# Ovarian Cancer

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## Objectives

- Define symptoms and risk factors for ovarian cancer  
- Review the evaluation for an adnexal mass  
- Discuss the diagnosis and management of ovarian cancer

## Initial Presentation

- 50 y/o presents with pelvic pressure and PCP ordered CT scan revealing a 15cm pelvic mass with solid and cystic components  
- 43 y/o presents with pelvic pain and ultrasound shows 4cm complex adnexal mass  
- 65 y/o had MRI for back pain, found to have a 9cm cystic lesion in the right adnexa

## Differential diagnoses

<table>
<thead>
<tr>
<th>Benign</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional cyst</td>
<td></td>
</tr>
<tr>
<td>Endometriosis/Endometrioma</td>
<td></td>
</tr>
<tr>
<td>Benign neoplasm</td>
<td></td>
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<tr>
<td>Teratoma</td>
<td></td>
</tr>
<tr>
<td>Cystadenoma</td>
<td></td>
</tr>
<tr>
<td>Leiomyoma</td>
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</table>

<table>
<thead>
<tr>
<th>Pregnancy related conditions</th>
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<tbody>
<tr>
<td>Ectopic pregnancy</td>
<td></td>
</tr>
<tr>
<td>Theca-Lutein cysts</td>
<td></td>
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<tr>
<td>Embryological remnants</td>
<td></td>
</tr>
<tr>
<td>Paratubal cyst</td>
<td></td>
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<tr>
<td>Paraovarian cyst</td>
<td></td>
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<tr>
<td>Tubal processes</td>
<td></td>
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<tr>
<td>Tubo-ovarian abscess</td>
<td></td>
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<tr>
<td>Hydrosalpinx/Pyosalpinx</td>
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</tbody>
</table>
### Differential Diagnoses

<table>
<thead>
<tr>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Epithelial ovarian cancers</td>
</tr>
<tr>
<td>Germ cell tumors</td>
</tr>
<tr>
<td>Borderline ovarian tumors</td>
</tr>
<tr>
<td>Sex cord-stromal tumors</td>
</tr>
<tr>
<td>Fallopian tube cancers</td>
</tr>
<tr>
<td>Primary peritoneal cancer</td>
</tr>
<tr>
<td>Uterine cancer</td>
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</tbody>
</table>

### Differential diagnoses

<table>
<thead>
<tr>
<th>Non-gynecologic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal conditions</td>
</tr>
<tr>
<td>Diverticular disease</td>
</tr>
<tr>
<td>Appendiceal abscess/mucocele</td>
</tr>
<tr>
<td>Meckel’s diverticulum</td>
</tr>
<tr>
<td>Small bowel tumors</td>
</tr>
<tr>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Urinary tract conditions</td>
</tr>
<tr>
<td>Ureteral diverticulum</td>
</tr>
<tr>
<td>Bladder diverticulum</td>
</tr>
<tr>
<td>Pelvic kidney</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroperitoneal tumors</td>
</tr>
<tr>
<td>Retroperitoneal sarcomas</td>
</tr>
<tr>
<td>Desmoid tumors</td>
</tr>
<tr>
<td>Schwannomas</td>
</tr>
<tr>
<td>Metastatic disease to adnexa</td>
</tr>
<tr>
<td>Bowel</td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
</tbody>
</table>

### When to worry about cancer

- Symptoms
- Risk Factors
- Exam
- Labs
- Imaging

### Symptoms

- Asymptomatic
- Pelvic pain
- Weight loss, early satiety, bloating
- Vaginal bleeding, breast tenderness, precocious puberty
- Hirsutism, deepening of the voice
- Flushing, diarrhea, hyperthyroid symptoms
**Risk factors**

- Incessant ovulation
  - Aberrant repair process of the epithelium
  - Nulliparity/infertility
  - Early menarche/late menopause
- Inflammation
  - Endometriosis
- Genetic predisposition
  - BRCA 1 and 2
  - Hereditary NonPolyposis Colorectal Cancer (Lynch syndrome)

**Genetic predisposition**

- BRCA 1
  - 90% lifetime risk for breast cancer
  - 40% lifetime risk for ovarian cancer
- BRCA2
  - 20% lifetime risk for ovarian cancer
- HNPCC (Lynch Family II)
  - Endometrial, colon and ovarian cancers

**Risk-reducing surgery**

- Genetic predisposition
  - Risk reducing bilateral salpingo-oophorectomy
    - Recommended by age 35 or after completion of childbearing
    - Occult cancer in ~8%
    - Risk of primary peritoneal cancer ~4%

**Physical Examination**

- General examination: cachexia, virilization, breast tenderness, lymphadenopathy, fever
- Abdominal exam: masses, pain, ascites
Physical Examination

- Pelvic/speculum exam: clitoromegaly, bleeding, cervical displacement
- Mass characteristics: contour, firmness, mobility
- RV exam: tenderness, nodularity, stool guaiac.

Biomarkers

- May aid in determining the malignant potential and histology of an adnexal mass
- CA-125 is most commonly used biomarker
  - May be elevated in benign conditions
  - Ordered selectively
    - Age
    - Presentation of symptoms
    - Findings on physical examination
    - Imaging

Biomarkers

- Cancer antigen (CA) 125
  - Epithelial ovarian cancer (serous)
  - Benign processes
- Alpha Fetoprotein (AFP)
  - Endodermal sinus tumors
  - Hepatocellular carcinoma
- Human chorionic gonadotrophin (hCG)
  - Choriocarcinoma, embryonal carcinoma
  - Pregnancy
  - Gestational trophoblastic disease
- Lactate dehydrogenase (LDH)
  - Dysgerminomas
  - Lymphomas
- Inhibin A and B
  - Granulosa cell tumors
- Cancer antigen (CA) 19-9
  - Pancreas and biliary tract
  - Mucinous tumors of the ovary
- Carcinembryonic antigen (CEA)
  - Colorectal cancer

Biomarkers

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumor Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30 years</td>
<td>AFP, hCG, LDH, Inhibin A, Inhibin B</td>
</tr>
<tr>
<td>30-50 years</td>
<td>Inhibin A, Inhibin B, +/- CA-125 (family history)</td>
</tr>
<tr>
<td>≥50 years</td>
<td>CA-125, CA 19-9, +/- Inhibin A &amp; B (if symptoms), +/- CEA</td>
</tr>
</tbody>
</table>
**OVA1™**

- Combines five immunoassays into a single numerical result
  - CA-125
  - Transthyretin (prealbumin)
  - Apolipoprotein A1
  - ß2-microglobulin
  - Transferrin

**OVA1 Scoring**

OvaCalc software uses assay results and calculates ovarian cancer risk index score

- Premenopausal
  - less than 5 = low risk
  - 5 or greater = high risk
- Postmenopausal
  - less than 4.4 = low risk
  - 4.4 or greater = high risk

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**HE4 and CA-125**

- Study of 531 patients with pelvic mass
  - Low risk: 352 cases
    - Benign ovarian tumors
  - High risk: 179 cases
    - Epithelial ovarian cancers (n=129)
    - 22 borderline tumors/6 non-epithelial ovarian cancers
    - 22 non ovarian cancers

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>92.3%</td>
<td>75.0%</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>76.5%</td>
<td>74.8%</td>
</tr>
</tbody>
</table>


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**Radiographic imaging**

- Ultrasound
  - Size, location, locularity, echogenicity, blood flow, septations, presence of ascites
Radiographic imaging

- **MRI**
  - May be helpful in further assessing those masses that have an indeterminate malignant potential on ultrasound
  - Expensive, but may prevent patients from undergoing an unnecessary surgical procedure.
- **CT scan**
  - Ovarian cancer pre-operative and post-operative treatment planning

Concerning for Malignancy

- Complex or solid mass
- Ascites
- Presence of blood flow within papillary projection
- Diameter >10cm
- Bilateral tumors
- Septation >3mm in width

Referral Guidelines

**SGO and AGC Referral Guidelines for a Newly Diagnosed Pelvic Mass**

**PREMENOPAUSAL (< 50 YEARS OLD)**
- CA-125 > 200 U/mL
- Ascites
- Evidence of abdominal or pelvic ascites
- Family history of breast or ovarian cancer (in a first-degree relative)

**POSTMENOPAUSAL (≥ 50 YEARS OLD)**
- CA-125 > 35 U/mL
- Ascites
- Nodular or fixed pelvic mass
- Evidence of abdominal or pelvic ascites (by exam or imaging study)
- Family history of breast or ovarian cancer (in a first-degree relative)

Only one criterion from the list is required to recommend referral

Ovarian Cancer

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The Ohio State University Comprehensive Cancer Center
Arthur G. James Cancer Hospital and Richard J. Solove Research Institute
Cancer statistics 2014

Estimated new cases | Estimated deaths
---|---

Types of ovarian cancer

- Epithelial cancer (85%)
- Serous
- Mucinous
- Clear cell
- Endometrioid
- Transitional cell (Brenner)
- Non-epithelial cancer
  - Germ cell tumors
  - Sex cord stromal tumors

Ovarian cancer staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Incidence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Confined to the Ovary</td>
<td>20%</td>
</tr>
<tr>
<td>Ia</td>
<td>Growth limited to one ovary.</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>Same as Ia but involves both ovaries</td>
<td></td>
</tr>
<tr>
<td>Ic</td>
<td>Above with positive washings or ruptured capsule</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>Extends to True Pelvis</td>
<td>5%</td>
</tr>
<tr>
<td>IIa</td>
<td>Involves fallopian tube or uterus</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>Extension to other pelvic tissues</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Extends Beyond the True Pelvis</td>
<td>58%</td>
</tr>
<tr>
<td>IIIa</td>
<td>Positive retroperitoneal nodes only</td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>Microscopic positive biopsy outside the pelvis</td>
<td></td>
</tr>
<tr>
<td>IIIc</td>
<td>Abdominal implants up to 2 cm</td>
<td></td>
</tr>
<tr>
<td>IIId</td>
<td>Positive lymph nodes or abdominal implants &gt; 2 cm</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Distant Disease</td>
<td>17%</td>
</tr>
<tr>
<td>IVa</td>
<td>Pleural effusion with positive cytology</td>
<td></td>
</tr>
<tr>
<td>IVb</td>
<td>Parenchymal and extra-abdominal metastases</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis

- Examination
- Imaging
  - Septation
  - Excrescences
- CA-125 level

Omental Cake
### Diagnosis

- Examination
- Imaging
- CA-125 level

Omental Cake

Surgery

### Role for surgery

- Establish diagnosis (surgery)
  - Laparotomy versus laparoscopy
  - Cytology only if unable to operate

- Surgical goals
  - Determine extent of disease (staging)
  - Cytoreduction (debulking)
  - Restore/preserve anatomy

### Surgical staging

- Cytology
- Assessment/biopsies of peritoneal surfaces
- Hysterectomy and salpingo-oophorectomy
- Pelvic and para-aortic lymph nodes
- Appendectomy

### Importance of surgical staging

- Clinically early stage
- Completion staging upstages 31%

- Therapeutic
  - Resection of metastatic deposits
  - Assign appropriate adjuvant treatment
  - Maximizes survival
**Cytoreductive Surgery**

- Goal is elimination of all tumor
  - No gross residual (microscopic)
  - Optimal (≤1 cm)
  - Suboptimal (>1 cm)
- Operative Technique
  - Radical resection

**Chemotherapy**

<table>
<thead>
<tr>
<th>Stage IA or IB</th>
<th>Grade 1: Observe</th>
<th>Grade 2: Observe or carboplatin/paclitaxel</th>
<th>Grade 3: Carboplatin/paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IC</td>
<td>Grade 1-3: Carboplatin/paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II-IV</td>
<td>Intraperitoneal chemotherapy</td>
<td>Carboplatin/paclitaxel</td>
<td>Completion surgery</td>
</tr>
</tbody>
</table>

**Importance of surgical debulking**

Resection of all visible disease should be the goal


**Survival outcomes**

Overall survival

- IV/IP Carboplatin/Paclitaxel
- Carboplatin/Paclitaxel
- Carboplatin/Doxorubicin
- Cyclophosphamide/Doxorubicin
Surgery and chemotherapy

- Goals of Treatment
  - Prolong survival
  - Delay time to progression
  - Control disease-related symptoms
  - Minimize treatment-related adverse events
  - Maintain or improve quality of life

Neoadjuvant chemotherapy

- Utilized when patients are not likely to undergo complete surgical resection

- Disease factors
- Patient factors
- Surgeon factors

Recurrent Ovarian Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>CR</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>~100%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Stage II</td>
<td>~100%</td>
<td>50%</td>
</tr>
<tr>
<td>Optimal stage III</td>
<td>&gt;90%</td>
<td>75%</td>
</tr>
<tr>
<td>Suboptimal stage III / IV</td>
<td>50%</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

- Most patients will have disease recur within 5 years
- Retreatment challenges
  - Low response rates
  - Shortened PFS

Chemotherapy Sensitivity

- Primary Treatment
- End of Front-Line Therapy
  - Refractory
  - Chemo Resistant
  - Chemo Sensitive
  - "Intermediate-Sensitive"
  - "High-Sensitive"

- 6 Months
- 12 Months
Future opportunities and directions

- Screening
  - New tumor markers/Better imaging
- Referral to gynecologic oncology
  - Majority of women do not receive standard care
- Prolonging recurrence free interval
  - The role of maintenance therapy
- Improving second line therapies
  - Role of biologics

Screening

- Ultrasound
- CA-125
  - High rate of false positives
  - Often not abnormal until advanced stages

Ovarian cancer screening

- Randomization of ~78,000 low risk women to screening or routine care
  - Women aged 55 to 74 years randomized
  - Screening: annual CA-125 (cut-off ≥ 35) and ultrasound
- Results
  - False-positive rate ~10%
  - No improvement in mortality rates
  - High rate of serious complications

Screening – US and CA 125

National Health Institutes:
“...there is no evidence available yet that the current screening modalities of CA 125 and transvaginal ultrasonography can be effectively used for widespread screening to reduce mortality from ovarian cancer...”
Screening – US and CA 125

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“...there is no evidence available yet that the current screening modalities of CA 125 and transvaginal ultrasonography can be effectively used for widespread screening to reduce mortality from ovarian cancer...”

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