## Disclosure of Potential Conflicts of Interest

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<tr>
<th>Name of Faculty or Presenter</th>
<th>Reported Areas of Conflict</th>
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<tr>
<td>Christine Walsh, M.D., M.S.</td>
<td>Research funding from Merck</td>
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<td>Advisory Board for Clovis Oncology</td>
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Ovarian Cancer

- Eighth most common cancer in US women
  21,000 cases per year

- Fifth most common cause of cancer death and leading cause of gynecologic cancer death in US women
  15,000 deaths per year

- Median age: 63 years

- 70 -75% present with advanced stage disease

- Peritoneal spread pattern
What’s NEW in Ovarian Cancer

• New Staging System
• Tissue of Origin for “Ovarian Cancer”
• Genetic Testing
• Standard of Care Treatments
• Drug Approvals & Emerging Targets
New Staging System
FIGO 2013
Stage I – Confined to the ovary

- IA – one ovary
- IB – both ovaries
- IC – one or both ovaries with any of the following
  - IC1 – surgical spill
  - IC2 – capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
  - IC3 – malignant cells in ascites or peritoneal washings
Stage II – Confined to the pelvis

- IIA – extension or implants on uterus, tubes
- IIB – extension or implants on other pelvic structures

What’s different
IIC gone

Prat, Int J Gyn Obstet 2013
Stage III – Spread to LNs, abdomen

- IIIA1 – Positive retroperitoneal lymph nodes only
  - IIIA1(i) – metastasis up to 10 mm in greatest dimension
  - IIIA1(ii) – metastasis more than 10 mm in greatest dimension
- IIIA2 – Microscopic metastases above the pelvic brim
- IIIB – Macroscopic metastases < 2 cm +/- LN mets
- IIIC – Macroscopic metastases ≥ 2 cm +/- LN mets
  - Includes extension to capsule of liver or spleen without parenchymal involvement

What’s different
+LN is IIIA IIIA categories

Prat, Int J Gyn Obstet 2013
Stage IV – Distant spread

- IVA – pleural effusion with positive cytology
- IVB – Distant metastases
  - Parenchymal metastases
  - Metastases to inguinal lymph nodes
  - Metastases to lymph nodes outside of the abdominal cavity

What’s different
IVA and IVB

Prat, Int J Gyn Obstet 2013
Histology drives behavior
- Record Histology and Grade

**EPITHELIAL (90%)**
- High-grade serous (70%)
- Endometrioid (10%)
- Clear Cell Carcinoma (10%)
- Mucinous (3%)
- Low-grade serous (<5%)

**GERM CELL (3%)**
- Dysgerminoma
- Yolk Sac
- Immature Teratoma

**SEX CORD-STROMAL (2%)**
- Granulosa cell tumor

Prat, Int J Gyn Obstet 2013
Tissue of Origin for "Ovarian Cancer"
Insights from Hereditary Ovarian Cancer

• Approximately 10-15% of ovarian cancers arise from germline mutations in BRCA1 or BRCA2
  – BRCA1 – 39% risk of ovarian cancer
  – BRCA2 – 11% risk of ovarian cancer

• Distinct histologic phenotype
  – High grade serous
  – Fallopian tube, peritoneal cancers part of spectrum

• Risk-reducing salpingo-oophorectomy recommended after childbearing complete, ideally between ages 35-40
  – Reduces risk of ovarian cancer by 80 – 90%

Antoniou, Am J Hum Genet 2003
NCCN Guidelines
Rebbeck, JNCI 2009
Occult Carcinoma at time of RRSO

- Approximately 4% risk of finding occult ovarian or tubal carcinoma at time of RRSO

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<th>Patients</th>
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<td>50</td>
<td>2 (4.0%)</td>
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<td>Colgan, AJSP 2001</td>
<td>60</td>
<td>5 (8.3%)</td>
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<td>Leeper, Gyn Onc 2002</td>
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<td>Rebbeck, NEJM 2002</td>
<td>259</td>
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<td>Kauff, NEJM 2002</td>
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<td>3 (3.1%)</td>
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<td><strong>TOTAL</strong></td>
<td><strong>497</strong></td>
<td><strong>21 (4.2%)</strong></td>
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- More occult tumors are found in the fallopian tube than in the ovaries

  Powell, JCO 2005
P53 signature and TICs

Karst, J Oncol 2010
Fallopian Tube
Tissue of origin for “Ovarian Cancer”

- P53 signature
- TIC
- Invasive serous carcinoma
- Implants on ovary
Integrated Model of OVCA Pathogenesis

Type II (high-grade) serous carcinoma

Type I (low grade) tumors

BRCA deficiency
P53 signature
Tubal Intraepithelial Carcinoma
High-grade Serous Carcinoma

Endometriosis
Incessant Ovulation
Gonadotropins
Inflammation

Levanon et al, 2008
Genetic Testing
Hereditary Ovarian Cancer

Cellular Metabolism
- UV light
- Radiation
- Chemicals
- Replication Errors

Double-Strand DNA Breaks

Homologous Recombination (HR)
Uses sister chromatid as template
G2/M, after DNA replication
High fidelity, error-free

BRCA1  BRCA2

Non-Homologous End Joining (NHEJ)
No template
DNA trimmed and ligated
Error-prone, leads to genetic instability

Genome Caretaker Genes
Homologous Recombination

- Double-strand break
- End resection
- Strand invasion

ATM and ATR recognize ds-DNA break.

CHEK2, P53, BRCA1, and H2AX are involved in the response to DNA damage.

BRCA1 acts as a scaffold, organizing repair proteins such as BARD1 and BRIP1.

Mre11, RAD50, and NBS1 form the MRN complex, which resects DNA.

RPA binds to 3' overhangs of ss-DNA.

BRCA2 loads RAD51 onto RPA-coated DNA.

RAD51B, RAD51C, RAD51D, and PALB2 are involved in the RAD51 nucleoprotein filament invasion of homologous DNA (Strand Invasion).

Sung et al., Nat Rev Mol Cell Biol 2006
Homologous Recombination

Double-strand break
End resection
Strand invasion
DNA synthesis

ATM
ATR
Recognize ds-DNA break

CHEK2
P53
BRCA1
H2AX

BRCA1 acts as scaffold, organizes repair proteins

BARD1
BRIP1
Interact with BRCA1

Mre11
RAD50
NBS1
MRN complex resects DNA

RPA
Binds 3’ overhangs of ss-DNA

BRCA2
Loads
RAD51
onto RPA-coated DNA

RAD51B
RAD51C
RAD51D

RAD51 nucleoprotein filament invades homologous DNA (Strand Invasion)

PALB2

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PALB2

Sung et al., Nat Rev Mol Cell Biol 2006
## HR Genes & Hereditary Cancer Risk

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- Next-generation sequencing in unselected ovarian cancer patients
  - 30% with a HR gene mutation had no family history of breast or ovarian cancer
Association for Molecular Pathology v. Myriad Genetics

- June 13, 2013
  - U. S. Supreme Court – Unanimous landmark decision
  - Genes are not patent eligible
  - Broke monopoly on BRCA1/2 genetic testing in U.S.

- June 14, 2013
  - Many other companies begin to offer BRCA1/2 testing
  - Testing offered alone or in larger multi-gene panels
## Genetic Testing Options

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<th>Company</th>
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<th>Panel (number of genes)</th>
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<td>BRCA1 single site analysis</td>
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<td>BRCA1 and BRCA2 screen</td>
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<td>BRCA1 (only available outside North America)</td>
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# A Snapshot of Current Genetic Testing Panels

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<td>Neurofibromatosis</td>
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<tr>
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<td>Lynch</td>
<td>Lynch</td>
<td>Lynch</td>
<td>Lynch</td>
<td>Lynch</td>
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</tbody>
</table>

Additional genes in BROCA panel: AKT1, ATR, BAP1, CHEK1, CTNNA1, FAM175A, GALNT12, GEN1, GREM1, HOXB13, PIK3CA, POLD1, POLE, PRSS1, RAD51, RET, SDHB, SDHC, SDHD, TP53BP1
HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA

- Individual from a family with a known deleterious BRCA1/BRCA2 mutation
- Personal history of breast cancer\(^b\) + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - An additional primary\(^d\)
    - ≥1 close blood relative\(^e\) with breast cancer at any age
    - An unknown or limited family history\(^a\)
  - Diagnosed ≤60 y with:
    - Triple negative breast cancer
    - Diagnosed at any age with:
      - ≥1 close blood relative\(^e\) with breast cancer diagnosed ≤50 y
      - ≥2 close blood relatives\(^e\) with breast cancer at any age
      - ≥1 close blood relative\(^e\) with epithelial ovarian\(^f\) cancer
      - ≥2 close blood relatives\(^e\) with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
      - A close male blood relative\(^e\) with breast cancer
      - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required\(^a\)
- Personal history of epithelial ovarian\(^f\) cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or prostate cancer (Gleason score ≥7) at any age with:
  - ≥2 close blood relatives\(^e\) with breast and/or ovarian and/or pancreatic or prostate cancer
  - Gleason score ≥7 at any age
- For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative is needed

\(^a\) Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. The probability of mutation detection associated with these criteria will vary based on family structure. Individuals with unknown or limited family history/structure, such as fewer than 2 first- or second-degree female relatives having lived beyond age 46 in either lineage, may have an underestimated probability of familial mutation detection. The likelihood of mutation detection may be very low in families with a large number of unaffected female relatives. Clinical judgment should be used to determine the appropriateness of genetic testing. The maternal and paternal sides should be considered independently.

\(^b\) For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

\(^d\) Patients who have received an allogenic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.

\(^e\) Two breast primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

\(^f\) Close blood relatives include first-, second-, and third-degree relatives on same side of family.

For the purposes of these guidelines, fallopian tube and primary peritoneal cancers are included. Ovarian/fallopian tube primary peritoneal cancers are component tumors of Lynch syndrome/hereditary non-polyposis colorectal cancer, be attentive for clinical evidence of this syndrome. See NCCN Guidelines for Genetically-Familial High-Risk Assessment: Colorectal.

\(^g\) For Ashkenazi Jewish founder-specific mutation(s) should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria are met. Founder mutations exist in other populations.
Multi-Gene Panel Testing

- **PROS**
  - Higher mutation detection rate
  - More cost effective and time effective
  - May reveal more than one pathogenic mutation

- **CONS**
  - More likely to detect a VUS
  - Limited data on degree of cancer risk with some mutations
  - Lack of guidelines for management of many mutations
## Breast and Ovarian Management Based on Genetic Test Results

<table>
<thead>
<tr>
<th>Intervention warranted based on gene and/or risk level</th>
<th>Recommend Breast MRI (≥20% risk of breast cancer)</th>
<th>Discuss Option of RRM</th>
<th>Recommend/Consider RRSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53</td>
<td>BRCA1, BRCA2, CDH1, PTEN, TP53, PALB2</td>
<td>BRCA1, BRCA2, Lynch syndrome, BRIP1</td>
<td>BRCA1, BRCA2, RAD51C, RAD51D</td>
</tr>
<tr>
<td>BRIP1</td>
<td>ATM, CHEK2, STK11</td>
<td>PALB2</td>
<td></td>
</tr>
</tbody>
</table>

RRM: risk-reducing mastectomy
RRSO: risk-reducing salpingo-oophorectomy
Standard of Care Treatments
Path to a standard of care

1986
GOG 47
Cisplatin improves survival

1989
GOG 52
Doxorubicin does not improve survival

1996
GOG 111
Taxol improves survival

2003
GOG 158
Carboplatin is equivalent to Cisplatin
Ovarian Cancer Standard of Care

Cytoreductive Surgery

Taxol/Carboplatin x 6 cycles

70 – 90% Achieve Remission

Surveillance

70 – 90% Recur

Only 10 – 15% of advanced ovarian cancer patients will be long-term survivors

Second Line Treatment
What’s new in ovarian cancer?

- Timing of cytoreductive surgery
- Cytoreductive Surgery
- Taxol/Carboplatin x 6 cycles
- Surveillance
- Second Line Treatment
- Alternative adjuvant chemo regimens
- Second line regimens
Cytoreductive Surgery

• Cornerstone of treatment of advanced ovarian cancer
  – Vertical incision: TAH, BSO, omentectomy, tumor debulking
  – May require radical surgical procedures

• Griffiths et al., 1975
  – Inverse correlation between residual tumor diameter and patient survival
  – Failure to remove all masses > 1.5 cm diameter did not influence survival

• Surgery provides optimum benefit when all gross tumor can be excised safely

Griffiths, Natl Cancer Inst Monogr 1975
Biologic Rationale for Cytoreduction

• Ovarian cancer is a chemo-responsive disease

• Reduced tumor burden:
  – Increases growth fraction: non-dividing cells are less susceptible to effects of cytotoxic therapy
  – Reduces areas of poorly perfused tumor and enhances drug delivery
  – Fractional cell kill
  – Decreases potential for developing chemoresistant disease
Cytoreductive Surgery

- Optimal cytoreduction: < 1 cm residual
- Cytoreduction to no visible residual: R0
- Does timing matter?
Phase III Trials Evaluating Timing/Impact of Cytoreductive Surgery

• EORTC 55971: Vergote NEJM 2010
• CHORUS: Lancet 2015
Neoadjuvant chemotherapy and Interval cytoreduction: EORTC 55971

- EORTC 55971
  - Randomized controlled trial, Multiple countries
  - Stage IIIC/IV epithelial ovarian cancer
  - Randomization to
    - Primary debulking + Platinum-based chemo (6 cycles)
    - Neoadjuvant platinum-based chemo (3 cycles) + Interval debulking + adjuvant chemo (3 cycles)

Vergote NEJM 2010
EORTC 55971: No difference in survival

29 months vs. 30 months

Vergote NEJM 2010
Neoadjuvant chemotherapy and Interval cytoreduction: CHORUS

- Randomized controlled trial, 87 hospitals
- Stage IIIIC/IV epithelial ovarian cancer
- Randomization to
  - Primary debulking + Platinum-based chemo (6 cycles)
  - Neoadjuvant platinum-based chemo (3 cycles) + Interval debulking + adjuvant chemo (3 cycles)

Kehoe, Lancet 2015
CHORUS – no difference in survival

22.6 months vs. 24.1 months

Kehoe, Lancet 2015
EORTC 55971: Subgroup Analysis

- Analysis to identify subgroups that do better with one of the study treatments
  - FIGO Stage
  - WHO performance status
  - Histologic type
  - Presence or absence of pleural fluid
  - Country
  - Size of tumor at randomization

NS

Vergote NEJM 2010
EORTC 55971: Survival based on pre-op tumor size

**OS: Largest metastatic tumor size**

<table>
<thead>
<tr>
<th>EORTC 55971</th>
<th>Events/Patients</th>
<th>Statistics (O-E)</th>
<th>Var. (Upfront debulking)</th>
<th>HR &amp; CI*</th>
<th>[1-HR]% ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upfront debulking</td>
<td>Neo-adj. chemo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-49 mm</td>
<td>53 / 94</td>
<td>65 / 95</td>
<td>-12.7</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>50-99 mm</td>
<td>69 / 90</td>
<td>64 / 88</td>
<td>6.9</td>
<td>32.5</td>
<td></td>
</tr>
<tr>
<td>100-199 mm</td>
<td>92 / 105</td>
<td>83 / 113</td>
<td>8.4</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>&gt;200 mm</td>
<td>22 / 28</td>
<td>21 / 24</td>
<td>-0.8</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>236 / 315</td>
<td>233 / 320</td>
<td>1.8</td>
<td>114.4</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity
Chi-square = 8.8, df = 3: p = 0.03

*90% CI everywhere

Vergote NEJM 2010
Neoadjuvant chemotherapy and Interval cytoreduction

• Conclusions
  – Neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy for patients with bulky stage IIIC/IV ovarian cancer
    • Better survival with primary debulking if largest tumor <5 cm at time of randomization

• Caveats
  – Overall survival in both trials was below standard

Vergote NEJM 2010
Kehoe, Lancet 2015
GOG 111 (Suboptimal Population)

- Taxol/Cisplatin replaces Cytoxan/Cisplatin
  - Phase III, randomized controlled trial
  - Suboptimally debulked, Stage III/IV ovarian cancer
    - Cytoxan 750 mg/m² + Cisplatin 75 mg/m²
    - Taxol 135 mg/m² + Cisplatin 75 mg/m²

McGuire NEJM 1996
GOG 158 (Optimal Population)

- Taxol/Carbo is as effective as Taxol/Cisplatin
  - Phase III, randomized controlled trial
  - Optimally debulked, Stage III ovarian cancer
    - Taxol 135 mg/m² + Cisplatin 75 mg/m²
    - Taxol 175 mg/m² + Carboplatin AUC 7.5

Ozols J Clin Oncol 2003
Reasons for poorer survival in EORTC/CHORUS?

- Less optimal chemotherapy?
  - About 15% got less than 6 cycles of chemo
  - About 15% did not get combination Taxol/Platinum
- Population of patients with bulkier disease?
  - >60% had > 5 cm disease
- Less aggressive surgery?
  - 40% versus 80% had optimal debulking (to <1 cm residual)
Controversies

Tumor biology vs. Surgical effort
What is the impact of tumor biology versus surgical effort?
Analysis of GOG 182: Impact of tumor distribution on survival

Stage III/IV Ovarian Cancers

**DS-low** – pelvic, retroperitoneal

**DS-mod** – additional spread, but sparing the upper abdomen

**DS-high** – involving diaphragm, spleen, liver or pancreas

Horowitz, J Clin Oncol 2015
Analysis of GOG 182: Impact of surgical complexity on survival

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TH-BSO</td>
<td>1</td>
</tr>
<tr>
<td>Omentectomy</td>
<td>1</td>
</tr>
<tr>
<td>Pelvic lymphadenectomy</td>
<td>1</td>
</tr>
<tr>
<td>Paraaortic lymphadenectomy</td>
<td>1</td>
</tr>
<tr>
<td>Pelvic peritoneum stripping</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal peritoneum stripping</td>
<td>1</td>
</tr>
<tr>
<td>Small bowel resection</td>
<td>1</td>
</tr>
<tr>
<td>Large bowel resection</td>
<td>2</td>
</tr>
<tr>
<td>Diaphragm stripping or resection</td>
<td>2</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>2</td>
</tr>
<tr>
<td>Liver resection</td>
<td>2</td>
</tr>
<tr>
<td>Rectosigmoidectomy with reanastomosis</td>
<td>3</td>
</tr>
</tbody>
</table>

CS-low – score 1-3
CS-mod – score 4-7
CS-high – score ≥ 8

Horowitz, J Clin Oncol 2015
Post-hoc analysis of GOG 182: Can surgical effort overcome tumor biology?

- Patients with low or moderate preop disease benefit from R0 resection (blue line)
- Patients with high preop disease do not have equivalent survival, even with R0 resection (yellow line)
- Complex surgery does not seem to affect survival when accounting for other confounding influences (particularly residual disease)

Horowitz, J Clin Oncol 2015
What is the best timing for cytoreductive surgery?

- **Offer primary cytoreduction for:**
  - Patients with less bulky tumors (< 5 cm)
  - Patients in whom extensive surgical procedures are not necessary to achieve optimal resection

- **Offer neoadjuvant chemotherapy and interval cytoreduction for:**
  - Bulky tumor, significant upper abdominal disease, poor performance status, medical co-morbidities or disease characteristics that preclude safe surgery
What’s new in ovarian cancer?

Cytoreductive Surgery

Taxol/Carboplatin x 6 cycles

Surveillance

Alternative adjuvant chemo regimens

Second Line Treatment
What’s new in ovarian cancer?

Cytoreductive Surgery

Taxol/Carboplatin x 6 cycles

Intraperitoneal Administration
  Add Third Agent
  Add Biologic Agent
  Dose-dense Administration
  Different Agent

Alternative adjuvant chemo regimens
Intraperitoneal Chemotherapy
Intraperitoneal chemotherapy

• Rationale for IP therapy
  – Ovarian cancer is an intraperitoneal disease
  – Cisplatin and Taxol have a pharmacologic advantage when given IP
    • High IP concentration of drugs
    • Longer half-life of drug IP compared to IV
    • Longer systemic exposure to chemo drugs
    • Cisplatin achieves 10 – 20x greater exposure IP than IV
Overall survival: IP vs. IV chemo

<table>
<thead>
<tr>
<th>Study</th>
<th>Rel Haz Var(\ln(HR))</th>
<th>i.p. regimen better</th>
<th>i.v. regimen better</th>
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<tbody>
<tr>
<td>SWOG/GOG 104 (1996)</td>
<td>0.760</td>
<td></td>
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<tr>
<td>GONO (2000)</td>
<td>0.670</td>
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<tr>
<td>GOG 114/SWOG (2001)</td>
<td>0.810</td>
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<td>Taiwan (2001)</td>
<td>1.130</td>
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<tr>
<td>EORTC 55875 (2003)</td>
<td>0.820</td>
<td></td>
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<tr>
<td>GOG 172 (2006)</td>
<td>0.750</td>
<td></td>
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</tbody>
</table>

Relative hazard
GOG 104 – SWOG 8501

Optimal Stage III (<2 cm residual)

IV Cytoxan 600 mg/m²
IV Cisplatin 100 mg/m²

IV Cytoxan 600 mg/m²
IP Cisplatin 100 mg/m²

OS: 41 months
OS: 49 months

Toxicity: 2 deaths in IP arm

Criticism: no taxane

Alberts NEJM 1996
GOG 114

Optimal Stage III (<1 cm residual)

- IV Taxol 135 mg/m²
- IV Cisplatin 75 mg/m²

- IV Carboplatin AUC 9 x 2
- IP Cisplatin 100 mg/m²
- IV Taxol 135 mg/m²

OS: 53 months
OS: 63 months

Toxicity: greater in IP arm

Criticism: High dose IV Carbo used pre-IP

Markman JCO 2001
GOG 172

Optimal Stage III (<1 cm residual)

- IV Taxol 135 mg/m²
- IV Cisplatin 75 mg/m²

- IV Taxol 135 mg/m² day 1
- IP Cisplatin 100 mg/m² day 2
- IP Taxol 60 mg/m² day 8

OS: 50 months
OS: 66 months

Toxicity: greater in IP arm, only 42% got 6 IP cycles

Criticism: Dose Density, Difficult regimen

Armstrong *NEJM* 2006
Overall Survival

- Two IP trials demonstrate median OS > 60 months
Based on the results of these randomized phase III trials, a combination of IV and IP administration of chemotherapy conveys a significant survival benefit among women with optimally debulked epithelial ovarian cancer, compared to IV administration alone.
Use and Effectiveness of Intraperitoneal Chemotherapy for Treatment of Ovarian Cancer

Alexi A. Wright, Angel Cronin, Dana E. Milne, Nancy L. Keesing, Ursula A. Matulonis, and Jane C. Weeks, Dana-Farber/Brighton and Women’s Cancer Center, Boston, MA; Michael A. Bookman, University of Arizona Cancer Center, Tucson, AZ; Robert A. Burger, University of Pennsylvania, Gina Manta-Smaladone, Fox Chase Cancer Center, Philadelphia, PA; David E. Cohn and David M. O’Malley, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Mihaela Cristea and Joyce C. Niland, City of Hope Comprehensive Cancer Center, Duarte, CA; Jennifer J. Griggs, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; and Charles F. Levenson and Larissa A. Meyer, The University of Texas MD Anderson Cancer Center, Houston, TX.

Purpose
A 2008 randomized trial demonstrated a 16-month survival benefit with intraperitoneal and intravenous (IP/IV) chemotherapy administered to patients who had ovarian cancer, compared with IV chemotherapy alone, but more treatment-related toxicities. The objective of this study was to examine the use and effectiveness of IP/IV chemotherapy in clinical practice.

Patients and Methods
Prospective cohort study of 823 women with stage III, optimally cytoreduced ovarian cancer diagnosed at six National Comprehensive Cancer Network institutions. We examined IP/IV chemotherapy use in all patients diagnosed between 2003 and 2012 (N = 823), and overall survival and treatment-related toxicities with Cox regression and logistic regression, respectively, in a propensity score-matched sample (n = 402) of patients diagnosed from 2008 to 2012, excluding trial participants, to minimize selection bias.

Results
Use of IP/IV chemotherapy increased from 0% to 33% between 2003 and 2006, increased to 50% from 2007 to 2008, and plateaued thereafter. Between 2006 and 2012, adoption of IP/IV chemotherapy varied by institution from 4% to 67% (P < .001) and 43% of patients received modified IP/IV regimens at treatment initiation. In the propensity score-matched sample, IP/IV chemotherapy was associated with significantly improved overall survival (3-year overall survival, 81% v 71%; hazard ratio, 0.68; 95% CI, 0.47 to 0.99), compared with IV chemotherapy, but also more frequent alterations in chemotherapy delivery route (adjusted rates discontinuation or change, 20.4 v 10.0%; adjusted odds ratio, 2.83; 95% CI, 1.47 to 5.47).

Conclusion
Although the use of IP/IV chemotherapy increased significantly at National Comprehensive Cancer Network centers between 2003 and 2012, fewer than 50% of eligible patients received it. Increasing IP/IV chemotherapy use in clinical practice may be an important and underused strategy to improve ovarian cancer outcomes.

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Adding a Third Cytotoxic Agent
GOG 182 - ICON5

- To determine if incorporation of an additional cytotoxic agent to Carboplatin and Taxol improves survival in epithelial ovarian cancer

- Agents that have activity in recurrence
  - Gemcitabine
  - Liposomal doxorubicin
  - Topotecan

Bookman *JCO* 2009
Eligibility
- Histologically confirmed epithelial ovarian or primary peritoneal cancer
- FIGO Stage III/IV with optimal or suboptimal residual disease after initial surgery

Stratification
- No gross residual disease
- Macroscopic residual disease with no intent to perform interval cytoreduction
- Macroscopic residual disease with intent to perform interval cytoreduction

Monitoring and Interventions
- Monitor clinical and biological disease status

Patients in clinical complete remission:
- No second-look surgical procedures
- No postremission therapy

Patients with gross residual disease:
- Optional interval cytoreduction after cycle 4

Endpoints
Primary endpoint:
- Overall survival

Interim analysis:
- Progression-free survival
Secondary endpoints:
- Response rate
- Toxicity
- Correlation with BRCA1/2 status

I Control doublet
Paclitaxel 175 mg/m² IV (3 hr) on day 1
Carboplatin AUC = 6 IV on day 1
× 8 cycles every 21 days

II Gemcitabine triplet
Paclitaxel 175 mg/m² IV (3 hr) on day 1
Carboplatin AUC = 5 IV on day 1
Gemcitabine 800 mg/m² IV on days 1 and 8
× 8 cycles every 21 days

III Liposomal doxorubicin triplet
Paclitaxel 175 mg/m² IV (3 hr) on day 1
Carboplatin AUC = 5 IV on day 1
Liposomal doxorubicin 30 mg/m² IV on day 1 of every other cycle
× 8 cycles every 21 days

IV Topotecan doublet
Carboplatin AUC = 5 IV on day 3
Topotecan 1.25 mg/m² IV on days 1–3
× 4 cycles every 21 days
Paclitaxel 175 mg/m² IV (3 hr) on day 1
Carboplatin AUC = 6 IV on day 1
× 4 cycles every 21 days

V Gemcitabine doublet
Carboplatin AUC = 6 IV on day 8
Gemcitabine 1,000 mg/m² IV on days 1 and 8
× 4 cycles every 21 days
Paclitaxel 175 mg/m² IV (3 hr) on day 1
Carboplatin AUC = 6 IV on day 1
× 4 cycles every 21 days
GOG 182 – ICON5
Survival

Median PFS: 16 months
Median OS: 44.1 months

Bookman JCO 2009
GOG 182 – ICON5
Survival based on residual disease

Median PFS
Microscopic: 29 months
≤ 1 cm: 16 months
> 1 cm: 13 months

Median OS
Microscopic: 68 months
≤ 1 cm: 40 months
> 1 cm: 33 months

Bookman JCO 2009
Overall Survival

• Patients with microscopic residual disease may do better irrespective of the type of adjuvant chemotherapy administered.
GOG 172 – IV/IP Chemotherapy

### Table 3. Summary of Comparisons between the Treatment Groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median Duration</th>
<th>No. of Events*</th>
<th>Relative Risk (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravenous-Therapy Group</td>
<td>Intraperitoneal-Therapy Group</td>
<td>Intravenous-Therapy Group</td>
<td>Intraperitoneal-Therapy Group</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>18.3 mo</td>
<td>23.8 mo</td>
<td>165</td>
<td>149</td>
</tr>
<tr>
<td>Gross residual disease</td>
<td>15.4 mo</td>
<td>18.3 mo</td>
<td>115</td>
<td>105</td>
</tr>
<tr>
<td>No visible residual disease</td>
<td>35.2 mo</td>
<td>37.6 mo</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>Overall survival</td>
<td>49.7 mo</td>
<td>65.6 mo</td>
<td>127</td>
<td>101</td>
</tr>
<tr>
<td>Gross residual disease</td>
<td>39.1 mo</td>
<td>52.6 mo</td>
<td>95</td>
<td>77</td>
</tr>
<tr>
<td>No visible residual disease</td>
<td>78.2 mo</td>
<td>NA§</td>
<td>32</td>
<td>24</td>
</tr>
</tbody>
</table>

* Events were a recurrence of disease or death without documented recurrence in the analysis of progression-free survival and death regardless of cause in the analysis of overall survival.

† The relative risk is the risk of recurrence or death in the intraperitoneal-therapy group as compared with that in the intravenous-therapy group. The primary estimate for the entire study group included the covariates of residual-disease status and the second-look surgery option.

‡ The P value was calculated by a test for the homogeneity of relative risk between the two categories of residual-disease status.

§ NA denotes not applicable because the medians for survival had not yet been reached.

Armstrong NEJM 2006
Patients with microscopic residual disease derive a survival benefit from IV/IP chemotherapy.
Adding a Biologic Agent
Bevacizumab (Avastin)

• Monoclonal antibody to VEGF-A that inhibits angiogenesis
**GOG 218**

- **Stage III (optimal/suboptimal)**
  - Carboplatin
  - Paclitaxel
  - Placebo

- **Stage IV**
  - Carboplatin
  - Paclitaxel
  - Bevacizumab*
  - Placebo
  - Carboplatin
  - Paclitaxel
  - Bevacizumab*
  - Bevacizumab*

*Bevacizumab 15 mg/kg every 21 days

Burger NEJM 2011
**ICON 7**

Stage I – IIA G3 or CC  
**Stage IIB/C, III, IV**

- Carboplatin  
- Paclitaxel

Carboplatin  
Paclitaxel

Carboplatin  
Paclitaxel  
Bevacizumab*

Bevacizumab*  
X 12 months

*Bevacizumab 7.5 mg/kg every 21 days

Perrin NEJM 2011
• PFS improved <4 months with Bev throughout
  – 10.3 vs. 11.2 vs. 14.1 months
• No difference in OS

Burger NEJM 2011
ICON7

- PFS: 22.4 months versus 24.1 months
- OS: no difference

Perrin NEJM 2011
Dose-Dense Administration
Dose-Dense Taxol

- Preclinical studies suggest that duration of exposure is an important determinant of the cytotoxic activity of paclitaxel

Katsumata *Lancet* 2009
JGOG 3016: Dose Dense Taxol

Stage II – IV Epithelial Ovarian Cancer

- Taxol 180 mg/m² d1
  Carboplatin AUC 6 d1
  q 21 days x 6 cycles

- Taxol 80 mg/m² d1, 8, 15
  Carboplatin AUC 6 d1
  q 21 days x 6 cycles

Katsumata *Lancet* 2013
JGOG 3016: Dose Dense Taxol Survival

PFS
17.5 months
28.2 months

OS
62.2 months
100.5 months
JGOG: Dose Dense Taxol Subgroup Analysis

![Diagram showing progression-free survival according to baseline characteristics](Katsumata_Lancet_2009)

*Figure 3: Progression-free survival according to baseline characteristics*

Katsumata *Lancet* 2009
Overall Survival

- Improved survival with dose dense administration (and in Japan?)
Dose Dense Taxol
GOG-0262

Suboptimal, Stage III or IV Epithelial Ovarian Cancer

- Taxol 175 mg/m² d1
  Carboplatin AUC 6 d1
  q 21 days x 6 cycles
  +/- Bevacizumab

- Taxol 80 mg/m² d1, 8, 15
  Carboplatin AUC 6 d1
  q 21 days x 6 cycles
  +/- Bevacizumab

Dose Dense Taxol  
GOG-0262

- 84% of patients received bevacizumab
  - **BEVACIZUMAB (84%)**
    - No difference in PFS – 14.7 months (q 3 weeks) vs. 14.9 months (DD)
    - HR 0.99, 95% CI 0.83 to 1.20
  - No Bevacizumab (16%)
    - DD treatment led to better PFS – 10.3 mo (q 3 wks) vs. 14.2 mo (DD)
    - HR 0.62, 95% CI 0.40 to 0.95

- **Conclusion:** DD taxol did not prolong PFS. Bevacizumab may reduce benefit from dose-dense administration

Dose Dense Taxol and Carbo
MITO-7

Stage IC – IV
Epithelial Ovarian Cancer

- Taxol 175 mg/m² d1
  Carboplatin AUC 6 d1
  q 21 days x 6 cycles
- Taxol 60 mg/m² d1, 8, 15
  Carboplatin AUC 2 d1, 8, 15
  q 21 days x 6 cycles

Pignata Lancet 2014
Dose Dense Taxol and Carbo
MITO-7

PFS
17.3 months
18.3 months

24 month probability of survival
78.9%
77.3%

Pignata Lancet 2014
Conclusions: Dose Dense Chemo

- JGOG 3016
  - Dose dense taxol improved PFS and OS
  - Toxicity Worse
  - Most appropriate for suboptimal, non-mucinous, non-clear cell

- GOG 262
  - Confirms benefit of dose-dense taxol, but only if no bevacizumab

- MITO-7
  - Dose dense taxol/carbo - No difference in PFS
    - Lower dose of paclitaxel
    - Weekly carboplatin may antagonize weekly taxol?
    - Difference in responses between Japanese and European populations?
  - Toxicity Better
Substituting a Different Agent
Alternatives to Taxol

- Docetaxel + Carboplatin
  - Alternative taxane, less neuropathy, more myelosuppression
  - SCOTROOC Trial

- Doxil + Carboplatin
  - Pegylated (polyethylene glycol coated) liposome-encapsulated from of doxorubicin
  - Less cardiotoxic, more palmar plantar erythrodysesthesia (PPE)
  - MITO-2 Trial
Conclusions

• What is the best adjuvant chemotherapy for newly diagnosed advanced epithelial ovarian cancer?

<table>
<thead>
<tr>
<th>Residual Size</th>
<th>Chemotherapy Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal, microscopic residual</td>
<td>IV chemotherapy</td>
</tr>
<tr>
<td>Optimal, &lt; 1 cm residual</td>
<td>IV/IP chemotherapy</td>
</tr>
<tr>
<td>Dose Dense Taxol</td>
<td></td>
</tr>
<tr>
<td>Suboptimal, &gt; 1 cm residual</td>
<td>Dose Dense Taxol</td>
</tr>
</tbody>
</table>
Now to really confuse you…

GOG 252
Presented at SGO 2016
GOG 252

• JGOG 3016 (DD taxol) showed improved survival, but this was not replicated in the US

• GOG 172 (IP chemo) showed improved OS, but was toxic.
  – Can IP carboplatin be substituted for IP cisplatin?
  – Can the IP cisplatin dose be reduced?

• GOG 218 (bevacizumab) showed improved PFS. Should we use it?
GOG 252 Schema

**JGOG 3016**
Taxol 80 mg/m² d1, 8, 15
Carboplatin AUC 6 d1
q 21 days x 6 cycles

**GOG 172**
IV Taxol 135 mg/m² day 1
IP Cisplatin 100 mg/m² day 2
IP Taxol 60 mg/m² day 8

**Arm 1 (Dose Dense)**
Taxol 80 mg/m² d1, 8, 15
Carboplatin AUC 6 d1
Bevacizumab C2-22

**Arm 2 (IP Carboplatin)**
Taxol 80 mg/m² d1, 8, 15
Carboplatin AUC 6 IP d1
Bevacizumab C2-22

**Arm 3 (IP Cis Lite)**
IV Taxol 135 mg/m² d1 (3h)
IP Cisplatin 75 mg/m² d1
IP Taxol 60 mg/m² d8
Bevacizumab C2-22
Progression Free Survival Optimal Stage II-III

Progression-Free Survival by Treatment Group
Stage II or III Optimally Debulked

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Crb(IV)+T+Bev</td>
<td>303</td>
<td>461</td>
<td>26.8</td>
</tr>
<tr>
<td>2: Crb(IP)+T+Bev</td>
<td>300</td>
<td>464</td>
<td>28.7</td>
</tr>
<tr>
<td>3: Cis(IP)+T+Bev</td>
<td>307</td>
<td>456</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Proportion Surviving Progression-Free

Months on Study

1  461  387  244  169  111  37  0
2  464  391  262  177  125  39  0
3  456  372  255  168  120  34  0
Conclusions

• Don’t use bevacizumab in the upfront setting
  – GOG 262 and GOG 252 show that interactions may be compromising efficacy

• Are dose dense and IP chemo dead?
Drug Approvals & Emerging Targets
Drug Approvals in Ovarian Cancer

- **2006**
  - Gemzar

- **2014**
  - Bevacizumab – combined with chemotherapy in platinum resistant ovarian cancer
  - Olaparib – after 3rd line chemotherapy in BRCA1/2 positive patients
Immune Checkpoint Inhibition
Immunotherapy: Changing the tail of the curve

Ribas, Clin Can Res 2012
Phase II Clinical Trial at Cedars

**Screening Consent**

- Recurrent ovarian cancer within 6 months of treatment
- Measurable disease on CT scan
- CT-guided biopsy for tissue
- Blood draws

- Gemcitabine 750 mg/m² IV d1 and d8 q 21 days x 6 cycles
- Cisplatin 30 mg/m² IV d1 and d8 q 21 days x 6 cycles
- Pembrolizumab 200 mg IV d1 q 21 days starting cycle 3

→ Continue q 21 days x 1 year

**Assessments:** Blood draws each cycle, CT scan q 6 weeks during chemotherapy, q 9 weeks x 1 year

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Questions?