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>ACCP/ASCCP/ASCP (2012)</td>
<td>21</td>
<td>65</td>
<td>PAP test q 3 yrs (preferred)</td>
</tr>
<tr>
<td>ASCO/ASGO (2015 interim guidelines)</td>
<td>21</td>
<td>NA</td>
<td>Can consider primary HPV testing q 5 yrs for women &gt;25</td>
</tr>
<tr>
<td>USPSTF (2012)</td>
<td>21</td>
<td>65</td>
<td>PAP test q 3 yrs</td>
</tr>
<tr>
<td>ACOG (2012)</td>
<td>21</td>
<td>65</td>
<td>PAP test q 3 yrs</td>
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</tbody>
</table>

- Guidelines intended for the general population
  - Not for women with a history of cervical cancer
  - High-grade cervical precancer,
  - DES 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 SCI

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

**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

**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

**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 + carbo 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.
Case Study

- 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 IIIC 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 – 2016 Estimates

<table>
<thead>
<tr>
<th>New Cases (843,820)</th>
<th>Est. Deaths (281,400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (29%)</td>
<td>Lung &amp; Bronchus (26%)</td>
</tr>
<tr>
<td>Lung &amp; Bronchus (13%)</td>
<td>Breast (14%)</td>
</tr>
<tr>
<td>Colon &amp; rectum (8%)</td>
<td>Colon &amp; rectum (8%)</td>
</tr>
<tr>
<td>Uterine Corpus (7%)</td>
<td>Pancreas (7%)</td>
</tr>
<tr>
<td>Thyroid (6%)</td>
<td>Ovary (5%)</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (4%)</td>
<td>Leukemia (4%)</td>
</tr>
<tr>
<td>Melanoma of the skin (3%)</td>
<td>Uterine Corpus (4%)</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>
</tbody>
</table>

Ovarian Cancer - Facts

- Leading cause of death from GYN cancer
- 5th most common cause of cancer mortality
  - Deaths – 14,240
- Lifetime risk 1 in 75
  - New Cases – 22,280
- < 40% are cured
- Incidence increases with age
- Median age at diagnosis – 63
- > 70% present with advanced disease
- Overall 5 yr survival is 44%

Ovarian Cancer Risk Factors

- Patient Characteristics
  - Age - >63
  - Personal Hx breast cancer

- Reproductive factors
  - Nulligravity
  - Early menarch
  - Late menopause
  - Infertility
  - Polycystic ovarian syndrome
  - Endometriosis

- Genetic – 5%
  - Family hx of ovarian cancer
  - BRCA 1 / 2 mutations
  - Lynch syndrome

- Environmental factors
  - Obesity & high-fat diet
  - Talc exposure
  - Cigarette smoking
Ovarian Cancer
Decreased Risk

- Reproductive factors
  - Use of oral contraceptives
  - Pregnancy/multiparity
  - Breastfeeding
- Gynecologic surgery
  - Salpingo-oophorectomy
  - Tubal ligation

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 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

- 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 Diagnosis & Evaluation

- 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 Preoperative Workup

- History of present illness
  - Symptom index tool
- Family history
  - HBOC
  - Lynch syndrome
- GYN history

- Labwork
  - Full panels plus
    - CA-125 (consider HE4)
    - B-HCG
    - AFP
- Imaging
  - Transvaginal ultrasound
  - CT abd/pelvis
  - Chest x-ray

Ovarian Cancer Surgical Treatment

- Laparotomy
  - En bloc TAH, BSO tumor removal/debulking
    - Comprehensive staging
  - Fluid sampling
  - Pathologic assessment of the abdomen
    - Diaphragm
    - Pericolic gutters
    - Serosal surfaces

- Comprehensive staging
- Fluid sampling
- Pathologic assessment of the abdomen

Ovarian Cancer - Treatment

- Laparotomy
  - Goal – optimally debulk remove visible disease to < 1 cm
    - Small volume residual
      - improved response rate
      - longer disease free survival & overall survival
  - Second look laparoscopy/laparotomy
Ovarian Cancer - Treatment

• 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
      – Grade 1 – Observe
      – Grade 2 – Observe or IV Taxane/Carboplatin 3-6 cycles
      – Grade 3 – IV Taxane/Carboplatin 3-6 cycles
    • Stage IC
      – Taxane/Carboplatin 3-6 cycles

Ovarian Cancer - Treatment

– Adjuvant Chemotherapy
  • Stage II, III, and IV
    – Intraperitoneal chemotherapy
      » In optimally debulked Stage II and III
    – IV taxane/carboplatin 6-8 cycles
    – Completion surgery as indicated

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
  – Different side effect profile than IV
    • Leukopenia, infection, fatigue, renal toxicity, abdominal discomfort and neurotoxicity

Ovarian Cancer - Treatment

• Adjuvant chemotherapy
  – IV Regimens
    • Taxol 175 mg/m2 - over 3 hrs f/b Carboplatin AUC 5-6 - over 1 hr every 3 wks x 6 cycles
    • Dose dense Taxol 80 mg/m2 – over 1 hr days 1, 8, 15 + Carboplatin AUC 5-6 – 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 cycle
Ovarian Cancer - Treatment

- 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

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

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 sheet formation
  - 20 ml NS the 10 ml 100u/ml Heparin
- Rotation schedule
  - Side to side
  - Trendelenburg

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
Follow-up and Recurrence

- Recurrence
  - > 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

Symptom Management and Supportive Care

- Chemotherapy (usually paclitaxel and platinum)
  - Alopecia, allergic reaction, myelosuppression, N/V, peripheral neuropathy
- Nursing challenges for metastatic disease
  - Ascites
  - Intestinal obstruction
  - Malnutrition
  - Lymphedema
  - Pleural effusion
- Support
  - National Ovarian Cancer Coalition www.ovarian.org
  - Gilda’s Club www.gildasclubseattle.org

Survivorship

- Persistent treatment-associated effects at the completion of therapy
  - Physical Symptoms/treatment side effects
    - GI side effects
    - Neuropathy
    - Fatigue
    - Body image changes/problems with sexuality
  - Psychological issues
    - Depression/anxiety - guilt
    - Threat to the female image
  - Threat of recurrence
    - Preoccupation with lab values

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