Gynecologic Cancers

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What is Gynecologic Cancer?

- Any cancer that starts in a woman’s reproductive organs
- Each GYN cancer is unique
- 5 main types
  - Cervical
  - Ovarian
  - Uterine
  - Vaginal
  - Vulvar

Who is at risk for GYN Cancer?

- All women are at risk
  - Risk generally increases with age
- Incidence
  - 71,500 new diagnosed cases
  - 26,500 deaths

Case Study

- Presentation
  - 30 yo female presents to ER with abdominal vaginal bleeding
  - Bx reveals squamous cell carcinoma of cervix
  - CT reveals large 7cm mass
  - Stage IB-2 squamous cell carcinoma of cervix
  - Tx
    - External beam radiation & concurrent cisplatin and gemcitabine, followed by brachytherapy, followed by hysterectomy
    - Surveillance every 3 mos
- 3 years later
  - Presents with shortness of breath, CT reveals mass in lung
  - Palliative treatment with Taxol/Carbo and radiation to lung mass
Cervical Cancer - Facts

• 3rd most common GYN cancer in women in the U.S.
• Estimated Cases
  – New – 12,900
  – Deaths – 4,100

Rates are decreasing in the U.S.
  – Incidence remains high among
    • Hispanic/Latino, Black, Asian women
• Persistent human papillomavirus (HPV) infection
  – most important factor in development of cervical cancer
• The only GYN cancer that can be prevented with screening tests and routine follow-up

Screening Recommendations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Age to initiate</th>
<th>Age to discontinue</th>
<th>Recommended screening test and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG/ASCCP/ASCP (2012)</td>
<td>21</td>
<td>NA</td>
<td>PAP test q 3 yrs (preferred) Co-testing (pap test and HPV testing) q 5 yrs (preferred)</td>
</tr>
<tr>
<td>ASCO/ESGO (2015 interim guidelines)</td>
<td>21</td>
<td>NA</td>
<td>PAP test q 3 yrs</td>
</tr>
<tr>
<td>USPSTF (2012)</td>
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</tbody>
</table>

Screening Recommendations

• Guidelines intended for the general population
  – Not for women with a history of cervical cancer
  – High-grade cervical precancer,
  – DES un utero exposure
  – Immunocompromised i.e. (HIV infection)
• Age to discontinue - 65
  – Adequate negative prior screening
    • 3 or more negative cytology tests
    • 2 consecutive negative co-tests in past 10 years – most recent within past 5 years

Cervical Cancer – Risk Factors

• Human Papilloma virus
• Smoking
  • Carcinogens concentrated in cervical mucus
• Immunosuppression
• STD’s
  • Chlamydia
  • Genital herpes
• Multiple sexual partners

• Early age of onset of coitus
• Long term oral contraceptive use
• Multiple full term pregnancies
• Poverty
Cervical Cancer - Pathophysiology

- **Two major parts**
  - Endo and Exo cervix
- **Main cell types**
  - Columnar epithelium - Endocervix
  - Squamous epithelium - Exocervix
- **Squamo-columnar junction (SCJ)**
  - Transformation Zone (TZ)
  - Meeting point between endo & exo cervix
    - Glandular cells replaced by squamous cells
    - Response to hormonal changes - Metaplasia
- **Cervical cancer**
  - Culmination of progressive disease that begins as a series of events in the SCJ

Cervical Cancer - Pathophysiology

- **Histology**
  - 80-90% squamous
  - 10-20% adeno
- **Pre-invasive or Premalignant changes**
  - No invasion of cervical stroma
  - Squamous intraepithelial lesion
    - Low grade (LSIL)
    - High grade (HSIL)
  - Glandular tissue
    - Adenocarcinoma in situ (AIS)

Human Papillomavirus (HPV) & Cervical Cancer

- **Most significant risk factor**
- **Most common sexually transmitted disease**
- **> 100 types – most benign**
  - About 40 affect the genital tract
    - Low-risk HPV – visible benign lesions/warts – condylomata acuminata
      - HPV 6 & 11
    - High-risk HPV – tend to persist – assoc. with precancerous lesions
      - HPV 16 & 18
- **Virus enters through a break in the squamous epithelium**
  - HPV proteins bind to p53 – interfere with cell growth
  - Allows damaged cells and HPV infection to thrive
- **HPV Vaccine – Prevention**
  - Types 6, 11, 16 & 18

HPV Vaccine

- **2 Vaccines**
  - Cervarix (bivalent) – HPV 16 & 18
  - Gardasil (quadrivalent) – HPV 6, 11, 16 & 18
- **Quadrivalent HPV Vaccine (Gardasil)**
  - Types 16 & 18
    - 70% of Cervical Cancer
  - Types 6 & 11
    - 90% genital warts
  - 9 y.o. – 26 y.o.
- **CDC Advisory Committee on Immunization Practices**
  - 9-10 yrs: per physician
  - 11-12 yrs: recommend immunization
  - 13-26 yrs who have not been previously vaccinated
  - Can receive if previous:
    - Abnormal PAP, HPV test positive, genital warts
- **Studies**
  - Efficacy in men
  - Efficacy in women aged > 26 yrs
Cervical Cancer Presenting Signs/Symptoms

- Early signs / symptoms
  - Most are asymptomatic
  - Persistent vaginal discharge
  - Painless, intermittent, post-coital or intra-menstrual vaginal bleeding
  - Increase in menstrual length/flow
- Late signs / symptoms
  - Pelvic pain & referred pain to flank or leg; lower extremity edema
  - Urinary symptoms include: dysuria, urinary retention, urinary frequency or hematuria
  - Bowel symptoms may include: rectal bleeding, constipation or bowel obstruction
  - Weight loss

Diagnostic Testing

- HPV testing
- Pap test
  - Normal
  - Abnormal
- Colposcopy
  - Examination of the cervix
    - Evaluation of the transformation zone in its entirety
    - Any lesions noted are biopsied
- Endocervical curettage (ECC)
  - Tissue specimen from the endocervical canal

Pre-invasive Disease Management

- Goal
  - Excise/ablate high-grade lesions before they become invasive
  - Decrease progression to cancer
- Excision treatment for HSIL
  - Loop Electrosurgical Excision Procedure (LEEP)
    - Wire loop used to excise tissue—allows visualization of lesion during excision
  - Cone biopsy/Conization
    - Removal of cone shape piece of tissue under anesthesia

Pre-invasive Disease Management

- Ablative treatments
- Reserved for treatment of LSIL and condylomas
  - Cryotherapy (cold probe)
    - Liquid Nitrogen freezes tissue, leads to tissue necrosis
  - Laser Therapy
    - Carbon dioxide laser beam mounted on a colposcope
      - Allows for visualization and treatment of the entire TZ
      - Causes vaporization of the lesion
Staging Cervical Cancer

- Two systems in use
  - Federation of Gynecology and Obstetrics (FIGO)
    - Most commonly used
  - American Joint Committee on Cancer (AJCC)
- Staging – not staged based on surgical pathology
  - Clinical exam
    - Inspection, palpation, colposcopy, endocervical curettage, hysteroscopy, IVP of the ureters, chest x-ray
  - Diagnostic tests
    - MRI – tumor volume
  - Lymph node
    - Surgical biopsy
    - PET, CT, MRI

Staging Cervical Cancer

- Diagnostic tests
  - CT
    - not as effective in identifying parametrial involvement
  - MRI
    - better at localizing the tumor lymph node
    - Least effective in evaluating lymph nodes and distant metastasis
  - PET
    - Useful in treatment planning but not yet used for staging
    - Not universally available - yet
    - Rules for clinical staging not strictly followed – so difficult to compare results between clinicians and institutions

Staging Cervical Cancer

- FIGO

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>I A1/2 &amp; B 1/2</td>
<td>Carcinoma strictly confined to cervix</td>
<td></td>
</tr>
<tr>
<td>II A &amp; B</td>
<td>Carcinoma extends beyond cervix, has Not extended to the pelvic wall, involves Vagina, but not past lower third</td>
<td></td>
</tr>
<tr>
<td>III A &amp; B</td>
<td>Carcinoma has extended to the pelvic wall, involves lower third of vagina, tumor causing hydronephrosis or nonfunctioning kidney</td>
<td></td>
</tr>
<tr>
<td>IV A &amp; B</td>
<td>Invasion into bladder or rectum, or distant mets</td>
<td></td>
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Cervical Cancer - Treatment

- Stage IA – 5 year survival close to 100%
  - Conization, hysterectomy, brachytherapy + external beam pelvic radiation
- Stage IB (cure 80-90%) & IIA
  - Hysterectomy + lymph node dissection or brachytherapy + pelvic radiation + cisplatin
  - Surgery + radiation
- Stage IIB (60-79%), III(35-50%), IVA (<10%)
  - Pelvic radiation and concurrent platinum followed by brachytherapy
**Recurrent/Metastatic Cervical Cancer**

- **Surgery**
  - Pelvic exenteration (infrequent)
    - Radical hysterectomy, lymph node, removal bladder and rectosigmoid colon
    - Recurrent disease, not adherent to pelvic sidewalls & not involving lymph nodes

- **Radiation**
- **Chemotherapy**
  - First line
    - Cisplatin, carboplatin, paclitaxel, Topotecan
    - Combination: Paclitaxel + carb or cisplatin; Cisplatin/topotecan; cisplatin/gemcitabine

**Cervical Cancer - Complications**

- **Surgery**
- **Complications**
  - Ureteral fistulas, bladder dysfunction, pulmonary embolus, pelvic infection, bowel obstruction, rectovaginal fistula, hemorrhage

- **Radiotherapy**
  - Vaginal stenosis, fistula formation, sigmoid perforation or stricture, uterine perforation, rectal ulcer, intestinal obstruction, ureteral stricture, cystitis, pelvic hemorrhage, pelvic abscess
  - Sexual dysfunction
    - Radiation causes thinning of vaginal epithelium
    - Vaginal atrophy, stenosis, lack of lubrication
    - Instruct use of vaginal dilators

**Surveillance**

- Based on risk for recurrence
- Follow-up physical exam
  - Every 3-6 mos for 2 yrs
  - Every 6-12 mos for 3-5 yrs
  - Yearly
  - PAP test – yearly
  - Imaging as indicated based on symptoms
  - Lab work – CBC, BUN, creatinine as indicated
  - Patient education
    - Symptoms of potential recurrence, lifestyle, obesity, exercise and nutrition counseling
    - Regarding sexual health

**References**

- American Cancer Society Facts and Figures 2015
- American Cancer Society Statistics 2015
Case Study

• Presentation
  – 53 yo post menopausal woman presents to her PCP with – abd cramping and bloating after travel to Hawaii.
  – Infection work-up - Negative Symptoms persist
  – Imaging: CT – abd/pelvis show omental masses on the undersurface of the diaphragm and ascites. The ovaries were not well identified on exam.
  – CA-125 level 8400 10/01 postmenopausal spotting – had pelvic ultrasound – no masses were found.

• Presentation (con’t)
  – Modified radical hysterectomy, BSO, omentectomy, appendectomy, tumor found in ovaries, tumor nodules on bladder, peritoneum, bilateral hemidiaphragm, recto sigmoid, right abdominal side wall
  – Stage IIIIC Ovarian Cancer
  – Presentation – 4 years later : Chemotherapy
    – Paclitaxel and Carboplatin – 9 cycles CA-125 10
    – Paclitaxel maintenance x 1 yr
    – Gemcitabine and Cisplatin – 6 cycles
    – Doxil – 6 cycles
    – Paclitaxel/Carboplatin and Avastin – 4 cycles
    – Oxaliplatin

ACS Leading Sites of New Cancer Cases and Deaths in Females – Estimates 2014

<table>
<thead>
<tr>
<th>New Cases</th>
<th>Est. Deaths</th>
</tr>
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<tbody>
<tr>
<td>(810,320)</td>
<td>(275,710)</td>
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<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (25%)</td>
<td>Lung &amp; Bronchus (26%)</td>
</tr>
<tr>
<td>Lung &amp; Bronchus (33%)</td>
<td>Breast (15%)</td>
</tr>
<tr>
<td>Colorectum (8%)</td>
<td>Colorectum (9%)</td>
</tr>
<tr>
<td>Uterine Corpus (6%)</td>
<td>Pancreas (7%)</td>
</tr>
<tr>
<td>Thyroid (6%)</td>
<td>Ovary (8%)</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (4%)</td>
<td>Leukemia (4%)</td>
</tr>
<tr>
<td>Melanoma of the skin (4%)</td>
<td>Uterine Corpus (3%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis (3%)</td>
<td>Non-Hodgkin Lymphoma (3%)</td>
</tr>
<tr>
<td>Pancreas (3%)</td>
<td>Liver &amp; intrahepatic bile duct (3%)</td>
</tr>
<tr>
<td>Leukemia (3%)</td>
<td>Brain &amp; other nervous system (2%)</td>
</tr>
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Ovarian Cancer - Facts

• Leading cause of death from GYN cancer
• 5th most common cause of cancer mortality
  – Deaths – 14,180
• Lifetime risk 1 in 75
  – New Cases – 21,290
• < 40% are cured
• Incidence increases with age
• Median age at diagnosis – 63
• > 70% present with advanced disease
• 5yr survival with advanced disease 20%-30%
Ovarian Cancer - Screening

• Difficult to diagnose at an early stage
• Consensus guidelines for ovarian cancer symptoms (suggestive of ovarian cancer)
  – Bloating, pelvic/abdominal pain
  – Difficulty eating/feeling full quickly
  – Urinary symptoms – urgency, frequency
* if having symptoms > 12 times during a month

Ovarian Cancer - Screening Trials

• UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)
  – Ongoing trial
  – Multimodality screening
    • Ultrasound and Cancer Antigen 125 (CA-125) vs
    • Ultrasound alone or
    • No screening
  – Preliminary results
    • Multimodality screening more effective in detecting early stage cancers

Ovarian Cancer - Screening

• Screening - Average risk
  – Routine screening NOT recommended
  – Several Randomized Controlled Trials on going
    • CA-125 and/or TVU

• Screening - High risk
  – Pelvic exams
  – CA-125
  – Transvaginal ultrasound (TVU)

Ovarian Cancer - Risk Factors

• Genetic – 5%
  – BRCA1, BRCA2
  – Lynch Syndrome

• Increased Risk
  – Age >63
  – Personal Hx breast cancer
  – Family Hx ovarian or breast cancer
  – Reproductive Hx
    • Nulliparity
    • First birth > age 35
  – Ethnicity
  – Hormone replacement therapy

• Reduced Risk
  – Oral contraceptive use
  – Pregnancy
    • Younger age ≤ 25
  – Lactation
  – Diet
  – Salpingo-oopherectomy
Ovarian Cancer

- Epithelial cells - (85-90%)
  - Papillary serous
  - Endometrioid cell
  - Mucinous cell
  - Clear cell
- Germ Cell - 5%
  - Benign or malignant
- Sex-cord Stromal cells - 7%
- Metastasis
  - Direct extension
  - Peritoneal seeding
  - Lymph
  - Vascular

Ovarian Cancer - Symptoms

- Gastrointestinal
  - Bloating
  - Urinary symptoms
  - Difficulty eating/early satiety/dyspepsia
  - Nausea
  - Constipation/Diarrhea
  - Fatigue
  - Back pain

- Gynecologic
  - Abdominal distention/increased abdominal girth
  - Pelvic pain
  - Menstrual irregularities
  - Vaginal bleeding
  - Watery vaginal discharge

- 95% had symptoms prior to diagnosis
- 89% with early-stage disease


Ovarian Cancer - Presentation

- Palpable ovarian mass
  - Premenopausal – dependent on size of mass
    - < 4cm may watch through several cycles
    - 10 cm or > - suspicious for malignancy
- Ascites
- Pleural effusions

Ovarian Cancer - Diagnosis

- Transvaginal Ultrasound
  - Complex cysts (solid and cystic components)
- CA-125
  - NmI < 35 U/ml
  - >65 U/ml associated with malignancy in approx 90% of cases
- Exploratory laparotomy
  - Histologic confirmation
  - Staging
  - Tumor debulking
    - Optimal debulking 1cm or < increases survival
    - Vertical incision
  - TAH, BSO, omentectomy, lymph node & peritoneal biopsy, peritoneal washings
Ovarian Cancer - Staging

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<tr>
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<td>I</td>
<td>Tumor limited to ovary</td>
</tr>
<tr>
<td>II</td>
<td>Ovarian tumor with pelvic extension</td>
</tr>
<tr>
<td>III</td>
<td>Ovarian tumor microscopic peritoneal metastasis outside pelvis</td>
</tr>
<tr>
<td>IV</td>
<td>Distant organ involvement, including pleural space or hepatic or splenic parenchymal</td>
</tr>
</tbody>
</table>

Survival:
- Stage I or II: 80-95%
- Stage III or IV: 10-30%

Ovarian Cancer

- Prognosis is affected by:
  - Stage
  - Histologic grade
  - Volume of residual disease
  - Performance status
  - Patient age

Ovarian Cancer - Treatment

- Surgical Staging & Cytoreduction
  - Goal – optimally debulk remove visible disease to < 1 cm
  - Small volume residual
    - Improved response rate
    - Longer disease free survival & overall survival
  - TAH, BSO, omentectomy, para-aortic and pelvic LN assessment/biopsy, peritoneal surface biopsies & peritoneal washings
  - Risk-Reducing Surgery
    - Recommended for patients at risk for Hereditary Breast and Ovarian cancer

- Chemotherapy
  - Neoadjuvant
    - Therapeutic benefit controversial
    - Stage III/IV not surgical candidates (dx by biopsy)
    - Pathologic dx should be confirmed prior to chemotherapy
  - Adjuvant
    - Stage IA or IB grade 1 tumors
      - Observe or Taxane/Carboplatin 3-6 cycles
    - Stage II, III, and IV
      - Taxane/Carboplatin
      - Intraperitoneal chemotherapy
        - Stage II and optimally debulked Stage III
Ovarian Cancer - Treatment

• Adjuvant chemotherapy
  – IV Regimens
    • Taxol 175 mg/m2 - over 3 hrs f/b Carboplatin AUC 5 or 6 - over 1 hr every 3 wks x 6 cycles
    • Dose dense Taxol 80 mg/m2 – over 1 hr days 1, 8, 15 + Carboplatin AUC 5 or 6 – over 1 hr every 3 wks x 6 cycles
    • Taxol 60 mg/m2 – over 1 hr f/b Carboplatin AUC 2 – over 30 min weekly x 18 wks
    • Docetaxel 60-75 mg/m2 – over 1 hr f/b Carboplatin AUC 5 or 6 – over 1 hr day 1, every 3 wks x 6 cycles

• Intraperitoneal chemotherapy
  – Recommended regimen
    • Taxol 135 mg/m2 – continuous IV infusion over 3 or 24 hours Day 1
      – Published randomized trial used Taxol as a 24 hr infusion
      – 3 hour Taxol not proven to be equivalent
    • Cisplatin 75 – 100 mg/m2 IP on Day 2 after IV Taxol
    • Taxol 60 mg/m2 IP on Day 8
    • Every 3 weeks for 6 cycles
    • Initial studies only 42% able to complete all 6 cycles

Intraperitoneal Chemotherapy

• Rationale
  – Peritoneum the predominant site of tumor
    • receives sustained exposure to high concentrations of chemotherapy
    • Sparing normal tissues such as the bone marrow
  – Administered through an abdominal port
    • Variety of different regimens – Taxane + Platinum
    • Every 3 weeks for 6 cycles
  – Different side effect profile than IV
    • Leukopenia, infection, fatigue, renal toxicity, abdominal discomfort and neurotoxicity

Administration Considerations for IP Chemotherapy

• Type and location
  – Vascular or intraperitoneal
  – Implanted by rib or over abdominal muscle (instruct pt to “tense” abd muscle at time of access)
• Port access
  – Procedure similar to vascular port access
  – Non-coring needle
• Ensuring placement
  – Ability to flush
  – Aspirate?
  – Observe for infiltration
• Risk of dislodgement
  – Limit activity after access
  – Access IP port when ready to treat
• IP fluids
  – Warmed to body temperature
• Flushing
  – Heparin?
    • Fibrin sheath formation
    • 20 ml NS the 10 ml 100u/ml Heparin
• Rotation schedule
  – Side to side
  – Trendelenburg
Ovarian Cancer – Treatment

Targeted therapy

• Bevacizumab (Avastin)
  – In combination with chemotherapy
  – Relapsed advanced ovarian cancer
  – Improvement in progression free survival

• Side effects
  – High blood pressure, GI perforation, bleeding, proteinuria

• Olaparib (Lynparza)
  – Poly(ADP)-ribose polymerase inhibitor – PARP inhibitor
  – Germline BRCA mutation
  – Received 3 or more lines of therapy
  – Oral agent

• Side effects
  – N/V, diarrhea, fatigue, loss of appetite, muscle & joint pain

Follow-up and Recurrence

• Follow-up
  – Physical exam (PE) every 2-4 mos for 2 yrs, then every 3-6 mos for 3 yrs, then annually after 5 yrs
  – CA-125 if initially elevated

• 50%-75% relapse with advanced disease
  – < 6 mos – Platinum resistant
    • Single agent non-platinum based
      – Docetaxel, oral etoposide, gemcitabine, liposomal doxorubicin,
      – Weekly taxol, topotecan

Symptom Management and Supportive Care

• Chemotherapy (usually paclitaxel and platinum)
  – Alopecia, allergic reaction, myelosuppression, N/V, peripheral neuropathy

• Support for metastatic disease
  – Ascites
  – Intestinal obstruction
  – Malnutrition
  – Lymphedema
  – Pleural effusion
  – Support
    • National Ovarian Cancer Coalition www.ovarian.org
    • Gilda’s Club www.gildasclubseattle.org

Follow-up and Recurrence

• Recurrence Modalities
  – > 6 mos - platinum sensitive
    • Carboplatin/Taxol
      – Hypersensitivity reactions to Carboplatin > after 7th dose
    • Carboplatin/ Liposomal doxorubicin
      – Equivalent to Carbo/Taxol
      – Different toxicity profiles
      – Easier to tolerate

• Support for metastatic disease
  – Ascites
  – Intestinal obstruction
  – Malnutrition
  – Lymphedema
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  – Support
    • National Ovarian Cancer Coalition www.ovarian.org
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Survivorship

• Persistent treatment-associated effects at the completion of therapy
  – Physical Symptoms
    • Menopausal symptoms
  – Treatment side effect
    • Numbness/tinging
  – Psychological issues
    • Depression/anxiety
    • Threat to the female image
    • Threat of recurrence

Resources

• National Comprehensive Cancer Network
  – www.nccn.org
  – Practice guidelines for clinicians
  – Patient education
• National Cancer Institute
  – www.cancer.gov
  – Patient education pamphlets “What you need to know about…….”
• Gynecologic Oncology Group (GOG)
  – www.gog.org