CREOG Review: Oncology

I. Basic Science/Mechanisms of Disease

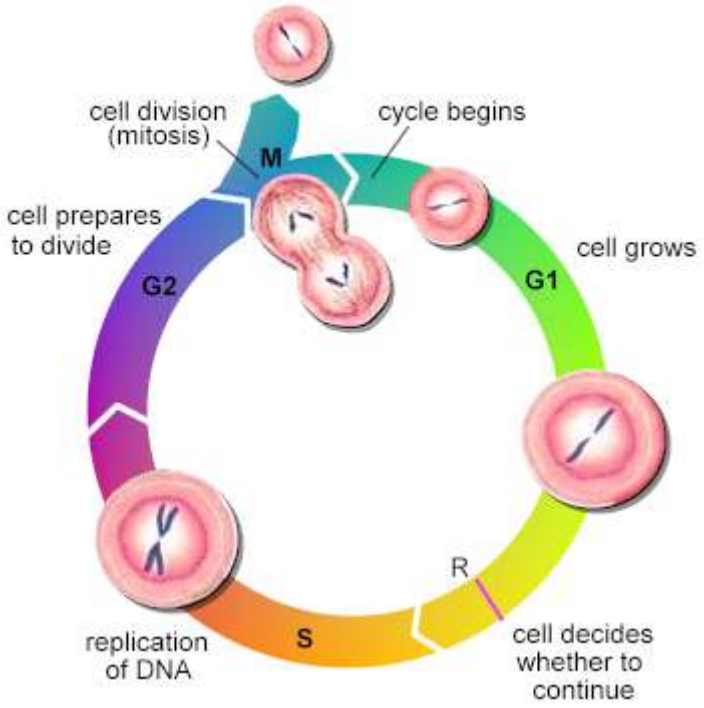
A. Genetics

Chromosomal Abnormalities:

1. Abnormalities of nuclear content: anueploidy
2. Deletions
3. Duplications
4. Rearrangements
5. Mutations of genes = proto-oncogenes, tumor suppressor genes, DNA repair genes
   - Proto-oncogenes:
     - Encode growth factors, membrane/cytoplasmic receptors and other proteins
     - Mutations behave in dominant fashion → alteration of one allele is enough to promote cancer progression
     - c-erb B and HER-2/neu → endometrial cancer
     - c-myc → cervical cancer
   - Tumor suppressor genes:
     - Prevent cell division or trigger cell death
     - Typically autosomal recessive
     - Include: p53, Rb, p16, NF1, WT1, BRCA1, BRCA2
     - Mutations are "loss-of-function" mutations such as frameshifts, nonsense, deletions
     - p53 mutation → chemoresistance to platinum-based therapy
   - DNA repair genes:
     - Encode protein products that repair or remove damaged DNA
     - Example: DNA mismatch repair errors cause 25% of endometrial cancers; deficient DNA repair predisposes to HNPCC

** Normal tissue demonstrates a balance between cell proliferation and cell death
When proliferation exceeds cell death → hyperplasia
When death exceeds cell proliferation → atrophy

Cell cycle



G1 (Gap 1) → Synthesis (S) → G2 (Gap 2) → Division

G1: preparation for DNA synthesis
Synthesis: DNA synthesis, DNA content doubles
G2: Resting period
Division: Mitosis

Phases of cell cycle most sensitive to chemotherapy

- **Alkylating agents**:
  - attack the negatively charged sites on the DNA (oxygen, nitrogen, phosphorous and sulfur atoms), bind to DNA, leads to DNA strand breaks and DNA strand cross-linking causing cell death
  - active in every phase of the cell cycle
  - Examples: Cyclophosphamide, Ifosfamide, Melphalan, Chlorambucil, Dacarbazine, Procarbazine, Busulfan, and Thiotepa.

-**Antimetabolites:**
  - Interfere with normal metabolic pathways, including those necessary for making new DNA.
  - Most widely used is Methotraxate (MTX), which is an antifolate that inhibits a crucial enzyme required for DNA synthesis, MTX exerts its effect on the S phase of the cell cycle.
  - Another example: 5-Fluorouracil (5-FU) prevents DNA synthesis by interfering with the nucleotide (DNA components) production.

- **Anthracyclines**:
  - Work by the formation of free oxygen radicals
  - Radicals result in DNA strand breaks and subsequent inhibition of DNA synthesis and function.
  - Examples: daunorubicin, doxorubicin.

- **Plant alkaloids**:
  - Etoposide (called topoisomerase II inhibitor) works in the late S and G 2 phases.
  -Vincristine, vinblastine, and vinorelbine bind to the tubulin and lead to the disruption of the mitotic spindle apparatus.

- **Taxanes:**
  - Specific for the M phase of the cell cycle
  -Bind with high affinity to the microtubules and inhibit their normal function.
  -Examples: paclitaxel and docetaxel.

-**Platinums:**
  - Cross-link DNA subunits
  -Can act in any cell cycle.

Inheritance patterns for malignancies of pelvic organs and breast

- Cervical, vaginal, vulvar: no known inheritance pattern
- Endometrial: most cases are sporadic; however rare cases due to HNPCC are autosomal dominant
- Ovarian: HNPCC, BRCA 1, BRCA2

BRCA1 and BRCA2

- BRCA 1 → on chromosome 17
- BRCA2 → on chromosome 13; may respond to radiation better than BRCA 1
- Most BRCA mutations result in truncated, nonfunctional proteins

- BRCA 1 mutation
  → lifetime risk of developing breast ca by age 80 = 73.5%
  → lifetime risk of developing ovarian ca by age 80 = 27.8%
  (baseline risk for general pop of developing breast ca is 12.5% (1 in 8 by age 90) and risk of ov ca is 1.5%)

- BRCA 2 mutation
  → risk of breast ca similar to that in patients with BRCA 1 mutation
  → risk of ovarian ca is lower than that in patients with BRCA 1 mutation

B. Physiology

Therapeutic index:

- a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxic effects
- commonly described as the lethal dose of the drug for 50% of the population (LD50) divided by the effective dose for 50% of the population (ED50) → LD50/ED50

C. Embryology and developmental biology

Gonadal migration:
- primordial germ cells (gonocytes) migrate the genital ridges
- the coelomic epithelium and underlying mesenchyme of the genital ridges proliferate
- the primordial germ cells (gonocytes) undergo mitosis
- the early gonad divides into a peripheral cortex (coelomic epithelium) and a medulla (mesenchyme and gonocytes)

Embryologic origins of cell types
- coelomic epithelium → ovarian surface epithelium = origin of epithelial tumors
- gonocytes → germ cells = origin of germ cell tumors
- mesenchyme → stroma = origin of sex cord stromal tumors

D. Anatomy

Anatomy of the Anterior and Abdominal Wall
- Skin
- Subcutaneous tissue
- Camper's fascia
- Scarpa's fascia
- External oblique mm
- Internal oblique mm
- Transversus abdominus mm
- Transversalis fascia
- Preperitoneal fat
- Peritoneum

Vascular, Lymphatic and Nerve supply to the pelvic organs/external genitalia

Blood vessels: visceral (supply organs) vs. parietal (supply supporting structures)

Ovarian
- arises from the ventral surface of the aorta just below the origin of the renal vessels
- crosses over the common iliac vessels
- crosses over the ureter and then runs lateral to the ureter when entering the pelvis as the infundibulopelvic ligament
- provides blood supply to the ovaries, fallopian tubes, broad ligament and ureter
- venous drainage drains on right into the IVC and on left into the renal vein

Inferior mesenteric
- retroperitoneal
- arises from the left side of the aorta 2-5 cm proximal to the bifurcation
- passes over the left psoas muscle
- divides into the left colic, sigmoid and superior rectal (hemorrhoidal) arteries
    - left colic supplies the left transverse colon, splenic flexure and descending colon
    - sigmoid supplies the sigmoid colon
    - superior rectal supplies the rectum
- inferior mesenteric vein empties into the splenic vein

Common iliac
- Terminal division of the aorta at the 4th lumbar vertebra
- Divides into internal (hypogastric) and external iliac arteries

Internal (hypogastric): divides into anterior and posterior divisions 3-4 cm after its origin off of the common iliac
- Anterior division: iliolumbar, lateral sacral, superior gluteal
- Posterior division: obturator, uterine, umbilical, middle rectal, internal pudendal, inferior gluteal, superior vesicle, vaginal
    - internal pudendal artery branches into the inferior rectal, perineal, clitoral

External iliac → femoral artery (when it passes under the inguinal ligament)
- branches into the superficial epigastric, external pudendal, superficial circumflex iliac, inferior epigastric, deep circumflex iliac

- superficial epigastric: supplies skin/subcutaneous tissue of the lower abd wall
- external pudendal: supplies skin/subcutaneous tissue of the mons and anterior vulva
- superficial circumflex iliac: supplies musculofascial layer of the lower abd wall
- inferior epigastric: supplies the musculofascial layer of the lower ant abd wall
- deep circumflex iliac: supplies the musculofascial layer of the lower abd wall

Middle sacral
- arises from the posterior aspect of the aorta in the midline
- courses over the lumbar vertebrae, sacrum and coccyx
- supplies the bones/muscles of the posterior pelvic wall

Lumbar
- multiple arteries that arise at each lumbar level from the posterior aorta
- supply the abd wall musculature (ext/internal oblique, and transverses abdominus)

Lymphatics
- Follow the course of the larger pelvic vessels
    - Obturator: where the obturator nerve and vessels enter the obturator canal
    - External iliac: lateral to the artery, between the artery and the vein on the medial aspect of the vein
    - Internal iliac: in the adipose tissue on the lateral pelvic sidewall, adjacent to the internal iliac artery
    - Inguinal: along the inguinal ligament, both superficial and deep
    - Sacral
    - Paraaortic: along the aorta
- Cloquet (Rosenmuller) node: highest of the deep inguinal nodes that lies within the opening of the femoral canal
- Vulva/lower vagina → drain to superficial and deep inguinal nodes and sometimes to the iliac nodes
- Cervix/upper vagina→ drain to the parametrial, obturator, external iliac nodes, sacral nodes
- Uterus → parametrial, internal/external iliac, paraaortic nodes
- Ovaries → internal/external iliac, paraaortic nodes

Nerves

Lumbosacral plexus = iliohypogastric, ilioinguinal, lateral femoral cutaneous, femoral, genitofemoral, obturator, superior gluteal, inferior gluteal, posterior femoral cutaneous, sciatic, pudendal
- provides motor and sensory innervation to the lower abd wall, pelvic and urogenital diaphragms, perineum, hip and lower extremity
- found on the anterior surface of the piriformis muscle, lateral to the coccyx, deep in the posterior pelvis

Ilioinguinal nerve (L1)
- anerior labial branch emerges from the inguinal canal through the superficial inguinal ring to the mons and labia majora
- provides sensory innervation to the upper medial thigh, mons and labia majora

Genitofemoral nerve (L1, L2)
- genital branch enters the inguinal canal with the round ligament and passes through the superficial inguinal ring to the anterior vulva
- sensory innervation to anterior vulva (genital branch), middle/upper thigh (femoral branch)

Obturator (L2, L3, L4)
- travels along the lateral pelvic wall and passes through the obturator foramen into the upper thigh (encountered during radial dissections (lymphadenectomy) and paravaginal repairs)
- provides sensory innervation to the medial thigh
- provides motor innervation to the adductor muscles of the thigh

Pudendal nerve (S2, S3, S4)
- crosses over the piriformis to travel with the internal pudendal vessels into the ischiorectal fossa
- divides into 3 terminal branches in the ischiorectal fossa and provides primary innervation of the perineum
- provides sensory innervation to perianal skin, vulva, perineum, clitoris, urethra, leg and foot muscles
- provides motor innervation to the external anal sphincter, perineal muscles, urogenital diaphragm

Posterior femoral cutaneous nerve (S2, S3)
- leaves the pelvis through the greater sciatic foramen, runs in front of the ischial tuberosity to the lateral perineum and labia majora
- sensory innervation to the vulva and perineum

Carcinoma of the Breast

A. Risk assessment of breast cancer (see table from Precis)
B. Screening methods
1) Mammography
- ACS: yearly mammo starting at age 40
- NCI: mammo every 1 or 2 years starting at age 40
- ACOG: mammo every 1 or 2 years from 40-49, then annually thereafter
2) Breast ultrasound
- used to distinguish between solid and cystic masses and as adjuvant for biopsy
- low specificity, therefore not a good screening tool
3) MRI
- no role in breast cancer screening
- high sensitivity, but low specificity

B. Who to refer for genetic counseling: high-risk family history; Gail model (age, age at menarche, previous breast biopsies, at at first live birth, family history of breast cancer in first-degree relatives (check it out online)

C. Diagnosis of suspicious breast lesion
Perform history and physical exam
Order appropriate tests:
- Bilateral mammo and other imaging studies as needed
- FNA (false neg rate 3-35%, false positive rate <1%)
- Return 4-6 wks if cyst aspirated and any remaining mass should be excised, recurrent cyst should also be excised
- Needle biopsy and localization
- tissue diagnosis is preferred over FNA prior to surgical management
- sterotactic biopsy
- uses specialized mammo equipment and is best for calcifications
- if atypia is seen surgical excision is recommended b/c 50% chance of finding coexistent carcinoma
- localizing clip can be placed through biopsy probe to facilitate localization
- if lesion is seen on sono, perform sono-guided biopsy with14-gauge core needle
-Surgical excision
-Ductal lavage

D. Invasive Cancer
- 2 types: ductal and lobular
-Ductal: most common, represents 65-80% of mammary carcinomas; associated with inflammatory carcinoma
- Lobular: 10-14% of invasive carcinomas, "Indian file"
- Mets: most commonly from lung, ovaries, uterus, kidneys, stomach

E. Staging
- Stage 1: tumor ≤ 2 cm
- Stage 2: tumor ≥ 2 cm but ≤ 5 cm
- Stage 3: tumor ≥ 5 cm
- Stage 4: tumor of any size with direct extension to chest wall, skin

F. Treatment
- Mastectomy: removal of breast, pectoralis, axillary contents
- Breast conservation therapy: wide local excision with 1-2 cm margin
-Sentinal node biopsy: blue dye and radioisotope used; successful ID occurs 92-98% of time

G. Prognostic factors
- axillary lymph node status: most important prognostic factor

F. Treatment
-Adjuvant chemo: standard treatment in those with positive nodes/large tumors/Her-2/neu/postmenopausal; Cyclophosphamide/MTX/5FU (CMF); 5FU/Adriamycin/Cyclophosphamide (FAC)
-Anti-Hormonal rx: for met dz for palliation, dz stabilization; tamoxifen, aromatase inhibitors (letrozole, anastrozole); 20% response in ER/PR + tumors
- Radiation: in conjunction with lumpectomy

Vulvar Malignancies

A. Epidemiology
- 3-5% of all gynecologic malignancies
- 90% of cases are invasive squamous cell cancers
- risk factors: sexual activity, genital condyloma, smoking, preinvasive/invasive genital tract lesions, chronic vulvar conditions (lichen sclerosis)
- develop slowly over years
- incidence in pts with HIV is 4-5x that of that in the general population

B. VIN = vulvar intraepithelial neoplasia
- VIN 1: neoplastic changes in lower 1/3 of epithelium
- VIN 2: neoplastic changes in $\geq$ 1/3 but $\leq$ 2/3 of epithelium
- VIN 3: CIS, neoplastic changes in $\geq$ 2/3 of epithelium

C. Evaluation/treatment of VIN
- Look for red, irritated, pigmented, ulcerated, thickened skin → no direct association b/t intraepithelial changes and their macroscopic appearance
- Punch biopsy
- Surgery: superficially removes abnormal cells via WLE in elliptical fashion or laser vaporization of VIN 3
- Topical chemotherapeutic treatment: usually painful and ineffective
- Asymptomatic VIN 1 and 2: can be observed
- Surgical evaluation of nodes not needed as is not an invasive process
- Recurrence at original site even with negative margins is 15-20%

D. Invasive vulvar cancer
- Staging is surgical:
    - Stage 1: tumor confined to perineum, vulva or both; $\leq$ 2 cm in greatest dimension; 1a stromal invasion no greater than 1 mm; 1b stromal invasion greater than 1 mm
    - Stage 2: tumor confined to perineum, vulva or both; $\geq$ 2 cm in greatest dimension
    - Stage 3: tumor of any dimension with one or both of the following: adjacent spread to lower urethra, vagina, anus
    - Stage 4a: tumor of any dimension with one or both of the following: spread to upper urethra, bladder mucosa, rectal mucosa, or pelvic nodelower urethra, vagina, anus; 4b distant mets

E. Treatment of invasive cancer: local excision +/- lymphadenectomy +/- chemoradiation
- Lateral lesion
- Medial lesion
- Depth of invasion: < 1 mm risk of spread to groin nodes is <1%, 1-2 mm invasion risk of spread 11%, 2-3 mm 15%, 3-5 mm 18%, > 5mm 46%

F. Prognostic factors
- Lymph nodes: number (1-2 < 5 mm: surgical removal; 3+ nodes: surgery and radiation), size (5-15 mm predict increased risk for mets), status of capsule (intact vs. ruptured)

G. Other invasive vulvar lesions:
- **Paget's disease:** postmenopausal women, itching, irritation, burning with urination; intraepithelial neoplastic process; associated with invasive adenoca of the apocrine glands; may be associated with breast, colon, bladder, cervix; WLE to 6 mm is needed
- **Verrucous carcinoma:** appears as large exophytic condylomatous lesion, rarely metastasizes; surgical excision required
- **Sarcoma:** cancers of mesenchymal elements of the vulva, usually are leiomyosarcomas; surgical excision required
- **Melanoma:** second most frequent malignancy of vulva, accounting for 6% of vulvar malignancies; occur mostly in Caucasians, mean decade of occurrence is 7th, presents with irritation/pruritis/mass/bleeding/irritation; treatment is WLE with > 2 cm margins in width/depth
- **Bartholin's gland carcinoma:** 4 types: squamous cell, transitional cell, adenocarcinoma, adenoid cystic carcinoma; if gland enlarges in postmenopausal woman or if gland enlargement recurs in a premenopausal pt prompt management with ipsilateral inguinal/femoral lymphadenectomy is recommended
- **Basal cell carcinoma:** rare, accounts for <2% of all vulvar neoplasms; occurs in 6^{th}-8^{th} decades of life; slowly growing ulcerative lesion with raised border and necrotizing center; palisading cells at edge of tumor; rarely metastasize; treatment is WLE

Vaginal malignancies

A. Epidemiology
- risk factors: HPV, smoking, previous abnormal cervical or vaginal cytologic studies
- rare → represents <1% of all gynecologic malignancies
- peak incidence age 65
- 90% of lesions are squamous
- 80% asymptomatic
- presentation: vag bleed, vag discharge (watery/malodorous), dysuria, urgency, constipation, pain

B. VAIN
- often presents as postcoital staining or unusual vag discharge
- usually occurs in the upper 1/3 of the vagina on posterior wall, often multifocal
- in postmenopausal women, VAIN 1 and 2 often result of lack of estrogen/atrophic change → treat with estrogen
- postirradiated vagina may be interpreted as VAIN 3

C. Staging
- Stage I: measure 0.5-1 cm in thickness; treated with irradiation
- Stage IIa: subvaginal infiltration without involvement of the parametrium; treatment with whole pelvic irradiation with intracavitary and possibly interstitial radiation + chemosensitization; if lesion involves vaginal apex, some consider radical surgery +/- postop irradiation
- Stage IIb: parametrial infiltration without extension to side wall
- Stage III: tumor extends to pelvic sidewall
- Stage IVa: tumor invades the mucosa of the bladder or rectum, extends beyond the true pelvis or both
- Stage IVb: distant meds

D. Other vaginal cancers:
- **Verrucous carcinoma:** rare variant of well-diff squamous cell carcinoma; presents as large cauliflower-like mass; strong relationship between HPV 6 and verrucous carcinoma
- **Malignant melanoma:** second most common vaginal neoplasm = 5% of all vaginal neoplasms; tumors may be pigmented, nonpigmented, eroded or ulcerated; frequently occurs in the distal 1/3 of the vagina; poor prognosis; treatment radiation followed by total vaginectomy
- **Endodermal sinus tumor:** rare; elaborate alpha-fetoprotein; BEP +/- conservative surgery
- **Lymphoma:** diffuse large cell; treated with combo of external and intracavitary irradiation and chemotherapy = CHOP
- **Clear cell adenocarcinoma:** associated with DES; 1:1000 exposed during fetal life; age at dx 7-34 yo; occurs mainly in upper 1/3 of ant vaginal wall; 90% are stage 1-2 at dx; treated with intracavitary or transvaginal radiation or possibly rad hyst and vaginectomy with PPALND; 5 year survival for stage 1 is 90% and for stage 2 is 80%; behaves less aggressively than clear cell that develops in absence of DES exposure

TOPIC:_Gynecologic Oncology/Critical Care

KEY TOPICS

1. Pre-invasive cervical disease

Epidemiology of cervical dysplasia:

- Incidence: 50 million women screened each year in U.S., 7% have abnormal test
  - ASCUS/ASC-H: 2 million/yr
    - ASCUS → 5-17% chance of histologic CIN2/3
    - ASC-H → 24-94% chance of histologic CIN2/3
  - LSIL: 1 million/yr → 15-30% chance of histologic CIN2/3
  - HSIL: 200-300,000/yr → 70-75% chance of histologic CIN2/3, 1-2% chance of invasive cancer
- Lifetime cumulative incidence of HPV: 70%+

Pertinent history: prior abnormal Pap smears, colpo, and ablation/excisions, lifetime and current sexual activity, history of sexually transmitted infections, condom use, smoking hx

Bethesda Classification (2001)

- Specimen adequacy
- Negative for intraepithelial lesion or malignancy
- Atypical squamous cells of undetermined significance (ASC-US)
- Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Atypical glandular cells (AGC)
- Endocervical adenocarcinoma in situ (AIS)

Diagnostic procedures for pre-invasive cervical disease:

- Papanicolaou smear (liquid-based)
  - Sensitivity 86%, specificity 88% for detection of ≥CIN3 with threshold of ASC-US in primary screening
  - Sensitivity 71%, specificity 96% for detection of ≥CIN3 with threshold of LSIL in primary screening

  (from Ferreccio *et al. Cancer Epidemiol Biomarkers Prev* 2003;12:815-23).
- HPV testing
  - Sensitivity 85%, specificity 88% for detection of ≥CIN3 in primary screening

  (from Ferreccio *et al. Cancer Epidemiol Biomarkers Prev* 2003;12:815-23).
- Colposcopy
  - Considered the gold standard
  - LSIL Pap → colpo sensitivity 56% for detection of ≥CIN3 over 2 yrs (ALTS)
  - ASC-US Pap → colpo sensitivity 54% for detection of ≥CIN3 over 2 yrs(ALTS)
  - Poor interobserver reliability
- Colposcopic-directed biopsy
  - Sensitivity 73% for detection of ≥CIN2 (ALTS)
  - Sensitivity increases with each biopsy taken
- Endocervical curettage
  - Sensitivity 12% for detection of ≥CIN2 (ALTS)
  - More useful in older women

Therapeutic procedures for pre-invasive cervical disease:

- Loop electrosurgical excision procedure (LEEP)
- Cold knife conization

- Cryotherapy ablation
- Carbon dioxide laser ablation

Complications of treatment for cervical dysplasia:
- Preterm delivery, PPROM, intraoperative hemorrhage

Follow-up of women treated for cervical dysplasia:
- CIN1 on cervical bx followed by CIN2/3 on LEEP
  - Pap smear at 6 and 12 months → colpo for ≥ASC-US
    OR
  - HPV testing at 12 months → colpo if hi-risk +
    OR
  - Repeat colpo and Pap smear at 12 months
  - Once Pap smears normal, pt may return to annual screening
- CIN2/3 in LEEP/CKC specimen
  - Negative margins → Pap smear every 4-6 months until 3 normal, then resume annual screening
  - Positive margins
    - Pap smear, colpo, and ECC every 4-6 months
      OR
    - Another excisional procedure
- Pregnancy
  - follow CIN1 and repeat colposcopy 6 wks postpartum
  - manage CIN2/3 conservatively unless invasion cannot be ruled out
  - biopsies are safe; ECC should not be performed

In-utero diethylstilbestrol (DES) exposure
- Structural changes in the cervix

2. Invasive cervical cancer
EPIDEMIOLOGY:
- Incidence 11,150 cases/yr
- Mortality 3,670/yr
- Mean age 47 years; bimodal distribution (peaks 35-39, 60-64 yo)
- 2nd most common cancer in women worldwide, 3rd most common gynecologic malignancy in U.S., 3rd most common cause of death from gynecologic cancers in U.S.

Risk factors:
- Persistent infection with carcinogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
- Early age at first intercourse
- Smoking
- Increased parity
- Infection with *Chlamydia,* HSV
- Socioeconomic status
- Race
- Immunosuppression (HIV; Fanconi's anemia)
- Oral contraceptive use (Lancet 2007;370:1609-21)

Clinical manifestations include postcoital bleeding, abnormal vaginal bleeding, weight loss, dyspareunia, urinary frequency, lower extremity edema, anemia

FIGO Staging: CLINICAL. Staging procedures include inspection, palpation, colpo, ECC, biopsy of cervix/bladder/rectum, conization, hysteroscopy, cystoscopy, proctoscopy, IV urography, xrays.

Stage	Criteria	Treatment
I	*Diagnosed by microscopy only; confined strictly to the cervix*	
A1	Stromal lesion ≤3mm deep, width ≤7mm wide	Conization, Type I or II hyst ± PLND
A2	Lesion depth 3-5 mm, width < 7mm	Type II hyst or rad trach ± adjuvant tx
B1	Lesion depth >5mm, width ≤ 4 cm	Type III hyst, PPALND ± adjuvant tx v. 1˚ chemoradx
B2	Lesion depth >5 mm, width > 4 cm	
II	Extension beyond cervix into the upper 2/3 of vagina. Pelvic wall not involved.	
A	No parametrial involvement	Type III hyst, PPALND ± adjuvant tx v. 1˚ chemoradx
B	Parametrial involvement	Chemoradxt
III	Extension into the pelvic wall; lower 1/3 of vagina; all cases of hydronephrosis or nonfunctioning kidney not due to other causes	
A	No extension to pelvic wall	Chemoradxt
B	Involve wall and/or hydronephrosis or nonfunctioning kidney	
IV	Beyond true pelvis, or in bladder, or rectal mucosa	
A	Spread to adjacent organs	Chemoradxt
B	Spread to distant organs	Palliative

Poor prognostic factors:

- Older age
- AA race
- Low socioeconomic status
- Immunocompromised
- Adenocarcinoma subtype
- Poorly differentiated
- Higher FIGO stage
- Positive lymph nodes and absolute number of positive lymph nodes
- Large tumor volume (bulky)
- Increased depth of invasion

5-year survival rates by FIGO stage:
Stage I – 85%
Stage II – 66%
Stage III – 39%
Stage IV – 11%

3. Carcinoma of the uterus
Endometrial hyperplasia

Risk factors:
- Obesity
- Anovulation
- Polycystic ovary syndrome
- Glucose intolerance
- Estrogen or antiestrogen exposure
- Family history
- Smoking, OCP use (protective)

Physical exam: hirsutism, acne, bimanual exam, Pap smear, endometrial biopsy

10-year risk of hyperplasia depends on histologic grade:
Simple hyperplasia, no atypia → 1%
Complex hyperplasia, no atypia → 3%
Simple hyperplasia with atypia → 8%
Complex hyperplasia with atypia → 29%

Endometrial cancer
EPIDEMIOLOGY:
- 4th most common cancer in women
- Most common gynecologic cancer: 39,000 cases/yr in U.S.
- 73% of cases localized at diagnosis

Hereditary Non-Polyposis Cancer (HNPCC) syndrome – 39% risk of endometrial cancer by age 70

Clinical manifestations of endometrial cancer:
- Postmenopausal bleeding (10% is cancer)
- Perimenopausal menometrorrhagia
- Endometrial cells on Pap smear in women >40yo
- Thickened endometrial stripe (>5mm) on pelvic ultrasound

FIGO Staging (SURGICAL):

Stage	**Description**	5-year survival
IA	Limited to the endometrium	**90%**
IB	Invasion to <1/2 myometrium	**90%**
IC	Invasion to >1/2 myometrium	**81%**
IIA	Endocervical glandular involvement	**80%**
IIB	Cervical stromal involvement	**72%**
IIIA	Tumor invades serosa and/or adnexa and/or positive peritoneal cytology	**63%**
IIIB	Vaginal metastases	**39%**
IIIC	Metastases to pelvic and/or paraaortic LN	**51%**
IVA	Tumor invasion of bladder and/or bowel mucosa	**20%**
IVB	**Distant metastases, including intra-abdominal and/or**	**17%**

	inguinal LN	

Treatment of endometrial cancer is based on:
- Stage
- Grade
- Histologic type
- Pt's ability to tolerate further tx

- Medical treatment (ideal for pts with early disease who wish to preserve fertility): progesterone

Surgical tx:
- Hysterectomy
- Radical hyst if cervical involvement (stage II)
- Optimal cytoreductive surgery (stages III, IV)

Adjuvant tx:
- Chemotherapy
  - Following optimal cytoreductive surgery
  - Carboplatin and taxol for clear cell and serous tumors
- Radiation therapy
  - Vaginal brachytherapy for cervical involvement or vaginal recurrence
  - Pelvic external beam radiation

4. Ovarian and tubal carcinoma

A. Carcinoma of the ovary

Epidemiology:
- Ranks 1st in gynecologic cancer deaths
- Incidence 22,430 women/yr in U.S.
- Mortality 15,280 women/yr in U.S.
- Types
  - Epithelial 85-90%
    - Papillary serous 75%
    - Mucinous 10%
    - Endometrioid 10%
    - Brenner
    - Clear cell
    - Mixed
  - Germ cell tumors 20-25%
    - Dysgerminoma
    - Endodermal Sinus (Yolk Sac) Tumors
    - Embryonal
    - Polyembryoma
    - Immature teratoma
  - Sex cord stromal tumors 5-8%
    - Granulosa cell
    - Thecoma
    - Fibroma
    - Sertoli-Leydig
    - Gynandroblastoma
  - Borderline tumors of low malignant potential

Risk of malignancy in an adnexal mass

- Premenopausal woman 7%
- Postmenopausal woman 30%

Risk factors for epithelial ovarian cancer:

- Family hx
- Age
- Race (Caucasian)
- Nulligravity
- Infertility
- Early age at menarche
- Late age at menopause
- OCP use (protective)
- Hysterectomy (protective)
- Tubal ligation (protective)
- Past pregnancy (protective)

Clinical manifestations include bloating, abdominal discomfort/pain, abdominal distention, constipation, fatigue, urinary frequency, dyspareunia, indigestion, nausea/vomting, dyspnea

Screening:

- currently no good screening method for the general population
- women with family hx, BRCA mutations, Lynch II Syndrome – pelvic exam, TVUS, CA-125, Doppler imaging Q 6 months; prophylactic oophorectomy after child-bearing complete

FIGO Staging (SURGICAL):

Stage	**Criteria**
I	*Growth limited to the ovary*
IA	Growth limited to one ovary; no malignant ascites. No tumor on the external surface; capsule intact
IB	Growth limited to both ovaries; no malignant ascites. No tumor on the external surface; capsule intact
IC	Tumor either stage Ia or Ib but with tumor on the surface of one or both ovaries; or with capsule ruptured, or with ascites present containing malignant cells or with positive peritoneal washings
II	*Growth involving one or both ovaries with pelvic extension*
IIA	Extension and/or metastases to the uterus and/or tubes
IIB	Extension to other pelvic tissues
IIC	Tumor either atage IIA or IIB, but with tumor on the surface of one or both ovaries; or with capsule ruptured, or with ascites present containing malignant cells or with positive peritoneal washings
III	*Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis = stage III. Tumor limited to true pelvis, but with histologically proven malignant extension to small bowel or omentum.*
IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces

IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative.
IIIC	Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
IV	*Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytologic test results. Parenchymal liver metastasis = stage IV.*

Treatment of epithelial ovarian cancers:

- Surgery - Optimal cytoreductive (<1 cm in diameter) surgery with staging (extent depends on size of tumor but may include free fluid ± washings, exploration and biopsies, appendectomy, omentectomy, splenectomy, pelvic and para-aortic lymph node dissection)
- Chemotherapy
    - carboplatin and taxol for 6-8 cycles following OCRS
    - Intraperitoneal for Stage III per GOG 172
    - Neoadjuvant: carboplatin/taxol for 3 cycles preceding OCRS
    - Second-line: doxorubicin, adriamycin, cytoxan

5-year survival rates:

- Stage I – 80-90%
- Stage II – 60-70%
- Stage III – 30-60%
- Stage IV - <20%

B. Carcinoma of the fallopian tube

EPIDEMIOLOGY

- <1% of all gynecologic cancers
- Incidence 3.3/1,000,000
- Potential risk factors
    - Age (peak in 60-70s)
    - Nulliparity
    - Infertility
    - BRCA mutation (0.6-3% lifetime risk)
    - Higher socioeconomic status
- Treatment
    - optimal cytoreductive surgery with staging
    - chemotherapy – platinum + paclitaxol
- 5-year survival rates:
    - Stage I – 80-95%
    - Stage II – 75-85%
    - Stage III – 60-70%
    - Stage IV – 30-45%

5. Gestational trophoblastic disease

EPIDEMIOLOGY:

COMPLETE MOLE

- 46,XX or 46,XY – from empty ova and 2 sperm
- 15% invade locally (malignant GTD)

- 4% metastasis
- Incidence 1/1945 pregnancies
- 25% have size>dates

PARTIAL MOLE
- 69,XXY or 69,XXX – from egg and 2 sperm
- 2-4% persist

CHORIOCARCINOMA
- 50% follow mole
- 25% follow normal pregnancy
- 25% follow miscarriage/termination

PLACENTAL SITE TROPHOBLASTIC TUMOR
- Human placental site lactogen (HPL) elevated
- Tx: hysterectomy

Clinical manifestations: delayed menses/pregnancy, vaginal bleeding, size>dates, PEC in 1st trimester, hyperthyroidism, respiratory distress

PROGNOSIS: WHO Scoring System

	0	1	2	**4**
Prognostic factors				
Age	<39	>39		
Previous pregnancy	Mole	Abortion	Term	-
Interval (months)	<4	4-6	7-12	**>12**
Beta-hCG (miU/ml)	<1,000	1,000-10,000	10,000 – 100,000	**>100,000**
ABO groups	-	O or A	B or AB	-
Largest tumor including uterine (cm)	-	3-5	>5	-
Site of metastases	Lungs, pelvis, vagina	Spleen, kidney	GI tract, liver	**Brain**
No. of metastases	-	1-3	4-8	**>8**
Prior ChemoTx	-	-	**Single**	**Multiple**

Low risk = 0-4
Intermediate risk = 5-7

High risk = >8

Treatment:

- Score<8 → single agent chemorx (actinomycin, methotrexate)
- Score>8 → EMA-CO (etoposide, methotrexate, dactinomycin, vincristine, cyclophosphamide)

Follow-up: beta-hCG levels every month for one year