CREOG Review: Oncology

I. Basic Science/Mechanisms of Disease

A. Genetics

Chromosomal Abnormalities:

1. Abnormalities of nuclear content: aneuploidy
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 frame shifts, 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 Methotrexate (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.

- **Anthacyclines:**
  - 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 G2 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
  - Paraaoortic: 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)
- anterior 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 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
      - stereotactic 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 with 14-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
   - Sentinel 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 \( \geq \frac{1}{3} \) but \( \leq \frac{2}{3} \) of epithelium
- VIN 3: CIS, neoplastic changes in \( \geq \frac{2}{3} \) 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 6th-8th 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 irrigation 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

- HPV testing
  - Sensitivity 85%, specificity 88% for detection of ≥CIN3 in primary screening

- 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.

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

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):**

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Growth limited to the ovary</td>
</tr>
<tr>
<td>IA</td>
<td>Growth limited to one ovary; no malignant ascites. No tumor on the external surface; capsule intact</td>
</tr>
<tr>
<td>IB</td>
<td>Growth limited to both ovaries; no malignant ascites. No tumor on the external surface; capsule intact</td>
</tr>
<tr>
<td>IC</td>
<td>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</td>
</tr>
<tr>
<td>II</td>
<td>Growth involving one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension and/or metastases to the uterus and/or tubes</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to other pelvic tissues</td>
</tr>
<tr>
<td>IIC</td>
<td>Tumor either stage 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</td>
</tr>
<tr>
<td>III</td>
<td>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.</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces</td>
</tr>
</tbody>
</table>
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

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**PROGNOSIS: WHO Scoring System**

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

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