Epithelial Ovarian Cancer

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Epidemiology

• 9\textsuperscript{th} most common cancer among women
  – 21,880 (3%)

• 5\textsuperscript{th} most common cause of cancer death
  – 13,850 (5%)

• Leading three malignancies among women: Breast, Lung, Colon

Jemal. Cancer Statistics 2010
Epithelial Ovarian Cancer (EOC)

- Most common type of ovarian cancer
  - Epithelial (75%)
  - Germ cell (15-20%)
  - Sex-cord Stromal (5%)
- Median age of presentation 65
- Overall lifetime risk is 1 in 70
- 75-80% of patients are diagnosed with Stage III or IV disease
Risk Factors

- Family history (primarily 2 or more first degree relatives)
- Age (besides family history, this is the most important risk factor)
- Nulliparity
- Early menarche, late menopause
- Late childbirth (age <35)
- Environmental factors not yet defined
Risk Reduction

• OCP’s
  – Several Case-controlled studies have documented that OCP users have a 30-60% smaller chance of developing EOC than non-users
  – WHO study documented a RR 0.75
  – Greater reduction in risk with nulliparous women and increased duration of use

• Breast Feeding
• Tubal ligation
• Risk reducing oophorectomy
Hereditary Ovarian Cancer

• Account for 10% of EOC

• BRCA1, BRCA2 (Hereditary Breast and Ovarian Cancer – HBOC)
  – Estimated 1/300 to 1/800 individuals carry a BRCA 1 or 2 mutation
  – Estimated 1/40 Ashkenazi Jews carry a BRCA 1 or 2 mutation

• Hereditary Nonpolyposis Colorectal Cancer (HNPCC), Lynch II
  – Colorectal Cancer before age 50
  – Endometrial cancer before age 50
  – 2 or more “Lynch” family members: colorectal, endometrial, ovarian, ureter/renal pelvis, gastric, biliary tract, small bowel, pancreatic, brain and sebaceous adenoma
Hereditary Ovarian Cancer

• Risk relative to family history
  – Overall risk (OR) for women with a single first degree relative is 3.1 (5% lifetime risk)
  – OR with 2 or 3 relatives is 4.6 (7.2% lifetime risk)
Hereditary Ovarian Cancer

- **BRCA 1 Germline Mutations**
  - Tumor suppressor gene on 17q21 (long arm)
  - Autosomal dominant
  - 65 to 74% Breast Cancer risk
  - 39-46% Ovarian Cancer risk
  - For women with Breast Cancer, the 10-year actuarial risk of developing Ovarian Cancer is 12%
  - Predominately high grade, serous or endometrioid adenocarcinoma

Hereditary Ovarian Cancer

• BRCA2 Germline Mutations
  – Tumor suppressor gene on chromosome 13q12
  – 65-74% Breast Cancer risk
  – 12-20% Ovary Cancer risk
  – For women with Breast Cancer the 10-year actuarial risk of developing Ovarian Cancer is 6%
  – Predominately high grade, serous or endometrioid adenocarcinoma
Genetic Counseling

• Patients with a >20-25% chance of having an inherited predisposition to breast or ovarian cancer and for whom genetic risk assessment is recommended
  
  – Women with a personal history of both breast and ovarian cancer
  
  – Women with ovarian cancer and a close relative with breast cancer at ≤50 or ovarian cancer at any age
  
  – Women with ovarian cancer at any age who are an Ashkenazi Jew
  
  – Women with breast cancer at ≤50 and a close relative with ovarian cancer or a male breast cancer
  
  – Women who are an Ashkenazi Jew and breast cancer ≤40
  
  – Women with a 1st or 2nd degree relative with a BRCA 1 or 2 mutation

Genetic Counseling

• Patients with a >5-10% chance of having an inherited predisposition to breast or ovarian cancer and for whom genetic risk assessment may be helpful

  – Women with breast cancer at ≤40
  – Women with bilateral breast cancer (particularly if breast cancer was at ≤50 years)
  – Women of Ashkenazi Jewish ancestry with breast cancer at ≤50 years
  – Women with breast or ovarian cancer at any age with two or more close relatives with breast cancer at any age (particularly if at least 1 breast cancer was at ≤50 years)
  – Unaffected women with a 1st or 2nd degree relative that meets one of the above criteria

Hereditary Ovarian Cancer

• HNPCC
  – Autosomal dominant
  – 80% risk of developing colon cancer
  – 60% risk of developing endometrial cancer
  – 10-15% risk of developing ovarian cancer
  – Mismatch repair gene defects
    • MSH2, MSH6, PMS2 and MLH1 (chromosome 3)
Patients with a >20-25% chance of having an inherited predisposition to endometrial, colorectal and related cancers and for whom genetic risk assessment is recommended

- Patients with endometrial or colorectal cancer who meet revised Amsterdam criteria as listed below
  - At least 3 relatives with a Lynch/HNPCC-associated cancer in one lineage
  - One affected individual should be a 1st degree relative of the other two
  - At least 2 successive generations should be affected
  - At least 1 HNPCC-associated cancer should be diagnosed before age 50
- Patients with synchronous or metachronous endometrial and colorectal cancer with 1st cancer diagnosed prior to age 50
- Patients with synchronous or metachronous ovarian and colorectal cancer with 1st cancer diagnosed prior to age 50
- Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (microsatellite instability or IHC loss of expression of MLH1, MSH2, MSH6 or PMS2)
- Patients with a 1st or 2nd degree relative with a known mismatch repair gene mutation

Genetic Counseling

• Patients with a >5-10% chance of having an inherited predisposition to endometrial, colorectal and related cancers and for whom genetic risk assessment may be helpful
  – Patients with endometrial or colorectal cancer diagnosed prior to age 50
  – Patients with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/HNPCC-associated tumor at any age
  – Patients with endometrial or colorectal cancer and a 1st degree relative with a Lynch/HNPCC-associated tumor diagnosed prior to age 50
  – Patients with endometrial or colorectal cancer diagnosed at any age with two or more 1st or 2nd degree relatives with Lynch/HNPCC-associates tumors, regardless of age
  – Patients with a 1st or 2nd degree relative that meets the above criteria

Risk-reducing Salpingo-oophorectomy (RRSO)

• Estimated 1000 cases of ovarian cancer could be prevented if elective SO was performed in all women undergoing hysterectomy at 40 years or older

• 5-10% of women with ovarian cancer have had a previous hysterectomy at age 40 or older

• Obtain a family history for BRCA and HNPCC
RRSO

• Factors favoring oophorectomy
  – Postmenopausal
  – Genetic susceptibility for ovarian cancer based on family history or genetic testing
  – Bilateral ovarian neoplasms
  – Severe endometriosis
  – PID or TOA

• Factors favoring preservation
  – Premenopausal
  – Future fertility
  – Impact on libido, quality of life in young women
  – Osteopenia, osteoporosis, or risk factors for osteoporosis
RRSO for BRCA

• BRCA1
  – Risk of cancer rises in late 30’s and early 40’s (2-3%)
  – Risk of ovarian cancer is 10-21% by age 50
  – Average age of ovarian cancer diagnosis 53 years

• BRCA2
  – Risk of ovarian cancer is 2-3% by age 50
  – Risk of breast cancer is 26-34% by age 50

• Women with BRCA1 and 2 mutations should be offered RRSO by age 40 or when child bearing is complete

• RRSO associated with 80% reduction in ovarian, fallopian and primary peritoneal adenocarcinoma

• Cumulative incidence of primary peritoneal cancer is 4-5% at 20 years after RRSO

• Incidence of occult ovarian carcinoma 10-12%

• RRSO reduces a woman’s risk of developing breast cancer by 40-70% (the protective effect is strongest among premenopausal women)

Finch et al. JAMA. 2006
RRSO for BRCA

• Domchek et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 2010; 304: 967-75.

• 2482 women with known BRCA1 or 2 mutation identified and divided among those who did or did not have SO

• Compared to women who did not undergo RRSO, undergoing SO was associated with:
  – Lower risk of ovarian cancer among women with breast cancer (6% vs 1%; HR 0.14 [CI 95%, 0.04-0.59])
  – Lower risk of ovarian cancer among women without breast cancer (6% vs 2%; HR 0.28 [CI 95%, 0.12-0.69])
  – Lower risk of breast cancer among BRCA1 carriers (20% vs 14%; HR 0.63 [CI 95%, 0.41-0.96])
  – Lower risk of breast cancer among BRCA2 carriers (23% vs 7%; HR 0.36 [CI 95%, 0.16-0.82])
  – Lower all-cause mortality (10% vs 3%; HR 0.40 [CI 95%, 0.26-0.61])
  – Lower risk of breast cancer mortality (6% vs 2%; HR 0.44 [CI 95%, 0.26-0.76])
  – Lower risk of ovarian cancer mortality (3% vs 0.4%; HR 0.21 [CI 95%, 0.06-0.80])
RRSO for HNPCC

• Average age of ovarian cancer 42 years
• Average age of endometrial cancer is 50 years
• RRSO associated near 100% reduction in endometrial, ovarian, fallopian and primary peritoneal adenocarcinoma
• Case reports of primary peritoneal adenocarcinoma after RRSO
• Women with HNPCC mutations should be offered hysterectomy/RRSO by age 35-40 or when child bearing is complete
Screening Guidelines for BRCA and HNPCC Patients

• BRCA
  – Begin at age 30-35 or 5-10 years before earliest diagnosed cancer in family
  – annual CA125
  – annual TVS

• HNPCC
  – Start at age 25 or 10 years before earliest diagnosed cancer in family
  – annual EMB
  – annual TVS
  – annual Colonoscopy
Screening for Ovarian Cancer

• There is **no evidence** that screening for Ovarian Cancer leads to earlier detection or improved survival...

• Nonetheless, the following **have been or are being used**
  – TVS
  – CA125
  – Multimodal
  – Symptoms
  – Biomarkers
Screening (TVS)


- 442 women with pelvic masses; all undergoing definitive surgery
- TVS prior to surgery

- **MI<5**, 1/315 tumors was malignant
  - Stage IA granulosa cell tumor (2 cm)
- **MI ≥5**, 53/127 tumors were malignant
  - Stage I-33
  - Stage II-6
  - Stage III-14

- Sensitivity 98%
- Specificity 81%
- PPV 41%
- NPV 99.7%
Screening (TVS)

- TVS for 25,327 women from 1987-2005
- Asymptomatic women ≥50 or women ≥25 who had a family history of ovarian cancer
- 364 patients underwent surgery (1.4%) for a persistent ovarian tumor
  - 35 ovarian cancers (Stage I: 28, Stage II: 8, Stage III: 8)
  - 9 LMP’s
  - 7 metastatic cancers
- 9 women developed cancer with a false negative screen
- Sensitivity 85%
- Specificity 98.7%
- PPV 14%
- NPV 99.9%
Screening (CA125)

- Tumor associated antigen
  - Not expressed in mucinous tumors
  - Normal value in 50-70% of stage I tumors and 20-25% of advanced tumors
- Associated with a variety of common, benign conditions including: endometriosis, fibroids, PID, adenomyosis, pregnancy and possibly menstruation
- Better predictive value in postmenopausal patients
- Abnormal
  - >35 u/ml: postmenopausal
  - >200 u/ml: premenopausal
Screening (Multimodal)

• 78,216 women aged 55-74
• 39,105 – annual screening (CA125 6 years, TVS 4 years)
• 39,111- no screening
• Maximum follow-up 13 years (median 12.4 years)
• Primary outcome: mortality from ovarian cancer
• Secondary outcome: ovarian cancer incidence and complications from screening examinations and diagnostic procedures
Screening (Multimodal)

• Ovarian cancer: 212 women (screening) vs. 176 (observation) RR 1.21 (CI 95%, 0.99-1.48)
• Deaths from ovarian cancer: 118 women (screening) vs. 100 (observation) RR 1.18 (CI 95%, 0.82-1.71)
• 3285 women had false-positive results; resulting in 1080 surgeries
• 163 women experienced at least one serious complication (15%) [infectious complications 40%]
• Conclusion: “simultaneous screening with CA125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality.”
Screening (Symptoms)


• Case-control study (n=637)
  – Ovarian cancer patients (n=149)
  – Ovarian cancer screening group (n=255)
  – Ultrasound/surgery group (n=233)

• Divided between 2 groups:
  – Exploratory group (n=317): used to develop odds ratios for symptoms. Significant symptoms were analyzed by a logistic regression model for their independent association with ovarian cancer. The results from the logistic regression analysis was used to create a risk index
  – Confirmatory group (n=320): the regression model and risk index were used in this group to determine the sensitivity and specificity of the risk index
Screening (Symptoms)

- Symptoms independently associated with ovarian cancer (logistic regression model)
  - Pelvic/abdominal pain (p<0.001)
  - Increased abdominal size/bloating (p<0.001)
  - Difficulty eating/feeling full (p<0.01)

- A symptom index was considered positive if these 6 symptoms were reported >12 a month but were present for <1 year

- Sensitivity
  - Early stage disease (56.7%)
  - Late stage disease (79.5%)

- Specificity
  - Women >50 (90%)
  - Women <50 (86.7%)

- Conclusion- “a symptom index may be useful for identifying women who are at risk”
  - (My opinion-???)
Screening (Biomarkers)


• OVA-1 is a combination of 5 tumor markers
  – CA125
  – Transferrin
  – Prealbumen
  – apolipoprotein AI
  – beta2 microglobulin

• Computer program takes each variable and patient age to create an ovarian malignancy risk score
  – Premenopausal >5 (high risk of malignancy)
  – Postmenopausal >4.4 (high risk of malignancy)
Screening (Biomarkers)

- Physician assessment and OVA-1 correctly identified 70% of ovarian malignancies missed by non-gynecologic oncologist and 95% by gynecologic oncologists.
- OVA-1 correctly identified 75% of ovarian cancer missed by CA125 alone.
- OVA-1 vs. CA125 (67) for ovarian malignancies:
  - Sensitivity: 93% vs. 77%
  - Specificity: 43% vs. 73%
  - PPV: 42% vs. 56%
  - NPV: 93% vs. 88%

<table>
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<tr>
<th>OVA-1</th>
<th>Premenopausal % malignant</th>
<th>Postmenopausal % malignant</th>
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<tbody>
<tr>
<td>4.4</td>
<td>-</td>
<td>49.1</td>
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<tr>
<td>5.0</td>
<td>29.5</td>
<td>52.2</td>
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<td>6.0</td>
<td>39.7</td>
<td>68.8</td>
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<td>7.0</td>
<td>54.2</td>
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<td>8.0</td>
<td>65.6</td>
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<tr>
<td>9.0</td>
<td>73.3</td>
<td>91.2</td>
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Management of Adnexal Masses

• Adnexal masses often present both diagnostic and management dilemmas

• Need to determine:
  – Malignant vs. benign
  – Surgery vs. conservation

Differential Diagnosis

- Gynecologic
  - Benign
    - Functional cyst
    - Leiomyomata
    - Endometrioma
    - TOA
    - Ectopic
    - Teratoma
    - Cystadenoma
  - Malignant
    - EOC
    - Germ Cell
    - Sex-cord stromal

- Non-gynecologic
  - Benign
    - Diverticular abscess
    - Appendiceal abscess
    - Nerve sheath tumors
    - Pelvic Kidney
  - Malignant
    - Colon cancer
    - Breast cancer
    - Gastric cancer
Clinical Tests

• **Ultrasound**
  – Size
  – Consistency- solid, cystic, mixed
  – Septations
  – Papillary excrescences
  – Pelvic fluid

• **Color Doppler**

• **Other Imaging Modalities**
  – CT scan should be used to evaluate for metastatic lesions

• **Serum Markers**
  – CA125
  – OVA-1
Management of Adnexal Masses

• Ultrasound findings suggestive of benign disease
  – Unilocular, thin-walled cysts <10 cm
  – Smooth regular borders
  – No septations
  – No free fluid
  – No papillary excrescences
Management of Adnexal Masses

• Observation
  – Simple, unilocular ovarian cysts <10 cm
    • 2763 women with a simple, unilocular cyst <10 cm
    • 2261 (69%) resolved within 1 year
    • 133 surgeries- no cancers
  – Compelling reason to avoid surgery i.e cirrhosis

• Surgery
  – Symptoms: pain, pressure, urinary frequency etc.
  – Complex ovarian cysts
  – Elevated serum markers
  – Pelvic fluid
Current GYN/Oncology referral guidelines for a pelvic mass

- ACOG committee opinion #477 (2011)
- Postmenopausal women with suspicious pelvic mass as suggested by at least one of the following:
  - elevated CA125
  - ascites
  - nodular or fixed pelvic mass
  - evidence of distant metastasis
Current GYN/Oncology referral guidelines for a pelvic mass

- Premenopausal patient with pelvic mass suspicious for ovarian cancer as evidenced by the presence of one of the following:
  - Very elevated CA125
  - ascites
  - evidence of metastasis
Old GYN/Oncology referral guidelines for a pelvic mass

• ACOG committee opinion #280 (2002, reviewed 2005)

• Postmenopausal women with suspicious pelvic mass as suggested by at least one of the following:
  
  • elevated CA125 (>35 u/ml)
  • ascites
  • nodular or fixed pelvic mass
  • evidence of distant metastasis
  • family history of 1 or more first degree relatives with breast or ovarian cancer
Old GYN/Oncology referral guidelines for a pelvic mass

- Premenopausal patient with pelvic mass suspicious for ovarian cancer as evidenced by the presence of one of the following:
  - CA125 >200 U/ml
  - ascites
  - evidence of metastasis
  - family history with 1 or more first degree relative with breast or ovarian cancer
2007 review of 2002 ACOG committee opinion


• Objectives- to evaluate the referral guidelines for an adnexal mass

• 837 women were evaluated according to ACOG referral guidelines: age, CA-125, imaging, physical findings and family history of ovarian cancer

• 44% (263/597) postmenopausal women were diagnosed with cancer

• 20% (48/240) premenopausal women were diagnosed with cancer

• 74% of ovarian cancer was late Stage disease (III/IV)
### 2007 review of 2002 ACOG committee opinion

<table>
<thead>
<tr>
<th></th>
<th>ACOG guidelines, 2002 (Dearking review)</th>
<th>Dearking Modified ACOG guidelines, 2007</th>
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<tr>
<td>Pre &amp; Postmenopause</td>
<td>Premenopause (CA125 &gt;67)</td>
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<tr>
<td>Sensitivity</td>
<td>79.2%, 93.2%</td>
<td>85.4%</td>
</tr>
<tr>
<td>Specificity</td>
<td>69.8%, 59.9%</td>
<td>59.9%</td>
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<tr>
<td>PPV</td>
<td>39.6%, 64.6%</td>
<td>34.7%</td>
</tr>
<tr>
<td>NPV</td>
<td>93.1%, 91.7%</td>
<td>94.3%</td>
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</table>

- Conclusion-
- Guidelines perform well for detecting advance-stage cancer
- Guidelines perform poorly for detecting early-stage cancer or cancer in premenopausal women
2011 review of (2002) ACOG committee opinion


- 516 women with an ovarian tumor and OVA-1 test
- 161 malignancies
  - 45 premenopausal
  - 116 postmenopausal
- CA-125 was replaced with OVA-1
2011 review of ACOG referral guidelines

• OVA-1 increased:
  – Sensitivity  80%
  – NPV  88%

• OVA-1 decreased:
  – Specificity  71%
  – PPV  55%

• Conclusion- Replacing CA-125 with OVA-1 increases the sensitivity and NPV of the ACOG guidelines. The high sensitivity is maintained in premenopausal women and early-stage disease.
# Ovarian Cancer triage summary

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<tr>
<td>MI &gt;5</td>
<td>MI &gt;5</td>
<td>Pre &amp; Postmenopause</td>
<td>Premenopause</td>
<td>&lt;50, &gt;50</td>
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<tr>
<td>Sensitivity</td>
<td>85%</td>
<td>98%</td>
<td>79.2%, 93.2%</td>
<td>85.4%</td>
<td>86.7%, 66.7%</td>
<td>80%</td>
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<tr>
<td>Specificity</td>
<td>98.7%</td>
<td>81%</td>
<td>69.8%, 59.9%</td>
<td>59.9%</td>
<td>86.7%, 90%</td>
<td>71%</td>
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<td>41%</td>
<td>39.6%, 64.6%</td>
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<td>NPV</td>
<td>99.9%</td>
<td>99.7%</td>
<td>93.1%, 91.7%</td>
<td>94.3%</td>
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**Sensitivity/Specificity**

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<tr>
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<th>Disease Ovarian Cancer +</th>
<th>Disease Ovarian Cancer -</th>
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<tr>
<td>Test OVA 1 +</td>
<td>True positive</td>
<td>False Positive</td>
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<tr>
<td>Test OVA 1 -</td>
<td>False Negative</td>
<td>True negative</td>
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<tr>
<td>Sensitivity:</td>
<td><strong>TP</strong></td>
<td>Specificity:</td>
</tr>
<tr>
<td></td>
<td><strong>TP + FN</strong></td>
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Sensitivity relates to the test's ability to identify positive results.
Specificity relates to the ability of the test to identify negative results.
EOC
Symptoms of Ovarian Cancer

• Largely non-specific
  – Increase in abdominal girth (ascites)
  – Bloating
  – Fatigue
  – Abdominal pain
  – Early satiety
  – Indigestion
  – Constipation
  – Weight loss, unexplained
  – New onset of urinary frequency or incontinence
FIGO Staging

• Stage I
  – IA  Tumor confined to a single ovary, negative washings, capsule intact, surface of ovary uninvolved
  – IB  Tumor found in both ovaries, negative washings, capsule intact, surface of ovary uninvolved
  – IC  Tumor on one or both ovaries, ruptured capsule, positive cytology or ovarian surface involvement

• Stage II
  – IIA  Extension or metastasis to uterus and/or tubes
  – IIB  Extension to other pelvic structures
  – IIC  Tumor on one or both ovaries, ruptured capsule, positive cytology or ovarian surface involvement

• Stage III
  – IIIA  Tumor on one or both ovaries with microscopic spread to abdominal peritoneal surface (ex. Liver serosa)
  – IIIB  Tumor implant <2cm to abdominal peritoneal surface
  – IIIC  Tumor implant >2cm to abdominal peritoneal surface and/or positive retroperitoneal or inguinal lymph nodes

• Stage IV
  – Distant metastasis
  – Pleural effusion with positive cytology
  – Parenchymal liver metastasis
5-year Survival Rates

• Stage I   76-93%
• Stage II  60-74%
• Stage III
  – IIIA 41%
  – IIIB 25%
  – IIIIC 20%
• Stage IV  11%
## Histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>Incidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>Serous</td>
<td>40-50%</td>
<td>Most common</td>
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<tr>
<td>Endometrioid</td>
<td>15-25%</td>
<td>2nd most common</td>
</tr>
<tr>
<td>Mucinous</td>
<td>6-16%</td>
<td></td>
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<tr>
<td>Clear Cell</td>
<td>5-11%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
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Principles of Ovarian Cancer Surgery

• Purpose of Surgery
  – Staging of disease
    • Prognosis and treatment depend upon surgical findings and subsequent stage
  – Debulking (cycloreduction)
    • Overall reduction of tumor burden to less than 1 cm (preferably no gross residual disease) improves survival
    • Palliation of symptoms
    • Goldie-Coldman Hypothesis
      – Resistance to chemotherapy will develop in fraction of remaining viable cells
Principles of Ovarian Cancer Surgery

• Midline, vertical incision
• Careful inspection of all peritoneal surfaces: liver, spleen, large and small bowel, stomach, diaphragms
• Any ascites is collected for cytology. If no ascites, then pelvic washings should be obtained
• If no gross disease beyond ovaries:
  – systematic biopsies of peritoneal surfaces and diaphragms
  – Pelvic and para aortic lymph node sampling
  – Infra-colic omentectomy
• If gross disease beyond ovaries:
  – Tumor debulking is **ideal** (goal is to leave no residual tumors or implants)
Principles of Ovarian Cancer Surgery

• In most cases, hysterectomy with bilateral salpingo-oophorectomy is indicated
• If fertility is a consideration, the contra-lateral ovary and uterus may be left *in-situ* if tumor is Stage IA, IC, IIA and appropriate counseling
Upstaging

- Incomplete surgical staging is a common issue
- Complete surgical staging offers a more accurate diagnosis and in some cases determines the need for adjuvant chemotherapy.
  - 31% of patients were upstaged after a second surgery
  - 77% of patients actually had Stage III disease
  - 25% of patients had an inadequate incision to properly perform staging (Pfannenstiel)
  - Examined completeness of staging in 291 women
  - 46% had inadequate staging
  - GO 97% correct
  - GYN 52% correct
  - Surgeon 35% correct

<table>
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<tr>
<th>Initial Stage</th>
<th>N</th>
<th>% upstaged</th>
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<tbody>
<tr>
<td>IA</td>
<td>37</td>
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<tr>
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<tr>
<td>Total</td>
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</table>
Early ovarian cancer (Stage I)

• 5-year survival for Stage I, 70-90%
• Grade 1 tumors have an excellent 5-year survival (87-94%)
• Grade 3 tumors more likely to have metastatic disease to pelvis or lymph nodes
• Treatment choices for an adequately staged Stage I ovarian cancer vary according to grade, stage, positive cytology and age of patient
Early ovarian cancer (Stage I)

- Large, retrospective study undertaken to identify prognostic factors in Stage I EOC
- Databases from UK, Canada, Sweden, Norway, Denmark and Austria
Early ovarian cancer (Stage I)

• 1545 patients

• Excluded-
  – Stage II or greater disease
  – LMP tumors
  – Adhesive disease/microscopic invasion of adjacent pelvic structures (classified as Stage II or III)
  – Concurrent or previous malignant disease

• Surgery-
  – Hysterectomy, BSO and infracolic omentectomy
  – Peritoneal washings or biopsies were not routinely performed
  – Pelvic and para aortic LNS was not routinely performed
  – The ovarian capsule was examined for rupture and excrescences (microscopic or macroscopic).
  – The occurrence and timing of ovarian rupture was also recorded as preoperative or during surgery.
Early ovarian cancer (Stage I)

• Adjuvant therapy
  – Observation
  – Cisplatin
  – Alkylating agents
  – Anthracyclines
  – IP P^{32}
  – Whole abdominal radiation
  – Radiation with or without alkylating agent

• Results
  – Median follow up 72 months
  – 345 (22.3%) recurred
  – 5-year DFS 80.4%
# Early ovarian cancer (Stage I)

<table>
<thead>
<tr>
<th>Grade</th>
<th>N (%)</th>
<th>5-year DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>529(34)</td>
<td>93.7</td>
</tr>
<tr>
<td>2</td>
<td>473(31)</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>347(23)</td>
<td>60.5</td>
</tr>
<tr>
<td>not graded</td>
<td>196 (13)</td>
<td>73.7</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>567(37)</td>
<td>86.6</td>
</tr>
<tr>
<td>IB</td>
<td>69(5)</td>
<td>76.8</td>
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<tr>
<td>IC</td>
<td>904(59)</td>
<td>76.8</td>
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<tr>
<td>not recorded</td>
<td>5</td>
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</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>470 (30)</td>
<td>87.8</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>1070 (69)</td>
<td>76.8</td>
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<tr>
<td>Rupture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>859(56)</td>
<td>83.3</td>
</tr>
<tr>
<td>Preoperative</td>
<td>89(6)</td>
<td>71.6</td>
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<tr>
<td>Intraoperative</td>
<td>122(8)</td>
<td>70.2</td>
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<td>475 (31)</td>
<td>75.4</td>
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<table>
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<tr>
<th>HR (95% CI)</th>
<th>p</th>
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</tr>
<tr>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>3.13  (1.68-5.85)</td>
</tr>
<tr>
<td>3</td>
<td>8.89  (4.96-15.9)</td>
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<td>Preoperative rupture</td>
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<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
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<td>2.65  (1.53-4.56)</td>
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<tr>
<td>Intraoperative rupture</td>
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<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.64  (1.07-2.51)</td>
</tr>
<tr>
<td>Age per year</td>
<td>1.02  (1.00-1.03)</td>
</tr>
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</table>

**Conclusions:**

- Grade is most powerful prognostic indicator in Stage I EOC.
- Rupture should be avoided during primary surgery of malignant ovarian tumors confined to the ovaries.
Early ovarian cancer (Stage I)

- GOG #157
- Phase III, randomized, controlled trial
- Objective- to evaluate 3 vs. 6 cycles of adjuvant carboplatin and paclitaxel with regard to recurrence rate of early stage EOC
Early ovarian cancer (Stage I)

- **Methods**
  - **Eligibility:**
    - Stage IA, grade 3
    - Stage IB, grade 3
    - Stage IC, any grade
    - Stage II, any grade, complete resection
    - Clear cell histology
  - **Surgery**
    - Total hysterectomy, bilateral salpingo-oophorectomy
    - Resection of all gross disease
    - Aspiration of free peritoneal fluid/peritoneal washings for cytology
    - Infracolic omentectomy
    - Selective bilateral pelvic and aortic node dissections
    - Peritoneal biopsies from four pelvic locations and bilateral paracolic areas
  - **Treatment**
    - 3 cycles of Carboplatin (AUC 7.5) and Taxol (175 mg/m2) Q21 days
    - 6 cycle of Carboplatin (AUC 7.5) and Taxol (175 mg/m2) Q21 days
Early ovarian cancer (Stage I)

• Methods-
  – “The study design provided an 85% chance of identifying a treatment regimen as active if it reduced the recurrence rate 50% when the type I error was set to 0.05 for a one-tail test. This treatment effect is comparable to increasing the expected percentage of patients who are recurrence-free at 4 years from 80.6% to 89.8%.”
Early ovarian cancer (Stage I)

• Results-
  – 427 women enrolled
  – Median age 55
  – 126/427 (29%) had less than adequate staging
  – Stage I, 293/427 (69%)
  – Stage II, 134/427 (31%)

– Histology
  • Serous, 97/427 (22.7%)
  • Endometrioid, 105/427 (24.5%)
  • Clear Cell, 130/427 (30.4%)

– Grade 3, 267/427 (62.5%)
Early ovarian cancer (Stage I)

• Results-
  – Toxicity
    • Neurotoxicity (Gr 3-4): 2% 3 cycle vs. 11% 6 cycle
      \[p<0.01\]
    • Neutropenia (Gr 4): 52% 3 cycles vs. 66% 6 cycles
      \[p<0.01\]
    • Anemia (Gr 2>): 32% 3 cycle vs. 48% 6 cycle \[p<0.01\]
Early ovarian cancer (Stage I)

• Results-
  – Median duration of follow-up 6.8 years
  – Estimated cumulative incidence of cancer recurring within 5 years
    • 25.4% (3 cycles) vs. 20.1% (6 cycles)
    • Adjusting stage and grade, 24% less recurrence rate for patients treated with 6 cycles [HR 0.761, (95% CI=0.512–1.13) p=0.18]
  – Estimated probability of surviving 5 years
    • 81% (3 cycles) vs. 83% (6 cycles) [HR 1.02; (95% CI=0.662–1.57) p=0.94].
  – No difference in recurrence rate between incompletely staged and completely staged patients
Early ovarian cancer (Stage I)

• Conclusions from GOG #157
  – No difference in recurrence or survival with 6 cycles of C/T vs. 3 cycles of C/T
  – Significantly more neurotoxicity, neutropenia and anemia with 6 cycles
  – Trend toward less recurrence with 6 cycles
  – Study designed to capture large differences in recurrence

– Personal Caveat
  • I treat young, healthy patients with 6 cycles; I treat older, unhealthy patients with 3 cycles
Early ovarian cancer (Stage I)


• Retrospective study, compiled data from GOG #95 and GOG #157

• Purpose is to identify risk factors for recurrence and survival

• Eligible patients:
  – Stage IA, grade 3
  – Stage IB, grade 3
  – Stage IC, any grade
  – Stage II, any grade, complete resection
  – Clear cell histology
  – All patients had full surgical staging
Early ovarian cancer (Stage I)

- Results:
  - 506 patients
  - Median age 56
  - Stage I, 347/506 (68.6%)
  - Stage II, 159/506 (31.4%)
  - 140 recurrences (28%)
  - 158 deaths (30%)
  - 5-year PFS 76%
  - 5-year OS 82%

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>69 (13.6)</td>
</tr>
<tr>
<td>IB</td>
<td>10 (2)</td>
</tr>
<tr>
<td>IC</td>
<td>258 (53)</td>
</tr>
<tr>
<td>IIA</td>
<td>43 (8.5)</td>
</tr>
<tr>
<td>IIB</td>
<td>28 (5.5)</td>
</tr>
<tr>
<td>IIC</td>
<td>88 (17.4)</td>
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<tr>
<td><strong>Histology</strong></td>
<td></td>
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<tr>
<td>Serous</td>
<td>108 (21.3)</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>134 (26.5)</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>137 (27.1)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>50 (9.9)</td>
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<tr>
<td>Other</td>
<td>77 (15.2)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
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<tr>
<td>1</td>
<td>95 (18.8)</td>
</tr>
<tr>
<td>2</td>
<td>127 (25.1)</td>
</tr>
<tr>
<td>3</td>
<td>147 (29.1)</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>137 (27.1)</td>
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<tr>
<td><strong>Cytology</strong></td>
<td></td>
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<tr>
<td>Positive</td>
<td>125 (25)</td>
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<tr>
<td>Suspicious</td>
<td>23 (4.6)</td>
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<tr>
<td>Negative</td>
<td>340 (68)</td>
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<tr>
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<td>12 (2.4)</td>
</tr>
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</table>
Early ovarian cancer (Stage I)

• Results-
  – Multivariate analysis revealed:
    • Age >60 [HR 1.57, (95% CI, 1.12- 2.19)]
    • Stage II [HR 2.70, (95% CI, 1.41- 5.76)]
    • Grade 2 [HR 1.84, (95% CI, 1.04- 3.27)]
    • Grade 3 [HR 2.47, (95% CI, 1.39- 4.37)]
    • Positive cytology [HR 1.72, (95% CI, 1.21- 2.45)]

  – Independent predictors of recurrence
Early ovarian cancer (Stage I)

• Results-
  – Prognostic model for recurrence (one point given for each factor)
    • Age >60
    • Stage II
    • Grade 2,3/Clear Cell
    • Positive cytology
  – Low-risk (0-1)
  – Intermediate (2)
  – High-risk (3-4)

– PFS
  • Low-risk 88%
  • Intermediate 71%
  • High-risk 62% p<0.001

– OS
  • Low-risk 88%
  • Intermediate 82%
  • High-risk 75% p<0.001
Early ovarian cancer (Stage I)

• Conclusions-
  – Age >60, Stage II, Grade 2-3/clear cell and positive cytology are independent risk-factors for recurrence
  – Women with multiple factors should be considered for novel therapies
  – Example- 6 cycles of C/T rather than 3 cycles
Early ovarian cancer (Stage I)


- Phase III, randomized, controlled trial

- European Study

- Objective- compare platinum-based chemotherapy versus observation following surgery for early-stage epithelial ovarian cancer
Early ovarian cancer (Stage I)

• Methods-
  – Eligibility (ACTION):
    • Stage IA, grade 2 or 3
    • Stage IB, grade 2 or 3
    • Stage IC, any grade
    • Stage II, any grade, complete resection
    • Clear cell histology
    • Comprehensive Surgical staging
  – Eligibility (ICON 1):
    • Stage I or II EOC
    • Surgery-hysterectomy/BSO/infracolic omentectomy
  – Treatment
    • ACTION: at least 4 cycles of a platinum-agent (single or combination)
    • ICON 1: 6 cycles of a platinum-agent (single agent carboplatin or Cyclophosphamide, Adriamycin and Cisplatin  **VERSUS**
      • Observation
Early ovarian cancer (Stage I)

• Methods-
  – Primary endpoint, OS
  – Secondary endpoint, PFS
Early ovarian cancer (Stage I)

- Results-
  - 925 women enrolled
  - 13 nations
  - 124 cancer centers
  - ACTION- 448
  - ICON 1- 477
  - Median age 55
  - Groups equal for age, Stage, histology and grade

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjuvant Chemotherapy, N=465 (%)</th>
<th>Observation N=460 (%)</th>
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<tr>
<td>Stage</td>
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<td></td>
</tr>
<tr>
<td>I</td>
<td>9 (2)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>IA</td>
<td>168 (36)</td>
<td>173 (38)</td>
</tr>
<tr>
<td>IB</td>
<td>46 (10)</td>
<td>43 (9)</td>
</tr>
<tr>
<td>IC</td>
<td>208 (45)</td>
<td>205 (45)</td>
</tr>
<tr>
<td>II</td>
<td>31 (7)</td>
<td>29 (6)</td>
</tr>
<tr>
<td>III</td>
<td>2 (&lt;1)</td>
<td>4 (1)</td>
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<td>2</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
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<tr>
<td>Serous</td>
<td>161 (36)</td>
<td>139 (31)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>90 (20)</td>
<td>90 (20)</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>94 (21)</td>
<td>129 (29)</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>68 (15)</td>
<td>62 (13)</td>
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<tr>
<td>Undifferentiated</td>
<td>9 (2)</td>
<td>7 (2)</td>
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<td>19 (4)</td>
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<td>14</td>
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<tr>
<td>Grade</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>97 (22)</td>
<td>100 (23)</td>
</tr>
<tr>
<td>2</td>
<td>210 (47)</td>
<td>203 (46)</td>
</tr>
<tr>
<td>3</td>
<td>139 (32)</td>
<td>141 (32)</td>
</tr>
<tr>
<td>Missing</td>
<td>19</td>
<td>16</td>
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</table>
Early ovarian cancer (Stage I)

• Results-
  – Median duration of follow-up 4 years
  – 181 patients died:
    • 78 in ACTION
    • 103 in ICON1
  – 245 patients had recurrence of disease:
    • 112 in ACTION
    • 133 in ICON1
  – 5-year OS
    • 82% (chemotherapy) vs. 74% (observation)
    • [HR 0.67, (95% CI=0.5–0.9) p=0.008]
  – 5-year PFS
    • 76% (chemotherapy) vs. 65% (observation)
    • [HR 0.64; (95% CI=0.5–0.84) p=0.001]
Early ovarian cancer (Stage I)

• Conclusions
  – Adjuvant chemotherapy with a platinum agent significantly improves OS and PFS compared to observation
Summary of early ovarian cancer

• Observation:
  – Stage IA, grade 1-2
  – Stage IB, grade 1-2

• Chemotherapy (3-6 cycles)
  – Stage IA, grade 3
  – Stage IB, grade 3
  – Stage IC any grade
  – Stage II
Advanced ovarian cancer (Stage III, Stage IV)

• Despite the best efforts at early detection, 70-80% of women will be diagnosed with advanced epithelial ovarian cancer
• Prognosis is poor 25-35% 5-year survival, 10% 10-year survival
• Maximal effort/time/expense has been dedicated to better screening and more effective therapy
• Over the past 20 years, we have not been successful in changing the survival rate...
Advanced ovarian cancer
(Stage III, Stage IV)

• Key topics for advanced ovarian cancer
  – Cytoreduction
  – History of GOG studies/rise of Carboplatin/Taxol
  – Intraperitoneal chemotherapy
  – Consolidation chemotherapy
  – Dense dose chemotherapy
  – Neoadjuvant chemotherapy
Cytoreductive Surgery


• GOG #97, Phase III trial
• One of the first studies to evaluate largest residual disease on survival
• Compared cisplatin (50 mg/m$^2$) and cyclophosphamide (500 mg/m$^2$) for 8 cycles vs. cisplatin (100 mg/m$^2$) and cyclophosphamide (1000 mg/m$^2$) for 4 cycles
• Stage III of IV ovarian cancer, suboptimal cytoreduction > 1 cm residual disease
Cytoreductive Surgery

- 294 women were enrolled
- Multivariate analysis RR of dying
  - Residual disease < 2 cm, RR 1.00
  - Residual disease 2-2.9 cm, RR 1.90
  - Residual disease 3-3.9 cm, RR 1.91
  - Residual disease 4-5.9 cm, RR 1.74
  - Residual disease 6-7.9 cm, RR 1.85
  - Residual disease 8-8.9 cm, RR 2.16
  - Residual disease ≥ 10 cm, RR 1.82

  - Significant difference in survival between women with < 2 cm of residual disease and those with ≥ 2 cm of residual disease (p<0.01)
  - No significant risk of dying between groups with residual disease ≥ 2 cm of disease

- Conclusion
  - “Among patients with suboptimal disease (> 1 cm of residual disease) EOC, those who have a small diameter residual disease (<2 cm) tend to survive longer than those who have larger residual disease”
Cytoreductive Surgery


• Prospective study designed to determine the feasibility of cytoreducing Stage III and Stage IV EOC

• 166 patients enrolled between 1990-96
  – 2 patients were excluded because of anesthetic concerns
  – 1 patient refused surgery (religious reasons)
Cytoreductive Surgery

- Procedures performed to achieve cytoreduction:
  - Infracolic/gastrocolic omentectomy (163, 100%)
  - TAH/BSO (162, 98.8%)
  - Retroperitoneal LAD (153, 93.2%)
  - Peritoneal implant ablation (145, 89%)
  - Resection of rectosigmoid colon with anastomosis (85, 52%)
  - Diaphragmatic stripping (66, 40.5%)
  - Extrapelvic bowel surgery (32, 19.6%)
  - Splenectomy, hepatectomy, distal pancreatectomy, urologic, abdominal wall (30, 19%)
Cytoreductive Surgery

- Morbidity included any untoward event within 30 days of surgery
- Mortality included any death within 30 days of surgery
- All patients received cisplatin (50-100 mg/m²) or carboplatin (AUC 5-7) within 6 weeks of surgery
- Most patients received cyclophosphamide (500 mg/m²)
- During last 24 months of surgery, patients received paclitaxel (135 mg/m²)
Cytoreductive Surgery

- 139 (85.3%) had no macroscopic disease
- 22 (13%) had ≤ 1 cm of disease remaining
- 2 (1.2%) had disease > 1 cm

- Mean operative time 254 minutes (75-435)
- Mean EBL 1190 ml (100-6000)
- Median hospital stay 12 days (2-61)
- 3 (1.8%) patients died within 30 days of surgery
Cytoreductive Surgery

- Overall median survival 54 months
- Estimated 5-year survival 48%
- Multivariate analysis revealed the following independent predictors of survival:
  - Age ≤ 61 vs > 61 (p=0.003)
  - Stage IIIIC vs. IV (p=0.04)
  - Ascites ≤ 1L vs. > 1L (p=0.01)
  - Any remaining disease (p=0.02)
- Conclusion
  - Complete cytoreduction is feasible and improves survival
Cytoreductive Surgery


- Retrospective analysis of Stage III EOC: GOG studies #111, #114, #132, #152, #158 and #172

- All patients treated with platinum and paclitaxel

- 1895 women were evaluated

- Patients divided into three groups
  - Microscopic residual disease
  - 0.1-1 cm of residual disease
  - > 1 cm of residual disease
Cytoreductive Surgery

• Results:
  – Median age 57
  – 73.5% serous histology
  – 52% grade 3
  – Microscopic residual 437 patients (23.1%)
  – 0.1 - 1 cm 791 patients (41.7%)
  – > 1 cm 667 patients (35.2%)
Cytoreductive Surgery

• For the entire group overall median PFS (17.1 mo) and OS (45.3 mo)

• Age, PS, tumor histology, and residual tumor volume were independent predictors of prognosis in patients with Stage III EOC.

• Increasing age was associated with increased risk of progression [HR 1.06 (95% CI, 1.02-1.11)] and death [HR 1.11 (95% CI, 1.06-1.18)]

• Mucinous or clear-cell histology was associated with a worse PFS and OS compared with serous carcinomas

• Compared with patients with microscopic residual disease:
  – Risk of recurrence
    • 0.1-1 cm (HR 1.96; 95% CI, 1.70-2.26; P<0.001)
    • > 1 cm   (HR 2.36; 95% CI, 2.04-2.73; P<0.001)
  – Risk of death
    • 0.1-1 cm (HR 2.11; 95% CI, 1.78-2.49; P<0.001)
    • > 1 cm   (HR 2.47; 95% CI, 2.09-2.92; P<0.001)

• Conclusion
  – Cytoreduction to microscopic residual disease improves PFS and OS among Stage III EOC patients
Cytoreductive Surgery


• Retrospective analysis of Stage IV EOC: GOG studies #111, #132, #152 and #162
• All patients treated with platinum and paclitaxel
• 360 women were evaluated
Cytoreductive Surgery

• Results:
  – Median age 59
  – 74% serous histology
  – 62% grade 3
  – Median size of residual disease 3 cm
  – 29 patients (8%) had microscopic residual disease
  – 107 patients (30%) had ≤ 1 cm of residual disease
  – 89 patients (24%) had ≥ 5 cm of residual disease
  – Malignant pleural effusion was most common cause for Stage IV EOC (48%)
Cytoreductive Surgery

• Microscopic residual disease had best prognosis
• 0.1-1 cm and 1.1 cm to 5 cm of residual disease had similar PFS and OS
• > 5 cm of residual disease had worst prognosis
• For the entire group overall median PFS (12 mo) and OS (29 mo)
• Median OS
  – microscopic residual 64 mo
  – 0.1-5 cm residual 30 mo
  – > 5 cm 19 mo

• Conclusion
  – Cytoreduction to microscopic residual disease can improve survival among Stage IV EOC patients

• Optimal cytoreduction has been shown to increase platinum sensitivity

• Every effort should be given to achieve microscopic residual disease while balancing the unique co-morbidities of the patient

• Food for thought... Should a 78-year-old patient with O$_2$ dependent COPD/DM/HTN/A-fib undergo an ovarian cancer debulking, hepatectomy, splenectomy and low anterior resection of rectosigmoid colon?
Historical GOG trials


• GOG #111

• Phase III, randomized, controlled trial

• Objective- to evaluate the response between 6 cycles of cyclophosphamide (750 mg/m$^2$) and cisplatin (75 mg/m$^2$) Q 21 days vs. 6 cycles of paclitaxel (135 mg/m$^2$) and cisplatin (75 mg/m$^2$) Q 21 days
Historical GOG trials

• Methods-
  – Eligibility:
    • Stage III
    • Stage IV
    • Residual disease > 1cm
  – Primary endpoint
    • PFS- measured from the date of randomization
  – Secondary endpoint
    • OS- measured from the date of randomization
Historical GOG trials

• Results
  – 386 patients
  – Majority of patients
    • Stage III
    • Grade 3
    • Serous adenocarcinoma

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<tr>
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<th>Cyclophosphamide / Cisplatin</th>
<th>Paclitaxel/ Cisplatin</th>
<th>P value</th>
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<tbody>
<tr>
<td>N</td>
<td>202</td>
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</tr>
<tr>
<td>Response Rate</td>
<td>60%</td>
<td>73%</td>
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</tr>
<tr>
<td>Complete Response</td>
<td>31%</td>
<td>51%</td>
<td>0.01</td>
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<tr>
<td>Partial Response</td>
<td>29%</td>
<td>22%</td>
<td>NS</td>
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<tr>
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<td>18 mo</td>
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</tr>
<tr>
<td>OS</td>
<td>24 mo</td>
<td>38 mo</td>
<td>0.001</td>
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</table>
Historical GOG trials

• Conclusion
  – For suboptimally debulked Stage III and Stage IV epithelial ovarian cancer, Paclitaxel and Cisplatin provides a superior OS and PFS compared with Cyclophosphamide and Cisplatin
  – Standard of care shifted to Paclitaxel and Cisplatin
Historical GOG trials


- GOG #132

- Phase III, randomized, controlled trial

- Objective- to evaluate differences in response between
  - paclitaxel (135 mg/m²) and cisplatin (75 mg/m²)
  - cisplatin (100 mg/m²)
  - paclitaxel (200 mg/m²)
Historical GOG trials

• Methods-
  – Eligibility:
    • Stage III
    • Stage IV
    • Residual disease > 1cm
  – Primary endpoint
    • PFS- measured from the date of randomization
  – Secondary endpoint
    • OS- measured from the date of randomization
Historical GOG trials

• Results
  – 648 patients
  – Majority of patients
    • Stage III (~70%)
    • Grade 3 (53%)
    • Serous adenocarcinoma (70%)

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel/ Cisplatin</th>
<th>Cisplatin</th>
<th>Paclitaxel</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>201</td>
<td>200</td>
<td>213</td>
<td></td>
</tr>
<tr>
<td>Response Rate</td>
<td>66%</td>
<td>65%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete Response</td>
<td>43%</td>
<td>42%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Partial Response</td>
<td>23%</td>
<td>25%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>14.1 mo</td>
<td>16.4 mo</td>
<td>10.8 mo</td>
<td>0.002</td>
</tr>
<tr>
<td>OS</td>
<td>26.3 mo</td>
<td>30.2 mo</td>
<td>25.9 mo</td>
<td>0.310</td>
</tr>
</tbody>
</table>
Historical GOG trials

• Conclusion
  – “Cisplatin alone or in combination yielded superior response rates and PFS relative to paclitaxel.”
  – OS was similar in all three arms
  – Combination therapy had a better toxicity profile
  – Standard of care continued to be Paclitaxel and Cisplatin
Historical GOG trials


• GOG #158

• Phase III, randomized, controlled trial

• Objective-\textit{non-inferiority} trial to evaluate the efficacy of Carboplatin and Paclitaxel vs. Cisplatin and Paclitaxel
Historical GOG trials

• Methods-
  – Eligibility:
    • Stage III
    • No residual disease > 1cm
  – Primary endpoint
    • PFS- measured from the date of randomization
    • Statistics set to determine a moderate difference in efficacy (carboplatin arm), a HR 1.25 would be detectable with 80% power
  – Secondary endpoint
    • OS- measured from the date of randomization
  – Treatment groups
    • Cisplatin (75 mg/m^2) and paclitaxel (135 mg/m^2, 24 hour infusion) Q 21 days
    • Carboplatin (AUC 7.5) and paclitaxel (175 mg/m^2, 3hour infusion) Q 21 days
Historical GOG trials

• **Results**
  – 792 patients
  – Serous histology (~70%)
  – Grade 3 (55%)
  – Microscopic/no residual disease (36%)
  – 50% (393) of patients had a second look laparotomy (SLL)
    • 50% (160) patients had a negative SLL

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel/Cisplatin</th>
<th>Paclitaxel/Carboplatin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>400</td>
<td>392</td>
<td></td>
</tr>
<tr>
<td>Completed 6 cycles</td>
<td>85%</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Leukopenia</td>
<td>25%</td>
<td>10%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Renal Metabolic toxicity</td>
<td>63%</td>
<td>59%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Grade 2-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5%</td>
<td>39%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Recurrence</td>
<td>76%</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>19.4 mo</td>
<td>20.7 mo</td>
<td>RR 0.88 (95% CI 0.75-1.03)</td>
</tr>
<tr>
<td>Deaths</td>
<td>58%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>48.7 mo</td>
<td>57.4 mo</td>
<td>RR 0.84 (95% CI 0.7-1.02)</td>
</tr>
</tbody>
</table>
Historical GOG trials

• Conclusions
  – “the combination of carboplatin plus paclitaxel is not inferior to cisplatin plus paclitaxel with regard to PFS and survival in patients with small-volume stage III epithelial ovarian cancer.”
  – “This trial was not designed to determine whether the carboplatin regimen was superior to the cisplatin regimen. Nonetheless, the 16% reduced risk of death is of interest because it is suggestive that carboplatin may provide a slight increase in efficacy over cisplatin.”
SCOTROC trial


• Phase III, randomized, controlled trial

• Objective- evaluate the efficacy of Docetaxol and Carboplatin vs. Carboplatin and Paclitaxel
SCOTROCO trial

• Methods-
  – Eligibility:
    • Stage IC-IV
    • Residual disease > 2 cm could be enrolled
  – Primary endpoint
    • PFS- measured from the date of randomization
    • The study was designed with an 80% power to detect a difference of 25% in median progression-free survival (from 17 to 21.25 months)
  – Secondary endpoint
    • OS- measured from the date of randomization
  – Treatment groups
    • Carboplatin (AUC 5) and Docetaxel (75 mg/m², 1 hour infusion) Q 21 days
    • Carboplatin (AUC 5) and Paclitaxel (175 mg/m², 3 hour infusion) Q 21 days
SCOTROC trial

- **Results**
  - 1077 patients
  - Stage III/IV (80%)
  - Serous histology (44%)
  - Residual disease
    - Microscopic (33%)
    - ≤ 2 cm (30%)
    - > 2 cm (37%)

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel/Carboplatin</th>
<th>Paclitaxel/Carboplatin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>539</td>
<td>538</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4 Neutropenia</td>
<td>94%</td>
<td>84%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 2-4 Neurosensory</td>
<td>11%</td>
<td>30%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Response rate</td>
<td>58.7%</td>
<td>59.5%</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>15 mo</td>
<td>14.8 mo</td>
<td>RR 0.97 (95% CI 0.83-1.13), p=0.707</td>
</tr>
<tr>
<td>2-year OS</td>
<td>64.2%</td>
<td>68.9%</td>
<td>RR 1.13 (95% CI 0.92-1.39), p=0.238</td>
</tr>
</tbody>
</table>
SCOTROC trial

• Conclusions
  – Docetaxel and Carboplatin have equal efficacy as Paclitaxel and Carboplatin
  – Docetaxel and Carboplatin have significant neutropenia and less neuropathy and hypersensitivity
Historical GOG trials


• GOG #182/ICON-5

• Phase III, randomized, controlled trial

• Objective- to evaluate the addition of a third chemotherapy to Carboplatin and Paclitaxel
Historical GOG trials

• Methods-
  – Eligibility:
    • Stage III/IV
    • Optimal residual disease ≤ 1 cm
    • Suboptimal residual disease > 1 cm
  – Primary endpoint
    • OS- measured from the date of randomization
    • determined by pair wise comparison to the reference arm, with a 90% chance of detecting a true hazard ratio of 1.33 that limited type I error to 5% (two-tail) for the four comparisons
  – Secondary endpoint
    • PFS- measured from the date of randomization
Historical GOG trials

- Treatment groups:
  - Carboplatin (AUC 6) D1 and Paclitaxel (175 mg/m²) D1 Q 21 days 8 cycles
  - Carboplatin (AUC 5) D1, Gemcitabine (800 mg/m²) D1,8 and Paclitaxel (175 mg/m²) D1 Q 21 days for 8 cycles
  - Carboplatin (AUC 5) D1, Doxil (30 mg/m²) D1 and Paclitaxel (175 mg/m²) D1 Q 21 days for 4 cycles and Carboplatin (AUC 5) D1 and Paclitaxel (175 mg/m²) D1 Q 21 days 4 cycles
  - Carboplatin (AUC 5) D1, Topotecan (1.25 mg/m²) D1,2,3 for 4 cycles and Carboplatin (AUC 6) D1 and Paclitaxel (175 mg/m²) D1 Q 21 days 4 cycles
  - Carboplatin (AUC 6) D8 and Gemcitabine (1000 mg/m²) D1,8 for 4 cycles and Carboplatin (AUC 6) D1 and Paclitaxel (175 mg/m²) D1 Q 21 days 4 cycles
Historical GOG trials

- **PFS**
  - CP: HR 1.00 Reference
  - CPG: HR 1.028 (95% CI 0.924-1.143), p=0.610
  - CPD: HR 0.984 (95% CI 0.884-1.095), p=0.796
  - CT + CP: HR 1.066 (95% CI 0.958-1.186), p=0.239
  - CG + CP: HR 1.037 (95% CI 0.932-1.153), p=0.503

- **OS**
  - CP: HR 1.00 Reference
  - CPG: HR 1.006 (95% CI 0.885-1.144), p=0.923
  - CPD: HR 0.952 (95% CI 0.836-1.085), p=0.462
  - CT + CP: HR 1.051 (95% CI 0.925-1.194), p=0.447
  - CG + CP: HR 1.114 (95% CI 0.982-1.264), p=0.093

- No statistical difference in PFS or OS with any regimen
- Median duration of follow-up 3.7 years
- For the entire group: PFS 16 mo and OS 44.1 mo

- Categorized by residual disease:
  - Microscopic: PFS 29 mo and OS 68 mo
  - < 1cm: PFS 16 mo and OS 40 mo
  - > 1cm: PFS 13 mo and OS 33 mo
Historical GOG trials

• Conclusions
  – “Compared with standard paclitaxel and carboplatin, addition of a third cytotoxic agent provided no benefit in PFS or OS after optimal or suboptimal cytoreduction.”
Historical GOG trials

• Points
  – Cisplatin/Paclitaxel became standard of care for ovarian cancer in 1996 (GOG #111)
  – Platinum agents are the single most effective agents (GOG #132)
  – Carboplatin/Paclitaxel is not inferior to Cisplatin/Paclitaxel; in fact, it might be superior (GOG #158)
  – Docetaxel/Carboplatin can be substituted for Paclitaxel/Carboplatin without compromising efficacy (SCOTROC)
  – The addition of a third chemotherapy does not improve OS or PFS (GOG #182)
Intraperitoneal Chemotherapy


- GOG #104

- Phase III, randomized, controlled trial

- Objective- to evaluate IP cisplatin versus IV cisplatin for Stage III EOC
Intraperitoneal Chemotherapy

• Methods-
  – Eligibility:
    • Stage III
    • Residual disease < 2cm
  – Primary endpoint
    • PFS- measured from the date of randomization
  – Secondary endpoint
    • OS- measured from the date of randomization
  – Treatment groups
    • Cyclophosphamide (600 mg/m²) IV and Cisplatin (100 mg/m²) IV Q 21 days for 6 cycles
    • Cyclophosphamide (600 mg/m²) IV and Cisplatin (100 mg/m²) IP Q 21 days for 6 cycles
Intraperitoneal Chemotherapy

- **Results**
  - 546 patients
  - Serous histology (66%)
  - Grade 3 (58%)
  - Residual disease ≤ 0.5 cm (72%)
  - 75% of patients finished 4 cycles of IP chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>IP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>279</td>
<td>267</td>
<td></td>
</tr>
<tr>
<td>Completed 6 cycles</td>
<td>58%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>69%</td>
<td>56%</td>
<td>0.04</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>50%</td>
<td>40%</td>
<td>0.002</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>25%</td>
<td>15%</td>
<td>0.02</td>
</tr>
<tr>
<td>Grade 2 &gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2%</td>
<td>18%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deaths</td>
<td>174 (62%)</td>
<td>147 (55%)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>41 mo</td>
<td>49 mo</td>
<td>RR 0.76 (95% CI 0.61-0.96), p=0.02</td>
</tr>
</tbody>
</table>
Intraperitoneal Chemotherapy

• Conclusions
  – “As compared with intravenous cisplatin, *intraperitoneal cisplatin significantly improves survival* and has significantly fewer toxic effects in patients with stage III ovarian cancer and residual tumor masses of 2 cm or less.”
  – This study was lost among the hoopla of GOG #111, which was released 1 month earlier.
  – GOG #104 had a better OS but all the patients enrolled had residual disease < 2cm
Intraperitoneal Chemotherapy

- GOG #114
- Phase III, randomized, controlled trial
- Objective- to evaluate PFS and OS among women with Stage III EOC being treated by IV cisplatin and paclitaxel versus IV carboplatin, paclitaxel and IP cisplatin for Stage III EOC
Intraperitoneal Chemotherapy

• Methods-
  – Eligibility:
    • Stage III
    • Residual disease ≤ 1cm
  – Primary endpoint
    • PFS- measured from the date of randomization
    • OS- measured from the date of randomization
  – Treatment groups
    • Paclitaxel (135 mg/m² for 24 hours) IV and Cisplatin (75 mg/m²) IV Q 21 days for 6 cycles
    • Carboplatin (AUC 9) IV Q28 days for 2 cycles then Paclitaxel (135 mg/m² for 24 hours) IV and Cisplatin (100 mg/m²) IP Q 21 days for 6 cycles
Intraperitoneal Chemotherapy

• Results
  – 462 patients
  – Serous histology (66%)
  – Grade 3 (48%)
  – Microscopic residual disease (35%)
  – 76% of patients finished 4 cycles of IP chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>IP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>227</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td>Completed 6 cycles</td>
<td>86%</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4 Neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>124 (54.6%)</td>
<td>109 (47.4%)</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>22.2 mo</td>
<td>27.9 mo</td>
<td>RR 0.78 (90% CI 0.66-0.94), p=0.01</td>
</tr>
<tr>
<td>OS</td>
<td>52.2 mo</td>
<td>63.2 mo</td>
<td>RR 0.81 (90% CI 0.65-1.00), p=0.05</td>
</tr>
</tbody>
</table>
Intraperitoneal Chemotherapy

• Conclusions
  – “it was recognized that a better result for the experimental arm would not give a clear answer about IP cisplatin separate from the effect of IV carboplatin, and vice versa. Rather, it was hoped that a major advancement in the management of ovarian cancer might be achieved by combining these two strategies.”
  – “The actual outcome has been a modest advance, with a significant improvement in PFS and borderline significant improvement in survival, but with greater toxicity”.
  – Opponents of IP chemotherapy argue that the carboplatin is responsible for the improved PFS
Intraperitoneal Chemotherapy

- GOG #172
- Phase III, randomized, controlled trial
- Objective- to evaluate PFS and OS among women with Stage III EOC being treated by IV cisplatin and paclitaxel versus IV paclitaxel and IP cisplatin, paclitaxel for Stage III EOC
Intraperitoneal Chemotherapy

• Methods-
  – Eligibility:
    • Stage III
    • Residual disease \( \leq 1\text{cm} \)
  – Primary endpoint
    • PFS- measured from the date of randomization
    • OS- measured from the date of randomization
  – Treatment groups
    • Paclitaxel (135 mg/m\(^2\) for 24 hours) IV and Cisplatin (75 mg/m\(^2\)) IV Q 21 days for 6 cycles
    • Paclitaxel (135 mg/m\(^2\) for 24 hours) IV and Cisplatin (100 mg/m\(^2\)) IP D2, Paclitaxel (60 mg/m\(^2\)) IP D8 Q 21 days for 6 cycles
Intraperitoneal Chemotherapy

- Results
  - 415 patients
  - Serous histology (86%)
  - Grade 3 (51%)
  - Microscopic residual disease (37%)
  - 52% of patients finished less than 4 cycles of IP chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>IP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>210</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td>Completed 6 cycles</td>
<td>83%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>64%</td>
<td>76%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>GI</td>
<td>24%</td>
<td>46%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4%</td>
<td>18%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Metabolic</td>
<td>7%</td>
<td>27%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>1%</td>
<td>11%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4%</td>
<td>12%</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>9%</td>
<td>19%</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>6%</td>
<td>16%</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Deaths</td>
<td>127 (60%)</td>
<td>101 (49%)</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>18.3 mo</td>
<td>23.8 mo</td>
<td>RR 0.77 (95% CI), p=0.05</td>
</tr>
<tr>
<td>OS</td>
<td>49.7 mo</td>
<td>65.6 mo</td>
<td>RR 0.73 (95% CI), p=0.03</td>
</tr>
</tbody>
</table>
Intraperitoneal Chemotherapy

• Conclusions
  – IP chemotherapy had a significantly better PFS and OS for women with optimally cytoreduced Stage III EOC
  – Significant toxicity with IP chemotherapy (only 40% of women completed 6 cycles)
  – Most patients had abdominal port/catheter issues that resulted in conversion to IV carboplatin rather than IP chemotherapy
  – Opponents of IP chemotherapy argue that the IP regimen is not being compared to the current standard of care (Carboplatin and Taxol)
  – Proponents argue that Cisplatin and Taxol is equally effective as Carboplatin and Taxol (GOG #158)
Consolidation Chemotherapy


• GOG #178

• Phase III, randomized, controlled trial

• Objective- to evaluate PFS among women with advanced ovarian cancer the efficacy of Carboplatin and Paclitaxel vs. Cisplatin and Paclitaxel
Consolidation Chemotherapy

• Methods-
  
  – Eligibility:
    • Stage III
    • Stage IV
    • Treatment with 5-6 cycles of platinum/paclitaxel
    • Clinical complete response (normal exam, normal CT scan, CA-125 ≤35)
  
  – Primary endpoint
    • PFS- measured from the date of randomization
    • “The median PFS after a clinical complete response to induction therapy for the control arm was estimated to be approximately 16 months for those with Stage IV or suboptimal (1 cm residual) Stage III disease and 24 months for Stage III patients with optimal (1 cm residual) disease”.
    • “A one-sided log-rank test at .05 significance level, the power to detect a hazard ratio of 1.33 in PFS is approximately 0.85”.
  
  – Treatment groups
    • Paclitaxel (175 mg/m², 3 hour infusion) Q 28 days for 3 cycles
    • Paclitaxel (175 mg/m², 3 hour infusion) Q 28 days for 12 cycles
Consolidation Chemotherapy

• Results
  – 262 patients
  – Optimal Stage III (66%)
  – Suboptimal Stage III (20%)
  – Stage IV (14%)

<table>
<thead>
<tr>
<th></th>
<th>3 cycles</th>
<th>12 cycles</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>128</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>Grade 2-3 Neuropathy</td>
<td>15%</td>
<td>23%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Recurrence</td>
<td>34 (26.5%)</td>
<td>20 (15%)</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>21 mo</td>
<td>28 mo</td>
<td>RR 2.31 (99% CI 1.08-4.94), p=0.0023</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td>NS, p=0.7</td>
</tr>
</tbody>
</table>
Consolidation Chemotherapy

• Conclusions
  – 12 cycles of consolidation paclitaxel significantly increases PFS
  – Once consolidation chemotherapy ended, high rate of recurrences documented
  – Issues with study
    • Lack of QOL (study designed in 1997)
    • Poor documentation of neuropathy
    • Rationale for 3 months of paclitaxel was to encourage women to enroll rather than choose a study which had a “no further therapy arm”
    • Study prematurely closed secondary to significant increase in PFS with 12 cycles of chemotherapy
Consolidation Chemotherapy


• Retrospective study analyzing PFS among patients with consolidation chemotherapy and a CA-125 ≤ 35.

• Two studies- GOG #178 and oral altretamine study
### Consolidation Chemotherapy

<table>
<thead>
<tr>
<th>CA-125</th>
<th>Patients (N=354)</th>
<th>PFS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10</td>
<td>58%</td>
<td>24 mo</td>
<td><strong>Categoric value &lt;0.001</strong>&lt;br&gt; Continuous value &lt;0.0001</td>
</tr>
<tr>
<td>11-20</td>
<td>34%</td>
<td>17 mo</td>
<td></td>
</tr>
<tr>
<td>21-35</td>
<td>8%</td>
<td>7 mo</td>
<td></td>
</tr>
</tbody>
</table>

- Conclusion
  - Patients with pre-maintenance baseline CA-125 values ≤ 10 have a superior PFS compared with higher levels in the normal CA-125 range
Dose-dense Chemotherapy


• Phase III, randomized, controlled trial

• Objective- to evaluate PFS between dose-dense paclitaxel and carboplatin compared to standard paclitaxel and carboplatin
Dose-dense Chemotherapy

- **Methods-**
  - **Eligibility:**
    - Stage II-IV
    - Residual disease $> 1$cm included
  - **Primary endpoint**
    - PFS- measured from the date of randomization
  - **Secondary endpoint**
    - OS- measured from the date of randomization
    - Response rate
    - Adverse events
  - **Treatment groups**
    - Paclitaxel (180 mg/m$^2$, 3 hour infusion) and Carboplatin (AUC 6) IV Q 21 days for 6 cycles
    - Paclitaxel (80 mg/m$^2$, 1 hour infusion) D1,8,15 and Carboplatin (AUC 6) D1 IV Q 21 days for 6 cycles
Dose-dense Chemotherapy

• Results
  – 632 patients
  – Stage
    • II (19%)
    • III (66%)
    • IV (15%)
  – Serous histology (56%)
  – Grade 3 (24%)
  – Residual disease ≤ 1 cm (46%)
  – Primary debulking surgery (89%)

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Dose-dense</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>320</td>
<td>312</td>
<td></td>
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<tr>
<td>Completed 6 cycles</td>
<td>73%</td>
<td>62%</td>
<td></td>
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<tr>
<td>Grade 3-4 Anemia</td>
<td>44%</td>
<td>69%</td>
<td>p&lt;0.0001</td>
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<tr>
<td>Response rate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Complete response</td>
<td>54%</td>
<td>56%</td>
<td></td>
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<tr>
<td>Partial response</td>
<td>16%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38%</td>
<td>36%</td>
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</tr>
<tr>
<td>Deaths</td>
<td>124 (39%)</td>
<td>96 (30%)</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>17.2 mo</td>
<td>28 mo</td>
<td>HR 0.71 (95% CI, 0.58-0.88), p=0.0015</td>
</tr>
<tr>
<td>OS (3-year)</td>
<td>65.1%</td>
<td>72.1%</td>
<td>HR 0.75 (95% CI 0.57-0.98), p=0.03</td>
</tr>
</tbody>
</table>
Dose-dense Chemotherapy

• Conclusions
  – Dose-dense paclitaxel significantly improved PFS and OS
  – 29% lower risk of progression
  – 25% lower risk of death
  – Low toxicity (anemia)
  – Median follow-up 42 months, median over-all survival has not yet been reached in either group
### Treatment for Stage III/IV ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>GOG #111</th>
<th>GOG #158</th>
<th>GOG #172</th>
<th>GOG #178</th>
<th>Dose-Dense Chemotherapy (Japanese study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Cisplatin (75 mg/m²) Paclitaxel (135 mg/m²)</td>
<td>Carboplatin (AUC 7.5) Paclitaxel (175 mg/m²)</td>
<td>Paclitaxel (135 mg/m²) IV D1, Cisplatin (100 mg/m²) IP D2 and Paclitaxel (60 mg/m²) IP D8</td>
<td>Paclitaxel (175 mg/m²), 12 cycles</td>
<td>Carboplatin (AUC 6) D1, Paclitaxel (80 mg/m²) D1,8,15</td>
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<tr>
<td>Optimal</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
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<tr>
<td>Stage</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III-IV</td>
<td>II-IV</td>
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<tr>
<td>Microscopic disease</td>
<td>n/a</td>
<td>36%</td>
<td>37%</td>
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<tr>
<td>PFS</td>
<td>13 mo</td>
<td>20.7 mo</td>
<td>23.8 mo</td>
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<td>28 mo</td>
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<tr>
<td>OS</td>
<td>18 mo</td>
<td>57.4 mo</td>
<td>65.6 mo</td>
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