Gynecologic Cancer Treatment –
The Latest and Greatest

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Overview

- Ovarian cancer
  - Awareness – symptoms?
  - Risk factors – genetics vs. environment?
  - Screening – blood test or ultrasound?
  - Treatment / prevention – surgery and chemotherapy
  - Personalized novel therapy – are we there yet?
- Endometrial cancer
  - Robotic surgery – man vs. machine?
  - Advanced surgery – cost analysis
  - Lymph node dissection controversy

Ovarian Cancer – clinical presentation
Symptoms of “silent killer”

72% of women had recurring symptoms - median of 2:
- Back pain (45%)
- Fatigue (34%)
- Bloating (27%)
- Constipation (24%)
- Urinary symptoms (16%)

Early stage (high risk) patients
Over 70% had one or more symptoms present 1-3 months before diagnosis:
- Abdomino-pelvic pain (38%)
- Fullness / girth (27%)
- Abnormal bleeding (16%)

Goff et al, JAMA 2004
Chan et al, SGO 2009
**Screening on ovarian cancer mortality: Prostate, Lung, Colorectal and Ovarian (PLCO) Trial**

- Total 388 cancers
- 212 screened (5.7 / 10,000 person years)
- 176 unscreened (4.7 / 10,000 person years)

No reduction in ovarian cancer mortality. False-positive screening test result associated with complications

Buys JAMA 2011

**UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)**

- MMS group - 42 ovarian & tubal cancers
- 8 borderline & 34 invasive (47% stage I or II)

Mortality data will be collected through 2014

Menon U et al Lancet oncol 2009

**Marker for evaluating ovarian mass - OVA1**

- An immunoassay 5 biomarkers –
  - (CA 125, transthyretin, apolipoprotein A1, β2microglobulin, & transferrin)
  - Commercial distribution by the FDA Sept 2009
- high probability of malignancy is defined as:
  - ≥5.0 in premenopausal women
  - ≥4.4 in postmenopausal women

- Of 516 with adnexal mass, 151 cancers,
  - sensitivity 92.5%, specificity 42.8%,
  - positive predictive value 42.3% negative predictive value 92.7%

Ueland et al Gynecol Oncol 2010;116:S23

- OVA1 improved the clinician's pre-surgical assessment
- Help decide on referral to a gynecologic oncologist
- Limitations - assay interference with rheumatoid factor of at least 250 IU/mL or high triglyceride
- OVA1 test not to replace clinical decision making
- Not reassurance as a negative test and negate referral
- Not approved for cancer screening in general patients

Ueland et al Gynecol Oncol 2010;116:S23
Gynecologic Cancer Treatment

Marker for evaluating ovarian mass - HE 4

• Human epididymis protein 4 (HE4)
  – protein expressed in ovarian cancer tissue
  – HE4 testing increases the sensitivity for detection of malignant pelvic masses
  – HE4 is not elevated in women with endometriosis in contrast with CA 125
  – FDA approval in 2008 for monitoring ovarian cancer for disease progression or recurrence
  – use for differentiating benign from malignant adnexal masses is still investigational

Moore et al Gynecol Oncol 2009
Nolen Gyn Onc 2010
Anastasi et al Tumour Biol 2010
Huhtinen Br J Ca 2009

Gynecologic Cancer Treatment

Ovarian cancer

• 1 out of 70 U.S. women
• 25,000 cases annually
• 14,000 deaths annually
• 4th in cancer related deaths among women
• Mean age at diagnosis 59 years

Gynecologic Cancer Treatment

Female Reproductive Tract

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Breast</td>
<td>192,200</td>
<td>40,200</td>
</tr>
<tr>
<td>Colorectal</td>
<td>68,100</td>
<td>29,000</td>
</tr>
<tr>
<td>Lung/Bronchus</td>
<td>78,800</td>
<td>67,300</td>
</tr>
<tr>
<td>Endometrium</td>
<td>38,300</td>
<td>6,800</td>
</tr>
<tr>
<td>Ovary</td>
<td>23,400</td>
<td>13,900</td>
</tr>
<tr>
<td>Cervix</td>
<td>13,900</td>
<td>4,400</td>
</tr>
<tr>
<td>Vulva</td>
<td>3,600</td>
<td>800</td>
</tr>
</tbody>
</table>

American Cancer Society

Gynecologic Cancer Treatment

Risk factors

• Family history:
  - One 1° relative - 3.6 times risk, or 5% lifetime risk.
  - 5-10% of all ovarian cancers associated with known gene mutations.
  - Three familial ovarian cancer syndromes:
    - site-specific ovarian cancer,
    - breast/ovarian cancer syndrome
    - Hereditary non-polyposis colorectal cancer syndrome.
**BRCA1/2**

- Associated with site specific and breast/ovarian cancer syndromes.
- BRCA1: 25-40% lifetime risk of ov ca, 80% lifetime risk of Breast Ca
- BRCA2: 10% lifetime risk of ov ca

- Early age-onset, 10yrs younger than relative, mean age 40’s

**Reproductive factors**

- Increased risk -
  - Nulliparity
  - Infertility
- Decreases risk -
  - Oral contraceptives protective - 50% decrease with 5 or more years of use.
  - Multiparity
  - Lactation

**Primary Therapy – ovarian cancer**

- Goals of Surgery
  - Diagnosis
  - Staging (early stage disease)
  - Cytoreduction (advanced disease)
- Adjuvant Chemotherapy
  - Except stage IA or IB and grade I or II or clear cell histology

**Surgery with maximum cytoreduction effort**

**Platinum + Taxane Chemotherapy**

*(Carboplatin + Paclitaxel)*
**Gynecologic Cancer Treatment**

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

*Median Survival vs % Cytoreduction*


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**RANDOMISED TRIAL COMPARING PRIMARY DEBULKING SURGERY (PDS) WITH NEOADJUVANT CHEMOTHERAPY (NACT) FOLLOWED BY INTERVAL DEBULKING (IDS) IN STAGE IIIC-IV OVARIAN, FALLOPIAN TUBE AND PERITONEAL CANCER.**

**Gynecologic Cancer Treatment**

- **Randomization**
  - Ovarian, tubal or peritoneal cancer
  - FIGO stage IIIc-IV (n = 718)

- **Primary Debulking Surgery**
  - Neoadjuvant chemotherapy
  - 3 x Platinum based CT
  - Interval debulking (not obligatory)
  - ≥ 3 x Platinum based CT

- **Neoadjuvant chemotherapy**
  - 3 x Platinum based CT
  - Interval debulking if no PD
  - ≥ 3 x Platinum based CT

**NACT + IDS versus PDS: ITT**

- Overall survival
- HR for IDS: 0.98 (0.85, 1.14)

**Number of patients at risk:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptfront debulking</td>
<td>259</td>
<td>188</td>
<td>68</td>
<td>16</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>357</td>
<td>191</td>
<td>56</td>
<td>11</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Neoadjuvant Chemotherapy vs. Initial Surgical Debulking – EORTC Study

- 700 patients
- Stage IIIC - IV
- TFI <= 12 mos
- Treat until progression or toxicity

Results –
- Median PFS 12 mos, OS 30 months
- Median fu 4.8 years
- Neoadjuvant chemo associated with decrease postoperative deaths, fever, hemorrhage, clots

Limitations:
- Poor PFS and OS than other clinical trials
- 30% did not have ovaries removed

Vergote et al, EORTC, IGCS 2008

Current recommendations
- Poor candidates for aggressive initial debulking
- Extensive disease – liver or pulmonary disease

Schema of JGOG 3016

Ovarian Epithelial, Primary Peritoneal, or Fallopian Tube cancer
FIGO Stage II-IV

Randomization
- Stratification:
  - Residual disease: <1cm, >1cm
  - FIGO Stage: II vs. III vs. IV
  - Histology: clear cell/mucinous vs. serous/others

Conventional TC (c-TC)
- Paclitaxel 180mg/m², day 1
- Carboplatin AUC 6.0, day 1
- every 21 days for 6-9 cycles

Dose-dense weekly TC (dd-TC)
- Paclitaxel 80mg/m², days 1,8,15
- Carboplatin AUC 6.0, day 1
- every 21 days for 6-9 cycles

N. Katsumata, Lancet 2009

Progression-free survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Event</th>
<th>Median PFS</th>
<th>P value</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-TC</td>
<td>319</td>
<td>200</td>
<td>17.2 mos.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dd-TC</td>
<td>312</td>
<td>160</td>
<td>28.0 mos.</td>
<td>0.0015</td>
<td>0.74</td>
<td>0.581-0.679</td>
</tr>
</tbody>
</table>
**Conclusions**

- Dose-dense paclitaxel with 3 weekly carboplatin should be a new standard chemotherapy for ovarian cancer

- Limitations –
  Pharmacogenetic and tumor difference – asians vs. non-asians toxicity and efficacy
  less convenient
  more toxic
  global implications
**Gynecologic Cancer Treatment**

**Mechanism of action of anti-angiogenic agents**

**Early effects**
- Regression
- Reduces tumor mass

**Continued effects**
- Normalisation
- Enhances activity of concomitant therapies

**Inhibition**
- Prevents growth of micrometastases

**Efficacy of continued therapy**

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**GOG-0218 study schema**

- **Carboplatin AUC 6**
- **Paclitaxel 175 mg/m²**
- **Placebo**

**Arm I**
- CP (n=625)

**Arm II**
- CP + BEV (n=625)

**Arm III**
- CP + BEV + BEV maintenance (n=623)

<table>
<thead>
<tr>
<th>Patients with event, n (%):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm I: 423 (67.7)</td>
</tr>
<tr>
<td>Arm II: 466 (66.9)</td>
</tr>
<tr>
<td>Arm III: 577 (57.4)</td>
</tr>
</tbody>
</table>

*Median PFS, months:*
- Arm I: 10.3
- Arm II: 11.2
- Arm III: 14.1

*Stratified analysis HR (95% CI):*
- Arm I vs Arm II: 0.080* (0.0001)*
- Arm I vs Arm III: 0.717

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**Gynecologic Cancer Treatment**

**Bevacizumab (rhuMAB VEGF)**

- Recombinant humanized monoclonal IgG1 antibody
- Recognizes all isoforms of VEGF-A
- Estimated half-life is approximately 20 days (range, 11-50 days)
- Randomized trials establish efficacy in colon, breast, lung, and renal cancer

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**Gynecologic Cancer Treatment**

**GOG-0218: Investigator-Assessed PFS**

**Arm I**
- CP (Arm I)

**Arm II**
- CP + BEV (Arm II)

**Arm III**
- CP + BEV + BEV maintenance (Arm III)

**Proportion surviving progression free**

- Median PFS, months:
  - Arm I: 10.3
  - Arm II: 11.2
  - Arm III: 14.1

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Sensitivity analysis (investigator-assessed PFS censoring for CA-125)

<table>
<thead>
<tr>
<th>Arm</th>
<th>CP (n=625)</th>
<th>CP + BEV (n=625)</th>
<th>CP + BEV → BEV (n=623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event, n (%)</td>
<td>339 (54)</td>
<td>324 (52)</td>
<td>255 (41)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>12.0</td>
<td>12.6</td>
<td>18.0</td>
</tr>
<tr>
<td>HR (stratified)</td>
<td>0.599 (95% CI: 0.772–1.044)</td>
<td>0.645 (95% CI: 0.551–0.756)</td>
<td>0.082* (stratified)</td>
</tr>
<tr>
<td>One-sided log-rank p-value</td>
<td>&lt;0.0001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One-sided log-rank p-value 0.082

Arm I CP (n=625)
Arm II CP + BEV (n=625)
Arm III CP + BEV → BEV maintenance (n=623)

Patients with events, n (%) 156 (25.0) 150 (24.0) 138 (22.2)
Median OS, months 39.3 38.7 39.7
Stratified analysis HR (95% CI) 1.036 (0.827–1.297) 0.915 (0.727–1.152) 0.361
One-sided p-value 0.361 0.252

Proportion surviving progression free

Months since randomisation

GOG-0218: Conclusions

- GOG-0218 met the primary objective in the front-line treatment of advanced ovarian (epithelial OV, PP and FT) cancer
  - PFS with CP + BEV → BEV maintenance statistically superior to CP alone
- Interpretation of survival analysis limited
- BEV - first molecular targeted and first anti-angiogenic agent to demonstrate benefit in this population
  - CP + BEV → BEV maintenance can be considered as a standard option
Recurrent ovarian cancer – OCEAN trial

Carboplatin AUC 6
Gemcitabine
Placebo

Arm I

Recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer
(platinum sensitive) n=484

Arm II

Bevacizumab 15 mg/kg
Until disease progression

Results – Longer PFS compared to chemotherapy alone. No new safety findings or adverse events. Third positive phase III trial

Roche press release, Feb 2011

OCEANS: Primary analysis of PFS

Events, n (%) 187 (77) 151 (62)
Median PFS, months (95% CI) 12.4 (8.3–9.7)
Stratified analysis HR (95% CI) Log-rank p-value 0.484 (0.388–0.605) <0.0001

Small Molecules

Molecular therapy
– block receptor
– inhibit tyrosine kinase
– conjugate ligand
– anti-sense ligand

Signal transduction
Signal transduction
Cell death
Protein synthesis

MAbs
TKIs
Conjugates
Antisense
Predicting Sensitivity: An Integrated Approach

- Array CGH
- mRNA Expression
- Mutations

Gynecologic oncologist care

- Kaplan-Meier 5 yr disease-specific survival - gynecologic oncologist care

Northern California California Cancer Registry
1994 and 1996
1,491 women stage IC-IV ovarian cancer

Gynecologic oncologist 39% (p<0.001)
No gynecologic oncologist 30%

Chan et al Obgyn 2007

The Role of the physicians in Early Detection

- Consider referral or consultation - Gynecologic Oncologist
  - Postmenopausal and one of the following:
    - elevated CA125, ascites, nodular or fixed mass, metastasis, or family history of breast or ovarian cancer
  - Premenopausal and one of the following:
    - elevated CA125 (>200), ascites, metastasis, or family history of breast or ovarian cancer

ACOG Committee Opinion #280, December 2002

Early-stage:
- Gynecologic oncologist 66%
- No gynecologic oncologist 61%
(p=0.157)

Late-stage:
- Gynecologic oncologist 31%
- No gynecologic oncologist 23%
(p<0.001)

Chan et al Obgyn 2007
• Ovarian cancer
  – Awareness – symptoms
  – Risk factors – genetics and environment
  – Screening – blood test or ultrasound for high risk pts
  – Treatment / prevention – surgery and chemotherapy
  – Personalized novel therapy is here

• Endometrial cancer
  – What is the role of laparoscopy or robotic assisted-laparoscopy in endometrial cancer surgery based on randomized clinical trials?
Robotic Surgical System

- Unparalleled Precision Dexterity and Control
  - High resolution 3D visualization
  - Fully articulating EndoWrist® instruments
  - Intuitive movement, motion scaling, tremor reduction

Robotic surgery – public perception

Robotic

- Advantages: 3-D high def optics, greater ROM with instruments, less change out instruments, ergonomics
- 7 Series for endo ca- N= 766 pts
  - Veljovich (2008)- 118 ROBOT vs 131 open
    - Med OR 283 vs 139 min, less EBL, shorter stay, similar nodes
  - Lowe (2009)- 405 ROBOT
    - Mean OR 170 min, EBL 87 cc, LOS 1.8 d, mean nodes = 15, conversion 6.7%
Robotic surgery vs. laparoscopic surgery

Safe and feasible. Better than laparoscopy
Advantages - Decreases physician tremor, fatigue
Disadvantages - Increase OR time, cost, bulky, no tactile feedback
Transition from open to laparoscopic surgery, Market pressures

Evidence based practice vs. state of art (novel technologies)

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**Research Objective**

- To determine the actual costs, charges, and reimbursements associated with robotic versus laparoscopic surgery for endometrial cancer

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**Identifying the Cases**

- Tumor Registry
- Chart Review
- Hospital Billing Data

Data interval: 2008-2010
Cases by a single surgeon
Cohorts matched by age, histology, and cancer stage

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**Venkat, Chan et al, Gyn Onc 2011**
### Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>L/S</th>
<th>Robotic</th>
<th>P- Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age</td>
<td>60.2</td>
<td>58.2</td>
<td>0.53</td>
</tr>
<tr>
<td>BMI</td>
<td>32.4</td>
<td>33.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Time in OR</td>
<td>3h57m</td>
<td>5h32m</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Actual Procedure Length</td>
<td>3h4m</td>
<td>4h25m</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EBL (mL)</td>
<td>316</td>
<td>220</td>
<td>0.1232</td>
</tr>
</tbody>
</table>

### Hospital Costs and Charges

<table>
<thead>
<tr>
<th></th>
<th>Robotic (n=27)</th>
<th>Laparoscopic (n=27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Cost</td>
<td>$15,375</td>
<td>$12,511</td>
<td>0.011</td>
</tr>
<tr>
<td>Hospital Charges</td>
<td>$64,266</td>
<td>$55,130</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*Direct Cost – includes variable and fixed components.

### Cost Breakdown

<table>
<thead>
<tr>
<th></th>
<th>Robot</th>
<th>L/S</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>$32,800 (51%)</td>
<td>$24,887 (45%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anesthesia Supply</td>
<td>$7981</td>
<td>$5546</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Room and Board</td>
<td>$9,570 (15%)</td>
<td>$12,423 (23%)</td>
<td>0.175</td>
</tr>
<tr>
<td>PACU</td>
<td>$2,235 (3%)</td>
<td>$2,024 (4%)</td>
<td>0.389</td>
</tr>
</tbody>
</table>

### Hospital Reimbursement

<table>
<thead>
<tr>
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<th>Robotic (n=27)</th>
<th>Laparoscopic (n=27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Reimbursement</td>
<td>$13,003</td>
<td>$10,245</td>
<td>0.288</td>
</tr>
</tbody>
</table>
Professional Charges and Reimbursements – Gyn Oncologists

- Robotic (n=27) L/S (n=27)
  - Charge: $6,824
  - Reimbursed: $6,327
  - $2,152
  - $2,032

Type of Surgery

Gynecologic Cancer Treatment

Robotic surgery cost analysis

- Our data showed that the direct costs and charges associated with robotic surgery were higher compared to laparoscopic surgery. However, actual reimbursements to the hospital, surgeon, and anesthesiologist were not significantly different between the two surgical approaches.

UCSF Cancer Center

Gynecologic Cancer Treatment

CONSORT Trial

- Trial: CONSORT 2008
  - Compared: Hyst +/- PLND N= 514
  - Dz Distrib: 38% IB 36% IC 13% IIIC vs 3% with LND
  - Adjuvant Rx: 17% XRT LND vs 25% no LND
  - PFS/OS: 5 yr PFS: 80% LND vs 83% no LND
  - OS: 81% LND vs 82 no LND

Limitations - usefulness of pelvic LND for guiding treatment after surgery since patients in the second phase of the trial were treated without taking into account lymph node status. In addition, since all patients underwent paraaortic node palpation and sampling, it does not address the benefit of paraaortic LND.

Benedetti. J NCI 2008;100:1707-1716

ASTEC Study

- Trial: ASTEC 2009
  - Compared: Hyst +/- PLND, 2nd randomization -> obs vs EBXRT N= 1408
  - Dz Distrib: Low risk (45%) + Adv ca (17%) -> choice, Int risk (37%) obs vs EBXRT+53-56% XRT
  - Adjuvant Rx: 12% IA 42% IB 24% IC
  - PFS/OS: 5 yr 73% LND vs 79% no LND 80% LND vs 81% no LND

No benefit (PFS/OS) for LND

Limitations - usefulness of pelvic LND for guiding treatment after surgery since patients in the second phase of the trial were treated without taking into account lymph node status. In addition, since all patients underwent paraaortic node palpation and sampling, it does not address the benefit of paraaortic LND.

**Effect of Gynecologic Oncologist on Early Stage Vs Late Stage Endometrial Cancer**

Yes GynOnc= 91%
No GynOnc= 91%
Early Stage P=0.6

Yes GynOnc=72%
No GynOnc= 64%
Late Stage P=0.0001

Chan et al JCO 2010

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**Effect Of Gynecologic Oncologist on High Risk Cell types and Grade 3 Uterine Cancer**

Yes GynONC= 79%
No GynONC= 70%
P= 0.01

Yes GynONC= 79%
No GynONC= 68%
P= 0.03

Chan et al JCO 2010

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**Overview**

- **Endometrial cancer**
  - Robotic surgery – additional option
  - Robotic surgery – cost analysis
  - Complete lymphadenectomy
  - Appropriate referral to subspecialists associated with improved survival

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**Chronic stress promotes tumor growth and angiogenesis**

Mouse model of ovarian cancer
Tumors in stressed

Animals showed markedly increased vascularization and tumor growth via cAMP–PKA signaling pathway

Thaker, Sood Nat Med 2006