angiogenic Switch

Small tumor
- Nonvascular
- "Dormant"

Larger tumor
- Vascular
- Metastatic potential

Regulation of Angiogenesis

Tumor Cell
- MMPs
- HIF1α
- ECM
- Integrins

Growth Factors
- EGF
- COX2
- Etc.

Soluble Factors
- VEGF
- PDGF
- FGF
- Etc.
Role of VEGF in Tumor Growth

- VEGF stimulates tumor angiogenesis
- Tumor blood vessels created by VEGF are abnormal
  - Leaky and twisted
  - Improperly matured
- VEGF may inhibit the tumoral immune response
- VEGF is overexpressed in a broad range of human tumors, including colorectal, ovarian non-small cell lung, and renal cell cancer

Anti-VEGF Approaches and Agents: Summary

- IMC-18F1
- Bevacizumab VEGF Trap
- Sunitinib VEGFR-2
- Sorafenib VEGFR-2
- Vandetanib VEGFR-2
- Motesanib VEGFR-2
- Axitinib VEGFR-2
- AZD2171 VEGFR-2
- Pazopanib VEGFR-2
- Temsirolimus mTOR
- Everolimus mTOR