Gynecologic Oncology

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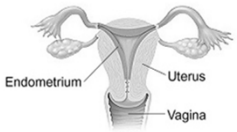
Endometrial cancer

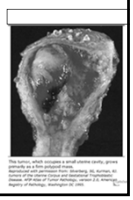
Endometrial Cancer

- The most common gynecologic cancer in US.
  - 81.3% survive 5 years
- Types:
  - Endometrial cancers (97%)
  - Uterine sarcomas (3%)
- Risk factors:
  - Excess estrogen (postmenopausal therapy, obesity, anovulatory menstrual cycles, tamoxifen), early menarche, nulliparity, late menopause)
  - Lynch syndrome
  - Older age



Endometrial Cancer

- Majority (67%) clinical stage 1
  - Prognosis dependent on stage
- Average age of diagnosis – 62
- Type 1 (80%)
  - Endometrioid cell type (Grade 1 & 2)
  - Estrogen-receptor positive
  - Endometrial intraepithelial neoplasia
- Type 2
  - Grade 3 and non-endometrioid histologic cell types (serous, clear cell, carcinosarcoma)



Clinical presentation

- Abnormal vaginal bleeding – 90%
  1. Post menopausal bleeding
  2. Pre- or perimenopausal abnormal bleeding
- Abnormal cervical cytology (pap smear)
  - Adenocarcinoma
  - Atypical glandular cells
  - Endometrial cells
- Incidental finding on hysterectomy

Work up

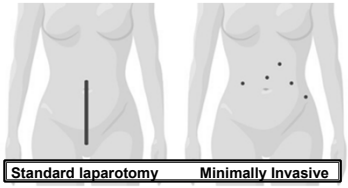
- Transvaginal ultrasound
- Endometrial sampling (EMB, D&C)
- Other imaging: CT, MRI, PET
- Colonoscopy, Barium Enema for bowel symptoms
- Serologic marker: CA125 (elevated with metastatic disease)

Treatment

- Medically fit for surgery:
  - Total hysterectomy and bilateral salpingo-oophorectomy.
  - Exploration of abdominal and pelvic cavity.
  - Surgical staging.
    - Systematic, selective or none
- Not medically fit for surgery:
  - Tumor directed radiation therapy.
  - Hormonal therapy
  - Chemotherapy.

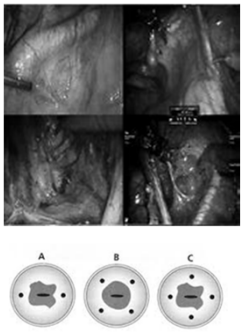
Surgery

- Open, robotic-assisted, laparoscopic and vaginal approaches
  - GOG-LAP2



Sentinel Lymph Node Mapping

- Methods
  - Radiocolloid (technecium 99) and Blue Dye
  - Flourescent medical dyes (Indocyanine Green – ICG)
- Bilateral cervical injection
- Video camera sensitive to NIR (700-900 nm)



Treatment

- High intermediate risk
  - VBT
- Advanced stages and for high risk types
  - Chemotherapy +/- tumor directed radiation
  - Endocrine therapy
- Recurrent disease
  - Chemotherapy
  - Immunotherapy
  - Targeted therapy
  - Tumor directed radiation
  - Endocrine therapy
  - Surgery

Fertility Sparing Therapy

- Hormonal
  - Progestins
    - Oral (continuous) vs. IUD
- Criteria:
  - Low risk group: grade 1-2, clinical stage IA.
  - Close monitoring with endometrial sampling.
- Results:
  - Median time to response: 6 months
  - 50-70% complete response.
  - 35% able to achieve pregnancy.
  - 35% recurrence rate.

Lynch syndrome

- 2-5% of endometrial cancers due to genetic mutations (Lynch syndrome).
- Women with Lynch syndrome with higher risk for endometrial cancer (17-70%) and other Lynch syndrome related cancers
  - gastro-intestinal, ovarian, upper genito-urinary, skin

5 year survival

Stage I	81-91%
Stage II	80%
Stage III	51.2-68.5%
Stage IV	21-22%

Ovarian/Fallopian Tube/Primary Peritoneal Cancer

Ovarian/Fallopian Tube/Primary Peritoneal Cancer

- Leading cause of death from gynecologic cancer in US.
  - 5th most common cause of cancer mortality in women.
  - Lifetime risk 1.3% (1 in 78).
  - Slow downward trend over the last 20 years
- Median age at diagnosis is 63.
- 46.5% survive 5 years
- More than 70% present with advanced disease.

Ovarian/Fallopian Tube/Primary Peritoneal Cancer

- 90% epithelial carcinoma
  - Others: germ cells, sex-cord stromal, mixed, metastatic from other sites.
- Histologic subtype
  - serous (70%), clear cell, mucinous, endometrioid, transitional cell.
- Origin
  - STIN – TP53 mutation and morphologic atypia

Risk Factors

- Incessant ovulation
  - Nulliparity, Older age at first birth (> 35 years)
- Age
- Postmenopausal hormonal therapy
- Ovarian stimulation for fertilization (for LMP tumors)
- Endometriosis
  - Increase in endometrioid and clear cell types
  - Risk of transformation 2.5%
- Obesity
- Ovarian cancer susceptibility genes
  - BRCA1(age 50) and BRCA2 (age 60)
  - Lynch syndrome
  - Others: BRIP1, RAD51C, RAD51D, CHEK2.
- Family history of ovarian cancer – 5.5%

Protective factors

- Use of oral contraceptive pills
  - RR decrease by 20% for each 5 years of use
  - Protective effect persist 30 years after cessation
- Multiparity
- Salpingo-oophorectomy
- Tubal ligation
- Breast feeding
- Younger age at first pregnancy and birth ($\leq$ 25 years)
- Hysterectomy

Screening test

- NO EFFECTIVE SCREENING TEST YET FOR GENERAL POPULATION.
- Previously studied screening methods
  - CA125 and pelvic ultrasound.
    - UK Collaborative Study, PLCO Cancer Trial.
  - Risk of Ovarian Cancer Algorithm (ROCA).
  - OVA1
  - OvaSure

Clinical Presentation

- Bloating
- Increase abdominal girth
- Difficulty eating, early satiety
- Abdominal and/or pelvic pain
- Urinary urgency or frequency
- Weight loss
- Shortness of breath
- Fatigue

- Adnexal mass
- Pleural effusion
- Bowel obstruction

Diagnostic Tests

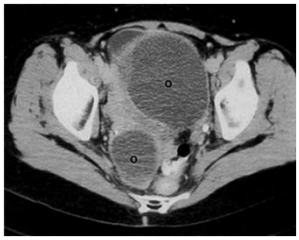
- Imaging
  - Ultrasound
  - CT scan
  - MRI
  - PET CT
- Laboratory evaluation
  - CA125
  - HE4
  - OVA1

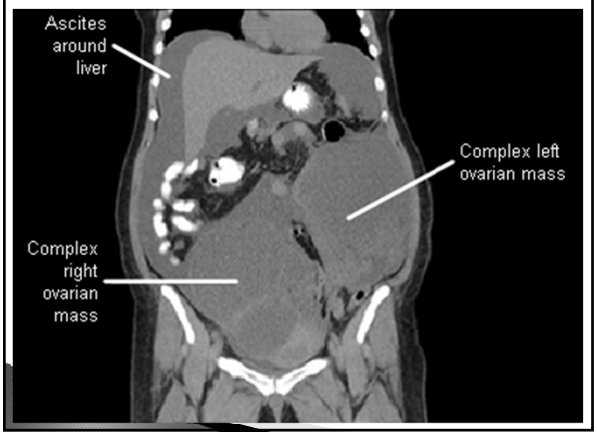
Sonographic findings

- Solid components
- Nodularity
- Papillary features
- Thick septations
- Ascites
- Peritoneal masses
- Internal blood flow

CT findings suggestive of cancer

- Pelvic masses
- Omental caking
- Lymphadenopathy
- Ascites
- Liver lesions
- Pleural effusions



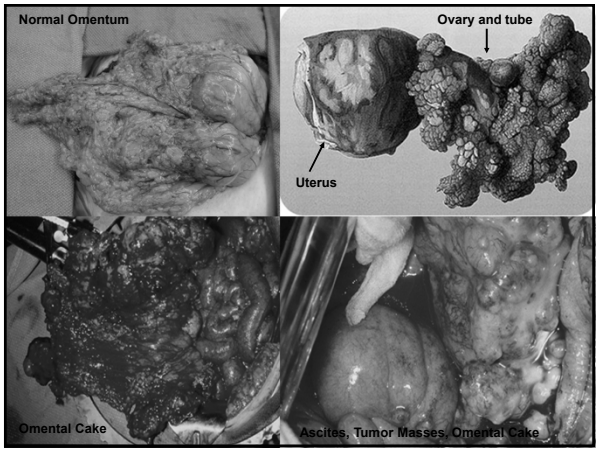


Diagnostic Tests

- Image-guided biopsy
- Paracentesis and thoracentesis
- Rule out extra-ovarian primary
  - Gastrointestinal evaluation
    - Colonoscopy
    - Barium enema
  - Mammography

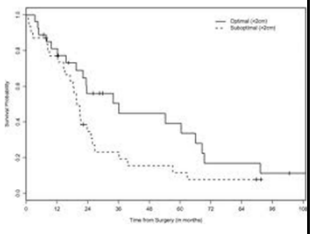
Treatment

- **Standard Surgery**
  - Exploratory laparotomy
  - Total abdominal hysterectomy
  - Bilateral salpingo-oophorectomy
  - Omentectomy
  - Lymphadenectomy
  - Appendectomy
  - Biopsies
  - Debulking
- **Radical debulking may include**:
  - Bowel resections
  - Bladder or ureteral resection
  - Splenectomy
  - Liver resection
  - Peritoneal stripping



Optimal Surgical Cytoreduction

- Residual disease after cytoreduction inversely correlates with survival.
- Debulking improves survival with 20 month improved median survival for optimal vs. suboptimal debulked.
- GOG definition = residual disease < 1 cm in maximal dimension.
- No residual disease is best



Adjuvant Chemotherapy

- Intravenous chemotherapy
- Intraperitoneal chemotherapy – IV/IP
- Hyperthermic intraperitoneal chemotherapy
  - Investigational
- Clinical Trial Enrollment

Neoadjuvant chemotherapy

- Candidates:
  - Stage IV disease
  - Stage III
    - Preoperative predictors of unresectable disease
  - Poor surgical candidate
- 3-4 cycles of IV Chemotherapy.
- Goals
  - decrease tumor burden/enhance patient's medical status
  - reduce surgical morbidity (ostomy)
  - increase possibility for complete cytoreduction
- Interval debulking.

Stage, Distribution, and Survival

Stage	Percent	Survival
I	24	95%
II	6	65%
III	55	15-30%
IV	15	0-20%
Overall		50%

American Cancer Society 2000

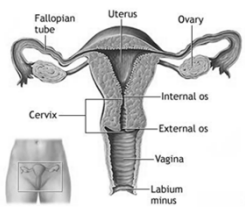
Recurrent Ovarian Cancer

- Dependent on disease free interval
  - Oligometastatic disease, 6+ months
  - Eligible for secondary debulking
- Clinical Trial
- Targeted therapy
  - PARPi, targeted therapy, checkpoint inhibitors
- Chemotherapy
- Endocrine therapy.
- Tumor directed radiation therapy.

Genetic testing

- Personal h/o of ovarian cancer
- BRCA and Lynch Syndrome.
- Why?
  - May influence treatment recommendations and options.
    - PARP inhibitors
  - Surveillance, healthcare maintenance, prophylactic surgery
  - Information for family members to help them make healthcare decisions for care/prevention.

Cervical cancer



From: Adam.inc

From: netterimages.com

Background

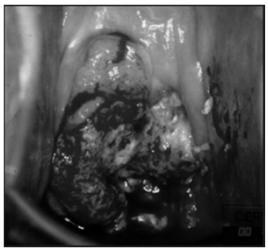
- Age related disease
- Mean age of diagnosis in US is 47
  - < 20 yr age – 0/100,000/yr
  - 20-24 yr age – 1.7/100,000/yr
  - **Peak at 45-49 yr age – 16.5/100,000/yr**
  - < 10% cases in women > 75
- Histology:
  - 80% are squamous cell.
  - 20% are adenocarcinomas.
  - Rare types: neuroendocrine, glassy cell, etc

Cervical cancer: Risk factors

- Early onset of sexual activity
- Multiple sexual partners
- High risk sexual partners
- History of sexually transmitted disease
- Smoking
- Chronic immunosuppression
- Certain autoimmune diseases
- Oral contraceptive use
- Parity

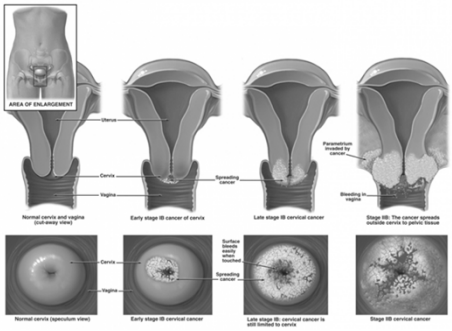
Clinical presentation

- Symptoms:
  - Asymptomatic early disease
  - Abnormal vaginal bleeding
  - Post-coital bleeding
  - Vaginal discharge: watery, mucoid, purulent, malodorous
- Exam:
  - Visible lesion: exophytic, ulcerative, endophytic
  - 15% have no visible lesions (likely adenocarcinoma)



Diagnosis

- Pelvic exam
- Pap smear
- Colposcopy with biopsies
- Conization of the cervix
- Cystoscopy
- Proctoscopy
- Imaging – CT, PET CT, MRI
- Blood work – CBC, LFTs, BMP



From: womeningovernment.org

Treatment

- Clinically staged (FIGO) versus TNM
- Early stage can be treated with surgery or chemoradiation.
  - If surgery:
    - Stage IA1 – simple hysterectomy or conization.
    - Stage IA1 with LVSI – Lymph node dissection/sentinel node.
    - Stage IA2 – IIA – radical hysterectomy with lymph node dissection.
- Stage IIB-IVA – chemoradiation.
  - May include some bulky stage IB2.
- Stage IVB – Cisplatin based chemotherapy.
  - Maybe radiation for local control, symptom management.

Surgery

- Surgical approach
  - Laparotomy – LACCS trial
- Fertility sparing surgery
  - Radical trachelectomy with lymph node dissection.
- Lymphadenectomy
  - Full pelvic +/- para-aortic dissection
  - Sentinel lymph node sampling
    - Best in tumors less than 2 cm

Recurrent disease

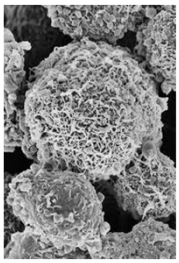
- Local recurrence
  - Surgery
    - Pelvic exenteration – morbid procedure
  - Chemotherapy
  - Radiation
- Metastatic
  - Chemotherapy
  - Radiation – if limited disease

5 year survival

- Stage IA–small IB 80 – 100%
- Large IB 75 – 90%
- Stage IIA 71 – 85%
- Stage IIB 60 – 75%
- Stage III 30 – 50%
- Stage IVA 8 –27%

Human Papilloma Virus

- Non–enveloped double stranded DNA–virus
  - HPV type 16 & 18 – 70%
  - 31, 33,45,52,58 – 20%
  - HPV 6 & 11 – 90% of anogenital warts



From: feidaunion.com

Cervical Cancer vaccines

- Recommended age 9–26
  - Approved in the US up to age 45 – particularly for increased risk individuals
- Cervarix (GSK)
  - Bivalent vaccine against HPV 16, 18 with cross protection against HPV 31
- Gardasil (Merck)
  - Quadrivalent vaccine against HPV 6, 11 (for treatment of genital warts) and HPV 16, 18.
  - Gardasil 9 – 9–valent vaccine against 6,11,16, 18, 31, 33, 45, 52, and 58

Cervical cancer vaccines

- ACIP also recommends:
  - males aged 13 through 21 years not adequately vaccinated previously.
- Gay, bisexual, and other men who have sex with men, transgender people, and for immunocompromised persons (including those with HIV infection) not adequately vaccinated previously

CDC.GOV 2018

Vulvar Carcinoma

Vulvar Cancer

- 4% of malignancies in female genital tract
- Average age 65 years but bimodal distribution
- Two etiologies:
  - Mucosal HPV infection
  - Chronic inflammatory or autoimmune process
    - Lichen sclerosus
- > 90% are squamous cell histology

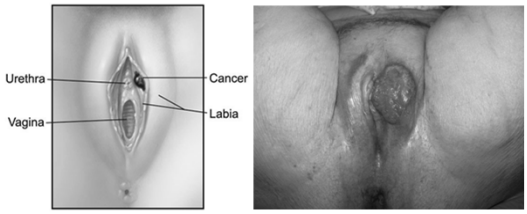
Risk factors

- Cigarette smoking
- Vulvar dystrophy (eg. Lichen sclerosis)
- Vulvar or cervical intraepithelial neoplasia
- HPV infection
- Immunodeficiency syndromes
- Prior history of cervical cancer
- Northern European ancestry

Clinical presentation

- Vulvar plaque, ulcer, or mass
- Pruritis (itching)
- Pain
- Vulvar bleeding or discharge
- Dysuria
- Enlarge lymph nodes in the groin
- Asymptomatic

Clinical presentation

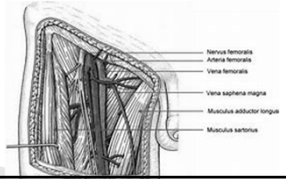


Evaluation

- Biopsy
  - Confirm diagnosis
- Rule out metastatic disease
  - PET/CT
  - MRI
- Cystoscopy
- Proctoscopy

Treatment

- Surgically staged
- Radical wide excision
- Groin lymph node dissection
  - Vulvar lesion with > 1mm depth of invasion
- Unilateral versus bilateral groin dissection
- Sentinel lymph node dissection



Treatment

- Advanced disease little chance of cure with surgery alone.
- Neoadjuvant chemotherapy and radiation.
  - Cisplatin day 1, 5 FU infusional day 1-4, repeat 3 weeks later.
  - Concurrent daily radiation.
  - Similar regimens for rectal/anal cancer.
- Followed by surgery with radical vulvectomy and inguinal lymph node dissection.
  - Adjuvant treatment allows for less morbid surgery.

Treatment

- Adjuvant radiation
  - Positive/close margins (< 8mm – fixed specimen)
  - Large tumors > 4.1 cm
  - Lymphovascular space invasion
  - 2 or more positive microscopic lymph nodes
  - 1 or more positive macroscopic lymph nodes
- Recurrent disease
  - Surgery, chemotherapy, radiation

5 year survival

- Stage I 78%
- Stage II 58%
- Stage III 43%
- Stage IV 13%

Gestational Trophoblastic Disease

Gestational Trophoblastic Disease

- Proliferative disorder from placental tissue.
  - Heterogenous group of lesions
  - Trophoblastic epithelium of the placenta
- Described by Hippocrates 400 BC
- Most curable gynecologic malignancy
  - First cure with chemotherapy 1956 Li et al

Clinical manifestations

- Vaginal bleeding
- Enlarged uterus (size > dates)
- Pelvic pressure, pain
- Theca lutein cysts
- Anemia
- Hyperemesis gravidarum
- Hyperthyroidism
- Pre-eclampsia before 20 weeks gestations
- Passage of hydropic vesicles

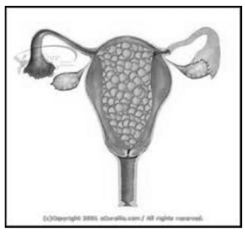
Types

- Hydatidiform Mole
  - Partial or complete
- Invasive mole
- Choriocarcinoma
- Placental Site Trophoblastic Tumor
  - Epithelioid Trophoblastic Tumor

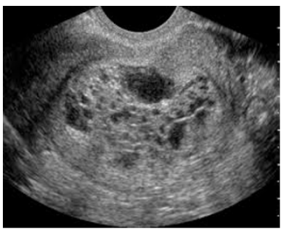
Complete mole

- Aberrant fertilization resulting in only paternal DNA (46 XX or 46 XY) by:
  - Fertilization of an empty ovum by 2 sperm
  - Fertilization of an empty ovum by single sperm that duplicates
- Lacks fetus
- Large uterine size (size > dates)
- Hydropic, edematous chorionic villi

Complete mole



From: Pregnan-cy.com



From: lookfordiagnosis.com

Partial mole

- Aberrant fertilization resulting in triploid DNA (69 XXX, 69 XXY, or 69 XYY)
  - Fertilization of ovum by 2 sperms
  - Fertilization of ovum by 1 sperm that duplicates
- Fetus/embryo present
- High rate of intrauterine death

Malignant GTN

- May follow any type of pregnancy
  - After molar pregnancy
    - Persistent disease after uterine evacuation
    - Rates: complete 15-20%, partial 3-5%
      - Follow HCG levels
    - Can be focal or metastatic
    - Most are due to invasive moles, but few choriocarcinoma
  - After regular pregnancy
    - Found by histology or noted rise/persistent of β-HCG
    - Almost always choriocarcinoma

GTN – choriocarcinoma

- Can arise from any type of pregnancy
- From cytotrophoblasts
- Aggressive
- Early vascular invasion and widespread metastasis
- Symptoms: irregular vaginal bleeding
- Exam: large uterus, ovarian cysts, vaginal metastasis (very vascular – never biopsy)

GTN – placental site trophoblastic tumor

- Can arise from any type of pregnancy
- From intermediate trophoblasts
- Rare < 0.2% of all GTNs
- Slow growing
- Diagnosed month – years after a term pregnancy.
- Tumor marker human placental lactogen (hPL)

Diagnosis and treatment

- Hydatidiform moles (benign)
  - β-HCG, ultrasound
  - Suction curettage
- Malignant GTN
  - β-HCG, Imaging (ultrasound, CT, MRI)
  - Chemotherapy first line treatment, high cure rate
  - Surgery in refractory focal disease, consider for choriocarcinoma if done with child-bearing, and for PSTT/ETT.

Staging and treatment

- Based on extent of disease involvement
  - Confined to uterus, local versus distant metastasis.
- Prognostic score
  - Based on factors such as size of lesion, β-hCG level, number and sites of metastasis, type and time from antecedent pregnancy, prior chemotherapy
  - Influences recommended treatment regimen
- Treatment with chemotherapy
  - Single agent versus combination therapy

Resources

- Education
  - Patients, primary care, specialists.
- Supportive resources
  - Social work, financial services, dietician, genetics counseling, STAR rehab program.
- Support groups/survivorship programs
- Palliative care
- Hospice

Thank you!