Optimizing First Line Treatment of Advanced Ovarian Cancer

Ira R. Horowitz, MD, SM, FACOG, FACS
John D. Thompson Professor and Chairman
Department of Gynecology and Obstetrics
Member, Winship Cancer Institute

Ira R. Horowitz, M.D., S.M.

Personal/Professional Financial Relationships with Industry within the past year

<table>
<thead>
<tr>
<th>External Industry Relationships</th>
<th>Company Name(s)</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers</td>
<td>None</td>
<td></td>
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<tr>
<td>Board of Directors or officer</td>
<td>Emory Healthcare Board of Directors</td>
<td>Department Chair Physician Director;</td>
</tr>
<tr>
<td></td>
<td>Clifton Casualty Insurance Company</td>
<td>Vice Chair</td>
</tr>
<tr>
<td></td>
<td>Atlanta Girls School</td>
<td>Member</td>
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<td>Emory Medical Care Foundation</td>
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<tr>
<td>Royalties from Emory or from external entity</td>
<td>None</td>
<td></td>
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<tr>
<td>Industry funds to Emory for my research</td>
<td>None</td>
<td></td>
</tr>
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<td>Other</td>
<td>None</td>
<td></td>
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</tbody>
</table>
Ovarian Cancer

• New Cases: 21,980
  – 3% of Female Cancers
  – 2nd Gynecologic Cancer

• Deaths: 14,270
  – 5% of Female Cancer Deaths
  – 1st Gynecologic Cancer Deaths

Ovarian Cancer Population

• Fatality:Case Ratio 70.3%
• Incidence  1/70
• Mortality  1/100
**Carcinoma of the Ovary: FIGO Nomenclature**

**Stage I** Growth limited to the ovaries
- Stage Ia Growth limited to one ovary
- Stage Ib Growth limited to both ovaries
- Stage Ic Stage Ia or Ib with tumor on surface of ovaries; or with capsule ruptured; or with ascites present containing malignant cells.

**Stage II** With pelvic extension
- Stage IIa Extension to reproductive organs
- Stage IIb Extension to other pelvic tissues
- Stage IIc Stage IIa or IIb with tumor on surface of ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells.

**Stage III** Tumor outside the pelvis or positive retroperitoneal or inguinal nodes.
- Stage IIIa microscopic seeding of abdominal peritoneal surfaces.
- Stage IIIb macroscopic disease measuring less than 2cm in diameter.
- Stage IIIc macroscopic disease measuring greater than 2 cm in diameter or positive retroperitoneal or inguinal nodes

**Stage IV** Extraabdominal extension.
- If a pleural effusion is present, there must be positive cytology; parenchymal liver metastasis

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**Ovarian Cancer Survival by Stage at Diagnosis**

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>89</td>
</tr>
<tr>
<td>II</td>
<td>65</td>
</tr>
<tr>
<td>III</td>
<td>33.5</td>
</tr>
<tr>
<td>IV</td>
<td>18</td>
</tr>
</tbody>
</table>

Kosary C. SEER Survival Monograph; 2001. p. 133-144
SURVIVAL

1970  30%
1996  50%

Advanced Ovarian Cancer

Median Survival: 1975 - 2006

- 1975: 12 months (Alkeran)
- 1983: 14 months (Cisplatin)
- 1986: 24 months (Cisplatin)
- 1996: 37 months (Cisplatin)
- 1998: 52 months (Paclitaxel)
- 2003: 57.4 months (optimal)
- 2006: 66.9 months (optimal)

Treatments:
- Alkeran
- Cisplatin
- Paclitaxel
- IP Tx
Omental Cake
Diaphragmatic Implants

Treatment of Ovarian Cancer

Role of Surgery

• Establish diagnosis
• Comprehensive staging for early disease
• Primary cytoreduction (debulking) removal of as much gross tumor as possible
• Secondary cytoreduction after neoadjuvant chemotherapy
**OVARIAN CANCER**

“STAGE I - LIMITED OVARIAN CANCER”

- 100 Stage IA - IIB
- 31% Upstaged
- 23/31 (77%) Stage III

**PELVIC NODES**

- Stage IB – IV 56%
- Stage III 61%
- Stage IV 80%
PARA-AORTIC NODES

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Stage I-IV</td>
<td>52.5%</td>
</tr>
<tr>
<td>Stage I</td>
<td>18%</td>
</tr>
<tr>
<td>Stage II</td>
<td>20%</td>
</tr>
<tr>
<td>Stage III</td>
<td>42%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>67%</td>
</tr>
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</table>

OVARIAN CANCER
Surgical Management
Conclusion

Stage III / IV - 40%
Did Not Receive Appropriate Therapy

J Clin Oncol. 2003; 21: 3488
Theoretical Benefits of Cytoreductive Surgery for Advanced Ovarian Carcinoma

- Removal of large bulky tumors with poor blood supply
- Improved sensitivity of residual masses to postoperative chemotherapy
- Greater likelihood of tumor eradication before chemoresistance develops

Residual Disease

- The maximum diameter of the largest tumor mass remaining after cytoreductive surgery
- By convention, measured in cm
- Optimal versus suboptimal cytoreduction or debulking refers to the amount of residual disease in relation to a certain cutoff point (e.g., 1.0, 1.5, 2.0, or 3.0 cm)
- GOG uses <1cm
### OVARIAN CANCER

#### PRIMARY CYTOREDUCTION

<table>
<thead>
<tr>
<th>opt.</th>
<th>bulky</th>
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</thead>
<tbody>
<tr>
<td>56%</td>
<td>11%</td>
</tr>
<tr>
<td>51%</td>
<td>19%</td>
</tr>
</tbody>
</table>

- PCR
- Survival

#### No Macroscopic Disease

- < 1 cm (20-30%)
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

AGGRESSIVE CYTOREDUCTION

- Diaphragm stripping/resection
- Splenectomy
- Distal Pancreatectomy
- Liver Resection
- Resection of Porta Hepatic Tumor
- Cholecystectomy

Resection of cul de sac Disease

Diaphragm Stripping
Splenectomy

Modified Posterior Exenteration
NEOADJUVANT CHEMOTHERAPY

ADVANCED STAGE OVARIAN CANCER
NEOADJUVANT CHEMOTHERAPY

- Attempt Debulking
- Laparoscopy
- Use CT/MRI/PET
**PRIMARY CYTOREDUCTION**

**Role of Neoadjuvant Therapy**

- Improved Cytoreduction
- Improved Survival
- Reduce Surgical Morbidity

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**Neoadjuvant vs Conventional**

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuvant</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>30 mos</td>
<td>29 mos</td>
</tr>
<tr>
<td>Morbidity</td>
<td>0.7%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>
Stage IIB-IV with suboptimal (>1 cm) residual

3 Cycles of Cyclophosphamide + Cisplatin

Evaluation

Complete response, partial response, or stable disease

257 pts

Progressive disease

Removal from study

Randomization

No debulking surgery

Debulking surgery

3 Cycles of Cyclophosphamide + Cisplatin

End points: Overall survival, Progression-free survival

Van der Burg et al. NEJM1995;332:629-34
Stage III or IV suboptimal GOG 152

3 Cycles of Paclitaxel + Cisplatin

Evaluation

Complete response, partial response, or stable disease
Progressive disease

Randomization
Debulking surgery

3 Cycles of Paclitaxel + Cisplatin

Secondary cytoreductive surgery required a laparotomy exploration of the entire abdominal cavity and a maximal effort to resect all gross residual ovarian cancer including but not limited to the uterus, tubes, ovaries, and omentum if they were not resected primarily.

End points: Overall survival, Progression-free survival
Recurrent Disease Patient Population

• A majority will not achieve long-term control of disease
  – Large-volume advanced disease  80-85%
  – Small-volume advanced disease  60-70%
  – High-risk limited disease  20%
  – Low-risk limited disease  10%

Overall, 65% will have either recurrent or persistent disease and be candidates for further therapy

Randomized Trials of First-Line Treatment of Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n</th>
<th>PFS (mos)</th>
<th>OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 111 (100)</td>
<td>cisplatin 75 mg/m^2 + cyclophosphamide 750 mg/m^2 vs cisplatin 75 mg/m^2 + paclitaxel 135 mg/m^2</td>
<td>386</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>OV10 (101)</td>
<td>cisplatin 75 mg/m^2 + cyclophosphamide 750 mg/m^2 vs cisplatin 75 mg/m^2 + paclitaxel 185 mg/m^2</td>
<td>680</td>
<td>11.5</td>
<td>25.8</td>
</tr>
<tr>
<td>GOG 132 (102)</td>
<td>cisplatin 75 mg/m^2 + paclitaxel 135 mg/m^2 vs cisplatin 100 mg/m^2 vs paclitaxel 200 mg/m^2 over 24 hours</td>
<td>386</td>
<td>14.1</td>
<td>26.6</td>
</tr>
<tr>
<td>ICON-3 (103)</td>
<td>carboplatin AUC &gt;5 + paclitaxel 175 vs carboplatin AUC &gt;5 OR cyclophosphamide 500 mg/m^2 + doxorubicin 50 mg/m^2 + platinum 50 mg/m^2</td>
<td>2074</td>
<td>17.3</td>
<td>36.1</td>
</tr>
<tr>
<td>GOG 158 (104)</td>
<td>carboplatin AUC &gt;7.5 + paclitaxel 115 mg/m^2 vs cisplatin 75 mg/m^2 + paclitaxel 135 mg/m^2</td>
<td>798</td>
<td>22.0</td>
<td>NR</td>
</tr>
<tr>
<td>AGO (105)</td>
<td>carboplatin AUC &gt;6 + paclitaxel 185 mg/m^2 vs cisplatin 75 mg/m^2 + paclitaxel 185 mg/m^2</td>
<td>798</td>
<td>69 wks</td>
<td>NR</td>
</tr>
<tr>
<td>SCOTROC (106)</td>
<td>carboplatin AUC &gt;5 + paclitaxel 175 mg/m^2 vs carboplatin AUC &gt;5 + docetaxel 75 mg/m^2</td>
<td>1077</td>
<td>15.4</td>
<td>2-year OS 69.8%</td>
</tr>
</tbody>
</table>

OS = overall survival, NR = Not Reported
# First Line Treatment in Ovarian Cancer

<table>
<thead>
<tr>
<th>Population/Treatment</th>
<th>Study</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Stage III Intraperitoneal</td>
<td>GOG 114 (111)</td>
<td>27.9</td>
<td>63.2</td>
</tr>
<tr>
<td>Optimal Stage III Intraperitoneal</td>
<td>GOG 172 (112)</td>
<td>23.8</td>
<td>65.6</td>
</tr>
<tr>
<td>Optimal Stage III Intravenous</td>
<td>GOG 158 (104)</td>
<td>20.7</td>
<td>57.4</td>
</tr>
<tr>
<td>Suboptimal Stage III, IV Intravenous</td>
<td>GOG 111 (100)</td>
<td>18</td>
<td>58</td>
</tr>
<tr>
<td>Suboptimal Stage III, IV Intravenous</td>
<td>GOG 132 (102)</td>
<td>14.1</td>
<td>26.3</td>
</tr>
<tr>
<td>Suboptimal Stage III, IV Intravenous</td>
<td>GOG 152 (75)</td>
<td>10.7</td>
<td>33.7</td>
</tr>
<tr>
<td>Suboptimal Stage III, IV Intravenous</td>
<td>GOG 162 (113)</td>
<td>12</td>
<td>80.0</td>
</tr>
<tr>
<td>Optimal and Suboptimal Stage III, IV</td>
<td>GOG 182 (108)</td>
<td>16</td>
<td>44</td>
</tr>
</tbody>
</table>

Neoadjuvant Stage III, IV: EORTC (76) | 12 | 29 |

PFS – Progression free survival
OS – Overall survival

## Randomized Trials of Intraperitoneal versus Intravenous Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Residual Disease</th>
<th>Regimen</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 104 (110)(1996)</td>
<td>546</td>
<td>&lt;1 cm</td>
<td>IV cisplatin 100 mg/m² + IV cytoxan 600 mg/m² vs IP cisplatin 100 mg/m² + IV cytoxan 600 mg/m²</td>
<td>N/A</td>
<td>41 vs 49 (p &lt; .02)</td>
</tr>
<tr>
<td>GOG 114 (113)(2001)</td>
<td>462</td>
<td>&lt;1 cm</td>
<td>IV cisplatin 75 mg/m² + IV paclitaxel 135 mg/m² vs IV carboplatin AUC 9 + IV cisplatin 75 mg/m² + IV paclitaxel 135 mg/m²</td>
<td>22 vs 28 (p= .06)</td>
<td>6.5 vs 5.2 (p= .05)</td>
</tr>
<tr>
<td>GOG 172 (112)(2006)</td>
<td>416</td>
<td>&lt;1 cm</td>
<td>IV paclitaxel 135 mg/m² on day 1 + IP cisplatin 100 mg/m² on day 1 + IP paclitaxel 80 mg/m² on day 8 vs IV paclitaxel 135 mg/m² on day 1 + IP cisplatin 100 mg/m² on day 1 + IP paclitaxel 80 mg/m² on day 8</td>
<td>18 vs 24 (p=.29)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
GOG 182 (ICON5)

- Carboplatin-paclitaxel x 8

- Carboplatin-gemcitabine → Carboplatin-paclitaxel
  x 4

- Carboplatin-topotecan → Carboplatin-paclitaxel
  x 4

- Carboplatin-paclitaxel-Doxil™ x 8

- Carboplatin-paclitaxel-gemcitabine x 8
GOG 158 And AGO Trials: Outcomes

<table>
<thead>
<tr>
<th>Study/Paclitaxel Regimen</th>
<th>N</th>
<th>Median PFI (mo)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>401</td>
<td>22</td>
<td>.86</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>393</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>AGO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>384</td>
<td>17</td>
<td>1.12</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>392</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

GOG #172

- Ovarian cancer
- Optimal (<1cm)
- Stage III
- Stratify: Gross residual
- Planned 2nd look
- BRCA Analysis
- DNA Banking

Second look Laparotomy (if chosen)

- Paclitaxel 135 mg/m²/24h
  Cisplatin 75 mg/m²
  q 21 days x 6
- Paclitaxel 135 mg/m²/24h
  Cisplatin 100 mg/m² IP D2
  Paclitaxel 60 mg/m² IP D8
  q 21 days x 6
**GOG 172**

**Survival**

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>IP</th>
<th>RR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td>18.3 m</td>
<td>23.8 m</td>
<td>0.80</td>
<td>0.05</td>
</tr>
<tr>
<td>Visible</td>
<td>15.4m</td>
<td>18.3m</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Micro</td>
<td>35.2m</td>
<td>37.6m</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>49.7m</td>
<td>65.6m</td>
<td>0.75</td>
<td>0.03</td>
</tr>
<tr>
<td>Visible</td>
<td>39.1m</td>
<td>52.6m</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Micro</td>
<td>78.2m</td>
<td>NA</td>
<td>0.69</td>
<td></td>
</tr>
</tbody>
</table>

Armstrong et al., NEJM 2006; 354:34-43

**GOG 172: Catheter Failure and IP Chemotherapy Success**

<table>
<thead>
<tr>
<th>Catheter Failure</th>
<th>Completed &lt; 6 cycles</th>
<th>Completed 6 Cycles</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>48 (40.7%)</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>No</td>
<td>70</td>
<td>83</td>
<td>153</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>87</td>
<td>205</td>
</tr>
</tbody>
</table>

RR=8.8 (3.0-25.7, P<0.001)

Walker et al, Gynecol Oncol 2006; 100:27
### GOG 172 vs 158 Survival

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>DDP</th>
<th>Carbo</th>
<th>IP</th>
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<tbody>
<tr>
<td><strong>PFS</strong></td>
<td>18.3 m</td>
<td>19.4m</td>
<td>20.7m</td>
<td>23.8 m</td>
</tr>
<tr>
<td>Visible</td>
<td>15.4m</td>
<td></td>
<td></td>
<td>18.3m</td>
</tr>
<tr>
<td>Micro</td>
<td>35.2m</td>
<td></td>
<td></td>
<td>37.6m</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>49.7m</td>
<td>48.7</td>
<td>57.4m</td>
<td>65.6m</td>
</tr>
<tr>
<td>Visible</td>
<td>39.1m</td>
<td></td>
<td></td>
<td>52.6m</td>
</tr>
<tr>
<td>Micro</td>
<td>78.2m</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

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**OVARIAN CANCER SURGICAL MANAGEMENT CONCLUSIONS**

Surgery remains the Cornerstone of Therapy
Primary Surgery - Ovarian Cancer

- **Apparent Early Stage**: Comprehensive surgical staging
  - Stage I
  - Stage II
  - Stage III-A
- **Apparent Advanced Stage**: Maximal cytoreduction
  - Stage III-B
  - Stage III-C
  - Stage IV

Ovarian Cancer - Surgery

- At what point in their episode of disease does surgical intervention benefit these women?
  - Surgery
    - who:
      - What is unresectable?
      - What is optimal?
    - when:
      - Neo-Adjuvant?
      - Interval debulking
    - how
• You've carefully thought out all the angles.

• You've done it a thousand times.

• It comes naturally to you.

• You know what you're doing, it's what you've been trained to do your whole life.

• Nothing could possibly go wrong, right?
Think Again.