• Ovarian Cancer Presentation
• Making the Diagnosis
• Staging
• Timing of Surgery
• Etiology/Origins of Ovarian Cancer
• Screening and Prevention
• Treatment of
  ◦ Newly diagnosed ovarian cancer
  ◦ Recurrent ovarian cancer
• PARP inhibitors

Overview of presentation
Ovarian Cancer Presentation
• **Insidious presentation**
  - Vague abdominal pain/cramping
  - Bowel habit changes, such as intermittent diarrhea or constipation
  - Sense of abdominal fullness
  - Abdominal distension
  - Abdominal mass
  - Changes in weight – weight gain (ascites) or weight loss (diet changes, feeling unwell)
• Examination:
  ◦ Supraclavicular lymphadenopathy
  ◦ Pleural effusions
  ◦ Abdomen:
    • Ascites
    • Omental mass (cake)
    • Inguinal lymphadenopathy
    • Pelvic mass
  ◦ Peripheral Edema
Making the Diagnosis
• **Labs tests:**
  ◦ CBC (usually not anemic – can have mild anemia in keeping with anemia of chronic disease)
    • MCV is usually normal
    • Marked anemia or microcytosis should lead to consideration of GI malignancy
  ◦ Lytes/Cr/LFTs – typically normal
  ◦ Tumour Markers:
    • CA-125 the most commonly elevated marker
    • CA19-9 and CA15-3 can also be elevated, but not usually as high as the CA-125
• **Imaging:**
  - **CXR** – pleural effusion (solitary lung mets are rare)
  - **U/S** – ascites, peritoneal masses, pelvic masses
  - **CT** – preferred imaging modality
    - Best view of visceral organs, retroperitoneum, and peritoneal cavity
    - Facilitates planning for biopsy +/- surgery
• **Biopsies**
  - Always correct to consider a biopsy of disseminated disease
    - Omental masses
    - Palpable lymphadenopathy (supraclav, inguinal)
    - In some cases, visceral mets (liver)
  - Core biopsy always preferable to FNA
    - Allows better architectural definition of the disease
    - Helps with disease subtyping
      - More material for IHC (can be essential in some cases)
    - Requires image guidance
  - FNA – if this is the only possibility, ask for a cell block
    - May allow for IHC to be done
  - **Fluid cytology**
    - Peritoneal and Pleural fluid
      - Easy and safe to get
      - Cell block can also be requested for IHC
Timing of Surgery
• Suspected/Diagnosed Ovarian Cancer: requires review with a Gynecologic Oncologist!

• Usually suitable for surgery if:
  • Pelvic mass
  • Omental cake
  • All disease felt to be removable by a gynecologic oncologist

• Usually delay surgery if:
  • Diffuse peritoneal disease/disease under the diaphragms
  • Massive ascites
  • Large retroperitoneal LNs
  • Acute medical problem – MI/unstable angina, acture PE/DVT
This case had upfront surgery
These cases had neoadjuvant chemotherapy.
• **Two randomized phase III trials**
  ◦ Pts with stage III or IV ovarian cancer
  ◦ Otherwise fit for surgery (no PE/DVT, or serious commorbidity)

  ◦ Outcomes are the same whether surgery first or chemo first.
Ovarian, Tubal, or Peritoneal Cancer
FIGO Stage IIIC/IV (N = 670)

Primary End Point: OS
Secondary End Points: PFS, QOL, AEs

NACT = neoadjuvant chemotherapy; IDS = interval debulking surgery; PDS = primary debulking surgery; FIGO = International Federation of Gynaecology and Obstetrics; CT = chemotherapy; PD = progressive disease; QOL = quality of life; AEs = adverse events.
NACT + IDS Vs. PDS (cont.)

ITT Analysis

HR = hazard ratio.
Vergote et al, 2010.
Staging
Stage I

- IA unilateral
- IB bilateral
- IC any of:
  - cyst rupture
  - positive peritoneal cytology
  - surface involvement

Stage 1
Tumor limited to one or both ovaries. Tumor may be found on ovarian surface.
Stage II

- 2A involvement of fallopian tubes or uterus
- 2B extension to other pelvic structures (bladder, rectum)
- 2C like 2B but with positive peritoneal washings

Stage 2
Tumor invades one or both ovaries, with extension into the pelvic region, but without spread to the abdomen.
Stage III

- 3A microscopic involvement of the peritoneum or the omentum
- 3B abdominoperitoneal implants <2cm
- 3C abdominoperitoneal implants >2cm
Disease within visceral organs or above the diaphragm (if a plural effusion must be confirmed cytologically to be considered stage 4).
Etiology and Classification
• Complexity of Ovarian Cancer long overlooked

• Used to believe that different histology = morphological variants

• What we have learned:
  ◦ Histotype broadly defines different diseases
    • High grade serous
    • Clear Cell
    • Mucinous
    • Endometrioid
    • Low grade serous
    • Other very rare types...
<table>
<thead>
<tr>
<th></th>
<th>HGSC</th>
<th>Clear Cell</th>
<th>Endometrioid</th>
<th>Mucinous</th>
<th>LGSC</th>
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</thead>
<tbody>
<tr>
<td>Portion of cases</td>
<td>70</td>
<td>12</td>
<td>11</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Genetic Risk Factors</td>
<td>BRCA1/2</td>
<td>HNPCC</td>
<td>HNPCC</td>
<td>none known</td>
<td>none known</td>
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<tr>
<td>Precursor Lesions/Cell of Origin</td>
<td><strong>STIC, p53 signatures</strong></td>
<td><strong>Endometriosis</strong></td>
<td><strong>Endometriosis</strong></td>
<td>not known</td>
<td>SBT</td>
</tr>
<tr>
<td>Common stage at presentation</td>
<td>advanced</td>
<td>early</td>
<td>early</td>
<td>early</td>
<td>advanced</td>
</tr>
<tr>
<td>Pattern of Spread</td>
<td>trans-coelomic</td>
<td>trans-coelomic/hematogenous</td>
<td>???</td>
<td>pseudomyxoma pertonei/hematogenous</td>
<td>transcoelomic</td>
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<tr>
<td>Response to Platinum-based therapy</td>
<td>chemo-sensitive</td>
<td>chemo-resistant, radiosensitive</td>
<td>chemo-sensitive</td>
<td>chemo-resistant</td>
<td>chemo-resistant</td>
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<tr>
<td>Molecular aberrations</td>
<td>p53, BRCA1, BRCA2, HR defects</td>
<td>PI3K, ARID1A, MSI</td>
<td>PTEN, bcatenin, ARID1A, MSI</td>
<td>KRAS, HER2</td>
<td>BRAF, KRAS, NRAS</td>
</tr>
</tbody>
</table>
Ovarian Cancer Screening and Prevention
No evidence to support screening for ovarian cancer in any population (low or high risk):

- U/S (TA and TV)
- CA125, HE4 (human epididymis protein 4)
- Ovarian cancer symptom index

- NOT specific
  - Leads to a high number of unnecessary surgeries/procedures
- Does not detect “early disease”
- Not proven to impact on survival

- Should not be done
  - False reassurance
  - Risk of false positive

- All major cancer groups discourage screening, even in high risk women
• **BRCA mutation carriers (high risk)**
  ◦ Bilateral salpingo-oopherectomy
    • Possible option: remove tubes early and consider oopherectomy closer to age of menopause

• **Non-BRCA (low risk)**
  ◦ Opportunistic salpingectomy
    • tubal ligation, C-section, hysterectomy etc.
      ◦ Society of Obstetricians and Gynecologists of Canada
      ◦ American Congress of Obstetricians and Gynecologists (January 2015 – Committee Opinion)
  ◦ No level 1 evidence
    • Population outcomes/complications - being tracked
First Line Treatment of Advanced Ovarian Cancer

“Neoadjuvant” or Pre-Operative
OR
“Adjuvant” or Post-Operative
First Line Treatment: Pre-Operative

- Carboplatin and Paclitaxel
  - 2 different schedule options:
    1. Q 3 weekly
    2. “dose dense”
      - Carboplatin q 3 weekly
      - Paclitaxel weekly

- Phase III date demonstrates that Dose Dense treatment is associated with a improvement in OS at 3 and 5 years
First Line Treatment: Pre-Operative
JGOG: Dose-Dense Wkly Paclitaxel

- EOC or PP
- Stage II–IV
- No prior therapy
- Stratified: Residual disease, stage, and histology
- Primary end point: PFS
- Secondary end point: OS

<table>
<thead>
<tr>
<th></th>
<th>Pac 180 mg/m²</th>
<th>x 6–9</th>
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<tr>
<td>I</td>
<td>Carb AUC = 6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Carb AUC = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Pac 80 mg/m²/wk x 3</td>
</tr>
</tbody>
</table>

- Dose-dense paclitaxel associated with greater hematologic toxicity, and fewer patients completed all protocol therapy
- Improved PFS with dose-dense wkly paclitaxel

Accrual: 637 patients (ITT)

EOC = epithelial ovarian cancer; PP = primary peritoneal cancer; OS = overall survival; JGOG = Japanese Gynecologic Oncology Group; ITT = intent-to-treat; AUC = area under curve. Isonishi et al, 2008.
JGOG: Dose-Dense Wkly Paclitaxel

Dose Dense Chemotherapy - JGOG 3016 Trial

- Updated 2013 – median 76 mo follow up

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Med OS</th>
<th>5-yr survival</th>
<th>P value</th>
<th>HR</th>
<th>95%CI</th>
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<tbody>
<tr>
<td>dd-TC</td>
<td>312</td>
<td>100.5</td>
<td>58.7%</td>
<td>0.039</td>
<td>0.79</td>
<td>0.63-0.99</td>
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<tr>
<td>c-TC</td>
<td>319</td>
<td>62.2</td>
<td>51.1%</td>
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</table>

*Katsumata, Lancet 2013*
• In most instances we chose dose-dense chemotherapy
  ◦ Exclusions:
    • Clear cell and mucinous tumours
      ◦ No advantage (highly resistant)
    • Cannot commit to weekly treatment
      ◦ Social factors
      ◦ Distance to travel
    • Medical reasons
      ◦ High risk of neuropathy
      ◦ Cannot tolerate dexamethasone
  ◦ Alternative:
    • Historical standard:
      ◦ 3 weekly therapy with carboplatin and paclitaxel
      ◦ or another platinum based doublet
Intraperitoneal Chemotherapy
- 3 trials
- IP therapy
- **stage 3, optimally debulked (< 1cm residual)**
- improvement in OS.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median PFS (mos)</th>
<th>HR</th>
<th>Median OS (mos)</th>
<th>HR</th>
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<tr>
<td></td>
<td>IV</td>
<td>IP</td>
<td>IV</td>
<td>IP</td>
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<tr>
<td>GOG 104</td>
<td>—</td>
<td>—</td>
<td>41</td>
<td>49</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.76 (p = .02)</td>
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<tr>
<td>GOG 114</td>
<td>22</td>
<td>28</td>
<td>52</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>0.78 (p = .01)</td>
<td></td>
<td>0.81 (p = .05)</td>
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</tr>
<tr>
<td>GOG 172</td>
<td>18.3</td>
<td>23.8</td>
<td>50</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>0.80 (p = .05)</td>
<td></td>
<td>0.75 (p = .03)</td>
<td></td>
</tr>
</tbody>
</table>

**Primary Therapy: IP**

GOG 172: Ovarian (Optimal III)

- EOC
- Optimal stage III
- No prior therapy
- Elective second-look

Accrual: 415 patients (evaluable)


**Arm 1**
- Pac 135 mg/m² (24 hrs) Day 1
- Cis 75 mg/m² Day 2

**Arm 2**
- Pac 135 mg/m² (24 hrs) IV Day 1
- Cis 100 mg/m² IP Day 2
- Pac 60 mg/m² IP Day 8

Carboplatin AUC 5-6 IV Day 1

Carboplatin AUC 5-6 IP Day 1
GOG-172 IP Chemotherapy

Survival
By Treatment Group

16 mo improvement in OS

Rx Group   Alive  Dead  Total
IV         93     117    210
IP         117    88     205

Proportion Surviving

Months on Study
Recurrent Ovarian Cancer
<table>
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<tr>
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<th>Response to Platinum</th>
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<tbody>
<tr>
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<td>Initial Response</td>
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<tr>
<td>Platinum-sensitive</td>
<td>Yes</td>
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<tr>
<td>Platinum-resistant</td>
<td>Yes</td>
</tr>
<tr>
<td>Platinum-refractory</td>
<td>No</td>
</tr>
</tbody>
</table>

*Defined as disease recurrence > 6 months after initial platinum-based therapy

Duration of Response to First Line Therapy

Effect of Platinum-Free Interval on Platinum Rechallenge

Recurrence After First-Line Chemotherapy

Platinum Refractory/Resistant

< 6 Mos

Non-Platinum Single Agent

Platinum Sensitive

> 6 Mos

Chemotherapy Doublet

The Traditional Treatment Paradigm

Ushijima, 2010.
• Consider the platinum-sensitive interval
  ◦ > 6 mo, sensitive
  ◦ < 6 mo, resistant
    • Assessed based on symptoms and imaging, and not on CA125 rise
      ◦ This definition was originally developed after the use of primary therapy and not in 2\textsuperscript{nd}, 3\textsuperscript{rd} recurrence, but most practitioners have expanded the definition beyond first line
• **Platinum sensitive:**
  ◦ Return to platinum
    • as single agent
    • as a doublet
      ◦ Carboplatin-paclitaxel
      ◦ Carboplatin-liposomal doxorubicin
      ◦ Carboplatin-gemcitabine
        • Choice is made by considering residual toxicity (neuropathy), comorbidities, convenience (travel)

• **Platinum resistant:**
  ◦ Consider sequential single agents
    • Carboplatin
    • Paclitaxel
    • Gemcitabine
    • Liposomal doxorubicin
    • Vinorelbine
    • Etoposide
Parp Inhibitors
PARP plays an important role in the repair of single-stranded DNA breaks
  - base excision repair pathway (BER) (high accuracy)

- Keep low-fidelity repair machinery in check
  - nonhomologous-end-joining DNA
  - Single strand annealing

- The other highly accurate DNA repair pathway is HR (double strand break repair)

- Many HGSC of the ovary have defects in the HR pathway
  - BRCA mutation
    - Germline = 25%
    - Somatic = 25%
• When is LOH either by germline or somatic mutation in BRCA1/2, cell survival dependent on BER

• PARP inhibition leads to loss of BER
  ◦ Mutation accumulation
  ◦ “mitotic catastrophe”
  ◦ Apoptosis
  ◦ Normal cells have preserved HR function and are not susceptible to the PARP inhibitor

• Synthetic Lethality
  ◦ whereby two conditions independently would not cause cell death, but in combination are lethal
Synthetic Lethality
• Used as single agents as do not combine well with chemotherapy
  ◦ Profound myelosuppression seen
  ◦ Can only be overcome by significant dose reductions of chemo and lower doses of the PARP inhibitor

• Oral drugs
• Well tolerated – fatigue, anorexia, nausea, anemia, thrombocytopenia, neutropenia, elevation of LFTs, rise in Cr
  ◦ No hair loss
  ◦ No neuropathy
  ◦ Most patients state that better than chemo in terms of side effects
Randomized Phase II of Maintenance PARPi in Plt Sensitive Recurrent Recurrent OvCa
• Many phase 3 trials are ongoing
• Some should be reporting in the next 12 - 24 months
• Several focus on BRCA mutation carries
• Others have enrolled all HGSCs and have tried to develop a companion predictive test
• **HGSC of the ovary**
  ◦ The presence of tumour infiltrating lymphocytes is associated with a better prognosis
  ◦ PD-L1 and PD-1 expression is seen on ovarian cancer cells and associated T-cells
  ◦ Checkpoint inhibition is being studied in ovarian cancer
Ovarian cancer is not ovarian...fallopian and endometrial origins explain most. No screening (should not be done). Surgery timing can be up front or delayed. IP chemotherapy has the best survival data so far. Altering drug schedules matters. Dose dense treatment appears to be better. Platinum Sensitive disease. Use platinum until no longer tolerated or responsive. Platinum resistant disease. Poor prognosis, use single agents. Potential future developments. Parp inhibitors. Immune therapy.