Gynecologic Cancers

Marge Ramsdell MN, RN, OCN
Madigan Army Medical Center

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

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

<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/ACCP/AAPC (2012)</td>
<td>21</td>
<td>65</td>
<td>Pap test q 3 yrs (preferred) Co-testing (pap test and HPV testing) q 5 yrs (preferred)</td>
</tr>
<tr>
<td>ASCOP/SGO (2015 interim guidelines)</td>
<td>21</td>
<td>NA</td>
<td>Can consider primary HPV testing q 3 yrs for women &gt; 21 Pap test q 3 yrs</td>
</tr>
<tr>
<td>USPSTF (2012)</td>
<td>21</td>
<td>65</td>
<td>Pap test q 3 yrs Alternative: Co-testing (pap + HPV testing) q 5 yrs</td>
</tr>
<tr>
<td>ACOG (2012)</td>
<td>21</td>
<td>65</td>
<td>Pap test q 3 yrs Co-testing (pap test and HPV testing) q 5 yrs (preferred) 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 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
- STI’s
  - Chlamydia
  - Genital herpes
- Multiple sexual partners
- Early age of onset of coitus
- Long term oral contraceptive use
- Multiple full term pregnancies
- Poverty

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**

- **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**

- **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) – CIN1
    - High grade (HSIL) – CIN2, 3
  - 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
    • CIN 2,3 if colposcopy is adequate
  – 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)
    - TNM – Stage 0-IV
- Staging – FIGO based on
  - 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

- Common types of treatment
  - Surgery
    - Cryosurgery
    - Laser surgery
    - Conization
    - Hysterectomy
      - Simple
      - Radical
    - Trachelectomy
    - Pelvic Exenteration

Cervical Cancer - Treatment

- Common types of treatment
  - Radiation therapy
    - Main treatment
    - Treat cancer that spread or recurred
  - Two main types
    - External beam
    - Brachytherapy
  - Long term effects
    - Vaginal stenosis
    - Vaginal dryness
    - Weakened bones
    - Leg swelling
Cervical Cancer - Treatment

• Common types of treatment
  – Chemotherapy
    • Depending on the stage concurrent therapy is preferred
      – Cisplatin weekly
      – Cisplatin + 5FU every 4 weeks
  – Recurrence
    – Cisplatin, Carboplatin
    – Paclitaxel
    – Topotecan
    – Gemcitabine

• Targeted therapy
  – Bevacizumab – can be used to treat advanced cancer

• Side effects
  – High blood pressure
  – Bleeding
  – Proteinuria

Surveillance

• Survivorship Care Plan
• Follow-up physical exam
  – Every 3-6 mos for 2 yrs
  – Every 6-12 mos for 3-5 yrs
  – 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
Ovarian Cancer

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 (282,500)</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>

ACS Facts and Figures 2017

Ovarian Cancer

- Leading cause of death from GYN cancer
- 5th most common cause of cancer mortality

- Lifetime risk 1 in 75
  - New Cases – 22,440
  - Deaths – 14,080

- < 40% are cured
- Incidence increases with age
- Median age at diagnosis – 63
- > 60% present with advanced disease
- Overall 5 yr survival is 46%

Ovarian Cancer - Facts

- 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 Risk Factors
Ovarian Cancer

Decreased Risk

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

Ovarian Cancer - Screening

- Screening - Average risk
  - Routine screening NOT recommended
  - Several large RCTs – now completed
    - CA-125 and/or TVU
- Screening - High risk
  - Pelvic exams
  - CA-125
  - Transvaginal ultrasound (TVU)

Ovarian Cancer

- Epithelial tumors - (85-90%)
  - Papillary serous
  - Endometrioid cell
  - Mucinous cell
  - Clear cell
- Germ Cell tumors – 5%
  - Benign or malignant
- Stromal tumors – 7%

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**

### Ovarian Cancer Labwork

- Full panels plus
  - CA-125 (consider HE4)
  - B-HCG
  - AFP

### Ovarian Cancer Imaging

- Transvaginal ultrasound
- CT abd/pelvis
- Chest x-ray

### Ovarian Cancer Surgical Treatment

- **Laparotomy**
  - En bloc TAH, BSO tumor removal
  - Comprehensive staging
  - Fluid sampling
  - Pathologic assessment of the abdomen
    - Diaphragm
    - Pericolic gutters
    - Serosal surfaces
  - Optimal debulking – remove visible disease to
    - < 1 cm tumors – small volume residual
      - improved response rate
      - longer disease free survival & overall survival

### Ovarian Cancer – Treatment Chemotherapy

- **Chemotherapy**
  - Neoadjuvant
    - Therapeutic benefit controversial
    - Stage III/IV not surgical candidates (dx by biopsy)
    - Pathologic dx should be confirmed prior to chemotherapy
  - Adjuvant
    - Combination of drugs
      - Platinum and a Taxane
    - Intraperitoneal (IP)
      - Chemotherapy directly into the abdominal cavity

### Ovarian Cancer - Treatment Intraperitoneal

- **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

- 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

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

- Antiangiogenesis inhibitors
  - Bevacizumab
    - IV every 2-3 weeks
- PARP inhibitors
  - BRCA gene mutation
    - Typically used after 2 or more lines of therapy
  - Oral agents
    - Olaparib
    - Rucaparib
  - No BRCA gene mutation
    - Niraparb

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
Surveillance

- Survivorship Care Plan
- Follow-up physical exam to include pelvic
  - Every 2-4 mos for 2 yrs
  - Every 3-6 mos for 3 yrs
  - Annually after 5 years
- Other tests
  - Imaging as clinically indicated
  - Lab work – CBC, chemistry profile as indicated
  - CA125 or other tumor markers
  - Genetic risk evaluation – if not done before
- Patient education
  - Symptoms of potential recurrence, lifestyle, obesity, exercise and nutrition counseling
  - Regarding sexual health

Surveillance

- 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

Recurrence

- 50%-75% relapse with advanced disease
  - < 6 mos – Platinum resistant
    - Single agent non-platinum based
      - +/- Bevacizumab
  - > 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

Recurrence

- Non-platinum base drugs used in recurrence
  - Docetaxel, oral etoposide, gemcitabine, liposomal doxorubicin,
  - Weekly taxol, topotecan
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