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 - estimated
  - 107,470 new diagnosed cases
  - 31,600 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 – 12,820
  - Deaths – 4,210
- 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

### Organization

<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>ACS/ASCO/ASCP (2012)</td>
<td>21</td>
<td>65</td>
<td>Pap test q 3 yrs (preferred)</td>
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<td>NA</td>
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</tr>
<tr>
<td>ASCCP/SGO (2015 interim guidelines)</td>
<td>21</td>
<td>NA</td>
<td>Can consider primary HPV testing q 5 yrs in women ≥ 25 Pap test q 3 yrs</td>
</tr>
</tbody>
</table>

Screening Recommendations

- Guidelines intended for the general population
  - Not for women with a history of cervical cancer
  - High-grade cervical pre-cancer,
  - 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 SCJ

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

- 3 Vaccines
  - Gardasil (quadrivalent) – HPV 6, 11, 16 & 18
  - Gardasil 9 (9-valent) – also covers HPV 31, 33, 45, 52
- 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

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)
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

Cervical Intraepithelial Neoplasia (CIN)

- CIN 1 – low grade lesions
  - Mildly atypical cellular changes
    - Low-grade squamous intraepithelial lesions (LSIL)
    - Low potential for developing malignancy
- CIN 2 – high grade lesions
  - Moderately atypical cellular changes
    - High-grade squamous intraepithelial lesions (HSIL)
- CIN 3 – high grade lesions
  - Severely atypical cellular changes
    - High-grade squamous intraepithelial lesions (HSIL)

CIN Management

- Approaches
  - Continued observation - (cervical cytology HPV testing, colposcopy)
    - For most women with CIN 1
    - Persistent CIN 1 - LEEP
  - Treatment
    - Excision or ablation
    - Excisional treatments
      - Cone biopsies/cervical conization
      - Loop electrosurgical excision procedure – LEEP
      - Large loop excision of the transformation zone (LEEP/LLETZ)
      - Laser conization
CIN Management

- Ablative treatments
  - For patients with
    - Persistent CIN 1
    - CIN 2,3 if colposcopy is adequate
    - No suspicion of invasive disease & no significant endocervical disease
  - Cryotherapy (cold probe)
    - Refrigerant gas freezes tissue
  - CO₂ Laser
    - Causes vaporization of the lesion
  - Cold coagulation
    - Heat (at lower temperatures) to ablate cervix
  - Diathermy
    - Electrically induced heat

Staging Cervical Cancer

- Two systems in use
  - Federation of Gynecology and Obstetrics (FIGO)
    - Most commonly used
  - American Joint Committee on Cancer (AJCC)
- Staging
  - Physical exam
    - Pelvic exam
  - Cervical biopsy
  - Endoscopy

Staging Cervical Cancer

- Imaging studies
  - CT
  - MRI
    - Describe disease extent and guide treatment options
  - PET-CT
    - Detect and r/o metastasis
- 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

Cervical Cancer - Treatment

- Early-stage disease
  - 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
### Cervical Cancer - Treatment

- **Advanced disease**
  - Stage IIB, III, IVA
  - Patient without nodal disease or with disease limited to the pelvis
    - RT with concurrent cisplatin based chemotherapy and brachytherapy
  - Patients with positive para-aortic and pelvic lymph nodes
    - Extraperitoneal lymph node dissection followed by extended field RT, concurrent cisplatin based chemotherapy, and 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
  - **Chemotherapy**
    - First line
      - Cisplatin, carboplatin, paclitaxel, Topotecan
      - Combination: Paclitaxel + carbo or cisplatin; Cisplatin/topotecan; cisplatin/gemcitabine

### 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 2017
- American Cancer Society Statistics 2017
 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 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 – 2017 Estimates

<table>
<thead>
<tr>
<th>New Cases (852,630)</th>
<th>Est. Deaths (281,400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (30%)</td>
<td>Lung &amp; Bronchus (26%)</td>
</tr>
<tr>
<td>Lung &amp; Bronchus (12%)</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 (5%)</td>
<td>Ovary (5%)</td>
</tr>
<tr>
<td>Melanoma of the skin(4%)</td>
<td>Uterine Corpus (4%)</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma (4%)</td>
<td>Leukemia (4%)</td>
</tr>
<tr>
<td>Leukemia (3%)</td>
<td>Liver &amp; intrahepatic bile duct (3%)</td>
</tr>
<tr>
<td>Pancreas (3%)</td>
<td>Non-Hodgkin’s Lymphoma (3%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis (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 – 14,080
- Lifetime risk 1 in 75
  - New Cases – 22,440
- < 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
  - 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

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
    - Interval cytoreduction

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

- Chemotherapy
  - Adjuvant
    - Stage II, III, and IV
      - Intraperitoneal chemotherapy
        - in optimally debulked Stage II and III
      - IV taxane/carboplatin 6-8 cycles
        - Completion surgery as indicated
Ovarian Cancer - Treatment

• Adjuvant chemotherapy
  – IV Regimens
    • Taxol 175 mg/m^2 – over 3 hrs f/b Carboplatin AUC 5-6 – over 1 hr every 3 wks x 6 cycles
    • Dose dense Taxol 80 mg /m^2 – over 1 hr days 1, 8, 15 + Carboplatin AUC 5-6 – over 1 hr every 3 wks x 6 cycles
    • Taxol 60 mg/m^2 – 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

• 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

• Intraperitoneal chemotherapy
  – Recommended regimen
    • Taxol 135 mg/m^2 – 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

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
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

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
      – +/- Bevacizumab

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

Ovarian Cancer

• 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

• Rucaparib
  – Accelerated approval Dec 2016
  – FoundationFocus CDxBRCA test
  – Received 2 or more lines of therapy
• Side effects
  – N/V, anemia, fatigue, constipation, decreased appetite, dysgeusia, diarrhea
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

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