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Cervical Intraepithelial Neoplasia

Incidence
- 1:1000

Age
- Range 30-40 years. Mean age for CIS is 38 years.

Etiology
- **High risk factors**: review invasive cervical cancer

Macroscopic
- Most patients have multifocal (multicentric) lesions.

Microscopic
- Columnar epithelium: cervical intraepithelial glandular neoplasia (adenocarcinoma in situ)
- Squamous epithelium:

<table>
<thead>
<tr>
<th>CIN</th>
<th>Histopathology findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>abnormal cells in the lower 1/3 of the epithelium (mild dysplasia)</td>
</tr>
<tr>
<td>II</td>
<td>abnormal cells in the lower 2/3 of the epithelium (moderate dysplasia)</td>
</tr>
<tr>
<td>III</td>
<td>abnormal cells in almost all layers of the epithelium (severe dysplasia)</td>
</tr>
<tr>
<td></td>
<td>abnormal cells in all layers of the epithelium (Carcinoma in situ)</td>
</tr>
</tbody>
</table>

- **criteria:**
  1. cells: irregular in size, shape, arrangement i.e., loss of polarity
  2. nuclei: larger, increased N/C ratio, darkly stained, hyperchromatic, well apparent nuclei, increased mitotic figures
  3. no invasion of the basement membrane

Diagnosis
- **cytology**: Pap smear is a screening test
  1. **protocol:**
     a. Initial screening: age 21. Screening **MUST** be initiated at the same age for women who have been vaccinated against HPV 16 and 18 because there are other **HIGH** risk subtypes of HPV that are **oncogenic**.
     b. Initial negative smear in low-risk individuals: repeat every 2 years. Following 3 negative smears, repeat every 3 years.
     c. Initial negative smear in high risk individuals (HPV infection, HIV infection, DES offspring): Repeat the smear **ANNUALLY**.
  2. **procedure:**
     a. NO vaginal douche for 24 hours before cytologic sampling.
     b. Smears should not be obtained during menses.
     c. STOP Intravaginal medications for at least 1 week before cytologic sampling.
     d. the cervix must be sampled at the squamocolumnar junction (Transformation zone is the region between the original & new SCJ):
        - (1) epithelium of the ectocervix by scraping it using a spatula (Ayre’s).
(2) epithelium of the endocervix by either a saline moistened cotton-tipped applicator or endocervical brush.

e. Fixation in 95% ethyl alcohol. After staining the smear is interpreted.

3. Interpretation: Bethesda classification:
   a. Within normal limits (negative for intraepithelial lesion or malignancy):
      (1) Infections: treat specific agent if symptomatic (i.e., candida, trichomonas).
      (2) Reactive and reparative changes: nonspecific inflammatory changes are probably not
          significant except if the patient is symptomatic. They generally do not require a
          response.
   b. Epithelial cell abnormalities
      (1) Squamous cells:
          (a) atypical squamous cells: repeat smear at 3-6 months.
          (b) Low grade SIL + cellular changes compatible with HPV: refer for colposcopy.
          (c) High grade SIL + cellular changes compatible with HPV: refer for colposcopy.
          (d) Squamous cell carcinoma: an obvious lesion should be biopsied; otherwise, refer
              for colposcopy.
      (2) Glandular cells:
          (a) atypical glandular cells: refer for colposcopy and endocervical curettage (ECC).
          (b) Adenocarcinoma: an obvious lesion should be biopsied; otherwise, refer for
              colposcopy and endocervical curettage (ECC).
      (3) Presence of endometrial cells should be evaluated by an endometrial biopsy if
          (a) it is out of phase in a menstruating woman or
          (b) in a post-menopausal woman who is not on estrogen.

   - HPV DNA testing: the HPV high-risk DNA test detects whether any of the high-risk (oncogenic)
     types of HPV are present.

   - Colposcopy:
      1. Lithotomy position. Insert a speculum of the appropriate size.
      2. Naked eye inspection of the vagina and cervix.
      3. Remove any excess mucus. Apply 3% acetic acid with a large cotton swab saturated with the
         solution.
      4. Position the colposcope and focus on the cervix.
      5. Inspect carefully to ensure that the entire TZ can be observed.
      6. If the entire TZ cannot be observed adequately, the evaluation is considered unsatisfactory.
      7. Identify and document with drawings and description the presence of any lesion
         a. acetowhite lesions
         b. vascular patterns: punctate appearance, mosaic appearance, atypical vessels
      8. Use of the green filter improves the ability to identify lesion margins and vascular patterns.
      9. Endocervical curettage should be performed. This is to rule out any disease inside the
         endocervical canal where colposcopic visualization is not possible.
     10. Colposcopy directed punch biopsies should be obtained from all lesions
     11. A hemostatic agent can be applied to each biopsy site immediately after sample collection.
         The speculum is removed, and patient instructions are provided.
         a. Spotting and a light discharge can be anticipated.
         b. Coitus should be avoided for 7-10 days.
Treatment

- Prophylactic: HPV vaccine (Types 16, 18)
- Therapy

- High rates of spontaneous regression, ranging from 70% to 90%, occur for CIN 1 lesions that remain untreated, and thus progression of CIN 1 to CIN 2 or worse is rarely observed.
- follow up: Repeat cytology every 3 months for 2 years, every 6 months for 3 years, and yearly thereafter
- An excision (cone) specimen may show no evidence of expected CIN:
  1. false negative histology in cone
  2. false positive cytology/punch biopsy
  3. complete excision with initial biopsy
  4. spontaneous regression
Invasive Cervical Carcinoma

Incidence

- It is the third most common cancer in women worldwide, 80% of cases occur in developing countries, where it is the second most frequent cause of cancer death in women.

Age

- Range 40-50 years of age. Average for invasive squamous cell carcinoma is 48 years & for adenocarcinoma is 35 years.

High risk factors

- role of oncogenic viruses:
  1. HPV infection of the cervix: at least 40 HPV types can infect the genital tract. Of those 15 types are high risk for CIN and invasive cervical cancer e.g. 16, 18, 31
  2. Human Immunodeficiency Virus

- sexual history:
  1. early sexual activity (before age 17) ++
  2. multiple sexual partners ++
  3. male sexual partner has multiple partners.
  4. non circumcised male partner

- racial: black and Hispanic
- low social class
- smoking
- high parity.
- DES exposure in-utero.

Macroscopic

- site: transformation zone (85% ectocervix, 15% endocervix)
- appearance: ulcerating, fungating or infiltrating

Microscopic

- type:
  1. *Squamous cell carcinoma 90%.*
     A variant of SCC called verrucous carcinoma is a well differentiated slowly growing exophytic tumor which spread superficially with minimal deep invasion.
  2. Adenocarcinoma: Endocervical, endometrioid, clear cell, adenoid cystic, adenoma malignum
  3. adenosquamous
  4. neuroendocrine small cell (rare): carcinoid tumor, oat cell tumor.

- Grade:

<table>
<thead>
<tr>
<th></th>
<th>G 1 highly differentiated</th>
<th>G 2 moderately differentiated</th>
<th>G 3 Poorly differentiated</th>
</tr>
</thead>
<tbody>
<tr>
<td>intracellular bridges</td>
<td>large cell keratinizing</td>
<td>large cell non keratinizing</td>
<td>small cell</td>
</tr>
<tr>
<td>cytoplasmic keratin</td>
<td>+</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>cell nests</td>
<td>+</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>mitotic figures</td>
<td>&lt; 2</td>
<td>2-4</td>
<td>&gt; 4</td>
</tr>
<tr>
<td>pleomorphism</td>
<td>Minimal</td>
<td>Moderate</td>
<td>marked</td>
</tr>
</tbody>
</table>
Spread

- **local**: bladder, rectum, vagina, corpus, parametrium (*early* spread)
- **lymph**: early & bilateral:
  1. primary group: parametrial, paracervical (ureteric), obturator, hypogastric, external iliac, interiliac, sacral
  2. secondary group: common iliac, para-aortic, inguinal
- **blood**: late: distant organs.

**Cause of death**

- Due to spread: ureteric obstruction (uremia is the cause of death in 50%).

**Diagnosis**

- **history**:
  1. Patients with endophytic and endocervical lesions may remain asymptomatic till the advanced stage of the disease.
  2. **early**:
     a. **abnormal bleeding**:
        1. Contact bleeding.
        2. Abnormal menses.
        3. Postmenopausal bleeding.
     b. **serosanguinous discharge**.
  3. **late or recurrent**: pain, secondaries or cachexia
- **signs**:
  1. in most patients the abnormal physical findings will be limited to the pelvis:
     a. **ulcer**: raised everted edges, necrotic floor that bleeds on touch, large ulcer crater, hard margin, base fixed to the underlying tissues
     b. **nodule**: infiltrating, irregular, hard, under an intact mucosa that may ulcerate
     c. **fungating mass**: large, friable, cauliflower, which outgrows its blood supply, necrosis, sloughing with secondary infection & hemorrhage.
     d. **barrel-shaped cervix**.
     e. **stony hard** (rock-hard) cervix.
     f. **fixed** cervix: nodular parametrial infiltration.
  2. Uncommon signs: lymphadenopathy (supracervical or inguinal), a swollen leg, ascites, hepatomegaly, a pleural effusion.
- **Investigations**.
  1. To confirm the diagnosis:
     a. **punch biopsy from any lesion**.
     b. Abnormal Pap smear, colposcopy, **cone biopsy** (*is a MUST to diagnose stage IA*).
  2. To assess the extent: **clinical staging**:
     a. Physical examination under anesthesis. Extension of the tumor into the parametrium or to the pelvic side wall is best determined by rectovaginal examination.
     b. **radiology**: chest x-ray, IVP, barium enema (for staging) and CT scan, MRI, PET-CT (to aid in treatment planning).
     c. **Endoscopy**: cystoscopy, proctosigmoidoscopy.
  3. Pre treatment evaluation.
FIGO Staging

Stage I: strictly limited to the cervix (extension to the corpus is disregarded).

I.A.: diagnosed ONLY by microscopy.
   I.A.1: invasion ≤3 mm in depth & extension ≤7 mm.
   I.A.2: invasion >3 mm but ≤5 mm in depth & extension ≤7 mm.

I.B.: lesions greater than I.A. or Clinically visible lesions limited to the cervix
   I.B.1: tumor ≤4 cm.
   I.B.2: tumor >4 cm.

Stage II: extends beyond the cervix

II.A.: spread to the vagina not reaching the lower third. NO parametrial involvement.
   II.A.1: tumor ≤4 cm.
   II.A.2: tumor >4 cm.

II.B.: spread to parametrium not reaching the pelvic wall.

Stage III

III.A.: spread to the vagina reaching the lower third. NO extension to the pelvic wall.
   III.B.: Extension to the pelvic wall (On rectal examination, there is no cancer-free space between the tumor and the pelvic wall) or hydronephrosis or nonfunctioning kidney.

Stage IV

IV.A.: Tumor involved (biopsy proved) the mucosa of the bladder or rectum (bullous edema does not permit a case to be allotted to stage IV).
   IV.B.: distant metastasis including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone.

Treatment

- Early Stage disease
  1. stage Ia1: Choose One option
     a. conization: ≤3-mm depth of invasion, no LVS involvement, no confluence, strong desire to preserve fertility, margins negative for invasion and dysplasia).
     b. Extrafascial hysterectomy
     c. Modified radical hysterectomy or trachelectomy + pelvic lymph node dissection if lymphovascular invasion
  2. Stage Ia2: Choose One option
     a. Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling
     b. Brachytherapy pelvic ± pelvic RT (total point A dose: 75-80 Gy)
     c. Radical trachelectomy + pelvic lymph node dissection ± para-aortic lymph node sampling.
  3. Stage Ib1 and Ia1: Choose one option
     a. Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling
     b. Pelvic RT + brachytherapy (total point A dose: 80-85 Gy)
     c. Radical trachelectomy for tumors ≤2 cm + pelvic lymph node dissection ± para-aortic lymph node sampling
  4. Stage Ib2 and Ia2: Choose One option
     a. Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy (total point A dose 85 Gy)
     b. Radical hysterectomy + pelvic lymph node dissection + para-aortic lymph node sampling
c. Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy (total point A dose 75-80 Gy) + adjuvant hysterectomy

5. Postoperative adjuvant therapy according to surgical findings
   a. Positive pelvic LN or positive parametrium: Pelvic RT + concurrent cisplatin-containing chemotherapy ± vaginal brachytherapy
   b. Positive paraaortic LN: Para-aortic lymph node RT + concurrent cisplatin-containing chemotherapy + pelvic RT ± brachytherapy

- Advanced disease (stage IIB-IVA): Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy
- Metastatic Disease (stage IVB): primary treatment is often cisplatin-based chemotherapy

<table>
<thead>
<tr>
<th>Advantages of surgery</th>
<th>Advantages of radiotherapy</th>
</tr>
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<tr>
<td>1. identify lymph node metastasis</td>
<td>1. non-operative candidates can be treated</td>
</tr>
<tr>
<td>2. preservation of ovarian function</td>
<td>2. avoid operative complications</td>
</tr>
<tr>
<td>3. shorter treatment interval</td>
<td></td>
</tr>
<tr>
<td>4. less vaginal dysfunction</td>
<td></td>
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<tr>
<td>5. better psychologically</td>
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</table>

Operative Complications of Radical Hysterectomy

- Bladder:
  1. Ischemia and vesicovaginal fistula
  2. Neurogenic dysfunction
- Ureteral injury: fistula, stricture
- Lymphocysts
- Infection: pelvic cellulitis
- Hemorrhage:
  1. Intraoperative
  2. Postoperative: rare
- VTE
- Neuropathies

Comments on Therapy

- Surgery: Extended Abdominal Hysterectomy has 5 classes:
  1. Class I: extrafascial. Removal of all cervical tissue without dissecting into the cervix itself. Pubocervical ligament is incised, allowing lateral deflection of ureter. Indications:
     a. CIN III
     b. microinvasive carcinoma (≤ 3 mm invasion)
     c. after preoperative radiation in adenocarcinoma & barrel shaped lesions
  2. Class II removal of medial half of cardinal & utersacral lig; upper third of vagina. Indications:
     a. microinvasive carcinoma.
     b. small post irradiation recurrence limited to cervix
  3. Class III removal of entire cardinal & utersacral ligaments; upper half of vagina. Indications: stage Ib1 and Ila1.
  4. Class IV: as class III plus removal of all periureteral tissue & the superior vesical artery is sacrificed. indication: anterior central recurrence where conservation of the bladder is feasible
  5. Class V: as class IV plus removal of portions of distal ureter & bladder. indication: central recurrence involving portions of distal ureter or bladder.
Radiotherapy:
1. Teletherapy (External):
   a. Pelvic RT:
      (1) upper border: middle of L5 vertebra
      (2) lower border: lower edge of obturator foramen.
      (3) lateral border: 1 cm lateral to the edge of pelvic inlet.
   b. extended field: if there is evidence of tumor spread to common iliac or paraaortic nodes
2. Brachytherapy (Internal):
   a. intracavitary: afterloading Fletcher-Suit colpostats and tandem
   b. interstitial: is well-suited for
      (1) advanced carcinoma with obliteration of fornices.
      (2) central disease recurrence.
      (3) stump carcinoma.
3. Dosage: total dose at point A is 75-80 Gy and at point B is 50 Gy (Point A is 2 cm lateral to the middle of the cervical canal and point B is 3 cm lateral to point A).

Chemotherapy:
1. indications of adjuvant chemotherapy:
   a. after primary surgery in early stage squamous cell carcinoma with positive lymph nodes using cisplatin combinations
   b. stage Ib2 and IIa2
   c. advanced disease
   d. metastatic disease
   e. neuroendocrine carcinoma
   f. as a radiosensitizer e.g. hydroxyurea
2. It is used with caution because most patients have impaired renal function

Prognosis

prognostic factors:
1. lymph node spread: is the most important factor:
   a. incidence:
      (1) I A 1: 0%
      (2) I A 2: 2%
      (3) I B: > 15%
   b. prognosis is better if:
      (1) There is no lymph node metastasis
      (2) Lymph node metastasis is microscopic
      (3) There are fewer numbers of lymph node metastasis.
2. tumor size
3. depth of stromal invasion
4. histological grade
5. Oncogenes c-myc & H-ras over expression

5-year survival rate:
1. stage IA: 98-100%
2. stage IB: 85-90%
3. stage II: 58-65%
4. stage III: 34-35%
5. stage IV: 9-15%

Recurrent Cervical Carcinoma

- Surveillance
  1. Interval History and physical examination: Patient must be educated regarding symptoms
     - symptoms: pain in pelvis, back, groin, or lower limbs, unilateral lower limb edema, vaginal bleeding or discharge
     - signs: ulceration of the vagina or cervix, paraaortic or supraclavicular lymphadenopathy, palpable mass in the pelvis or abdomen
  2. investigations:
     - Cervical/vaginal cytology every 3-6 months for 2 years, then every 6 months for 3-5 years, then annually
     - Chest x-ray annually
     - CBC, BUN, creatinine every 6 months
     - PET-CT scan as indicated
     - IVP as indicated
- treatment:
  1. Tumor-directed RT + platinum-based chemotherapy ± brachytherapy
  2. Prior RT:
     - Central recurrence: Pelvic exenteration
     - Non-central recurrence: resection or chemotherapy

Stump Carcinoma

- carcinoma in stump after subtotal hysterectomy. This is either
  1. coincidental: discovered within 2 years after operation
  2. true: discovered ≥ 2 years after operation
- Prognosis: guarded
  1. early invasion of bladder & rectum
  2. surgical treatment is difficult due to disturbed anatomy
  3. limited dose of radiotherapy with high incidence of complications as fistula & intestinal obstruction due to adhesions from the previous operation
- Treatment: stage for stage as carcinoma of an intact uterus.
Endometrial Carcinoma

Incidence

- It is the most common gynecologic malignancy. It forms 40% of all invasive malignant tumors of the genital tract.

Age

- Range 50-60 years: 75% of cases are postmenopausal & only 5% of cases occur before 40 years

High risk factors

- low parity, nullipara, infertile, nuns
- white,
- high social class
- early menarche (< 12 years), frequent anovulatory cycles, late menopause (> 52 years)
- unopposed estrogen:
  1. endogenous: PCOS, estrogen secreting tumor
  2. exogenous: sequential pills, ERT
- Drugs: Tamoxifen
- Obesity: the conversion rate of androstenedione to estrone via aromatization in adipose tissue correlates strongly with age & obesity.
- Dietary factors: the risk is increased with greater fat intake
- familial
- Irradiation

Macroscopic

- site: fundus.
- appearance: localized (polyp, fungating mass, ulcer) or diffuse.

Microscopic

- type:
  1. endometrioid (typical) adenocarcinoma: 75% of cases
     a. villoglandular or papillary
     b. secretory
     c. ciliated
     d. with squamous differentiation
        (1) adenoacanthoma: contains a benign squamous element
        (2) adenosquamous: contains a malignant squamous element
  2. clear cell carcinoma
  3. mucinous carcinoma
  4. serous (uterine papillary serous) carcinoma
  5. squamous cell carcinoma
  6. mixed
  7. undifferentiated
- grade: degree of differentiation of adenocarcinoma (see below)

Spread

- local:
1. transtubal: tubes & ovaries.
2. cervix (cervical obstruction + infection → pyometra),
3. vagina: direct implantation, retrograde lymphatic, blood through azygous veins
4. myometrium (late due to mucopolysaccharide barrier),
   - lymphatic: late: pelvic, paraaortic, inguinal.
   - blood: very late: Liver, Lungs, Bone, Brain. It may reach the brain via the paravertebral plexus of Batson.

**Cause of death**
- Due to spread

**Diagnosis**

**History**
- Abnormal uterine bleeding (most common symptom). *The amount of bleeding is not correlated with the possibility of cancer because even a small amount of spotting may represent cancer.*
  1. *Postmenopausal bleeding* (++),
  2. Metrorrhagia
- Discharge or pain
- metastasis

**Examination**
- symmetrically enlarged uterus
- secondaries in the vagina (suburethral metastasis in lower third of the anterior wall).

**Investigations**
- to confirm diagnosis: *endometrial sampling*. Any patient with postmenopausal bleeding MUST have endometrial sampling because End Ca accounts for 1/8 cases of postmenopausal bleeding
  1. *endometrial cytology*: Gravelee jet washing: detects 90% of cases
  2. endometrial biopsy:
     a. *office procedure*: Kevorkian curette, Novak curette, Vabra aspirator
     b. *fractional D&C under anesthesia*
     c. *hysteroscopic guided biopsy*
- to assess extent: surgical staging (extrafascial TAH+BSO plus cytology and pelvic and paraaortic lymphadenectomy). Note that clinical staging is inaccurate.
- Pre operative workup.

**FIGO Staging**

<table>
<thead>
<tr>
<th>I: confined to corpus</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>is limited to the endometrium or invades &lt;1/2 of the myometrium</td>
<td>invades ≥1/2 of the myometrium</td>
</tr>
<tr>
<td>II</td>
<td>Invades stromal connective tissue of the cervix but does not extend beyond the uterus</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>A</td>
<td>tumor invades serosa &amp;/or adnexa</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>vaginal or paramentrial involvement</td>
</tr>
<tr>
<td></td>
<td>C1</td>
<td>pelvic lymph node metastasis</td>
</tr>
<tr>
<td></td>
<td>C2</td>
<td>para-aortic lymph node metastasis</td>
</tr>
<tr>
<td>IV</td>
<td>A</td>
<td>bladder &amp;/or bowel mucosa</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>distant metastasis including inguinal LN metastasis, lung, liver, bone</td>
</tr>
</tbody>
</table>
Each stage is classified according to histopathologic degree of differentiation:

- **G1**: ≤5% non-morular solid growth pattern
- **G2**: 6-50% non-morular solid growth pattern
- **G3**: > 50% non-morular solid growth pattern

**Treatment**

- **Stage I** (> 75% of cases): completely surgically staged. Postoperative management matrix:

<table>
<thead>
<tr>
<th>Stage I A</th>
<th>G1</th>
<th>G2 or G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observe</td>
<td>Observe or vaginal BT</td>
<td></td>
</tr>
<tr>
<td>Observe or vaginal BT</td>
<td>Observe or vaginal BT and/or pelvic RT</td>
<td></td>
</tr>
</tbody>
</table>

- **Stage I B**

<table>
<thead>
<tr>
<th>Stage I B</th>
<th>G1</th>
<th>G2 or G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observe or vaginal brachytherapy</td>
<td>Observe or vaginal BT and/or pelvic RT for G3</td>
<td></td>
</tr>
</tbody>
</table>

- **Stage II** (10-15% of cases):

  1. Completely surgically staged. Postoperative management
     a. G1: vaginal BT and/or pelvic RT
     b. G2: Pelvic RT + vaginal BT.
     c. G3: Pelvic RT + vaginal BT ± chemotherapy
  2. Radical hysterectomy + BSO. Observation or vaginal BT is also an option for patients with stage II who had RH and negative surgical margins and no evidence of extra-uterine disease
  3. Preoperative irradiation followed by extrafascial TAH + BSO.

- **Stage III**:

  1. Completely surgically staged + debulking. Postoperative management
     a. Stage IIIA: chemotherapy ± RT or tumor-directed RT ± chemotherapy or pelvic RT ± vaginal BT
     b. stage III.B.: chemotherapy and/or tumor-directed RT
     c. Stage III.C.: chemotherapy and/or tumor-directed RT
  2. RT (75-80 Gy at point A). This is followed by TAH + BSO +PA lymphadenectomy.

- **Stage IV**:

  1. Completely surgically staged + debulking + chemotherapy ± RT
  2. RT or chemotherapy.

**Chemotherapy**

1. Cisplatin, carboplatin, Adriamycin, taxol.
2. Hormonal therapy: MPA, megestrol acetate, hydroxyprogesterone caproate. Higher response rates to progestin therapy are:
   a. well differentiated tumors
   b. minimal tumor burden
   c. a long disease-free interval
   d. pulmonary metastasis
   e. progesterone-positive & estrogen-positive receptors
Follow up after treatment: patient education plus

<table>
<thead>
<tr>
<th>Protocol</th>
<th>interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>history &amp; physical examination including pelvic</td>
<td>every 3 months for 2 years, then every 6 months for</td>
</tr>
<tr>
<td>examination, cuff Pap smear &amp; rectal examination</td>
<td>3 years, and then yearly for life</td>
</tr>
<tr>
<td>chest radiography</td>
<td>every 6 months for 5 years &amp; then yearly</td>
</tr>
<tr>
<td>Mammography</td>
<td>yearly for life</td>
</tr>
<tr>
<td>CT or MRI</td>
<td>As clinically indicated</td>
</tr>
</tbody>
</table>

Prognosis

- Endometrial adenocarcinoma is one of the least common causes of cancer mortality in women. The relatively low mortality rate because 85% of cases are confined to uterus at the time of initial diagnosis.

- Prognostic factors:
  1. FIGO stage.
  2. Depth of myometrial invasion.
  3. Histologic grade.
  4. Histologic type: adenosquamous carcinoma, papillary serous carcinoma, clear cell carcinoma have a poor prognosis.
  5. Pelvic & Para aortic lymph node metastasis.
  6. other factors that entail a poor prognosis:
     a. progesterone receptor levels < 100 fmol/mg of protein
     b. fraction of cells in the S-phase > 9%
     c. over expression of the HER-2/neu oncogene.

- 5-year survival rate: Total for all stages: 65.1%
**Leiomyoma (Fibroids)**

LM is a *true neoplasm* arising from single neoplastic smooth muscle cell (*unicellular*) as proven by study of G6PD iso-enzymes A & B. It is neither due to myometrial hyperplasia nor arising from the middle coat of an artery.

**Incidence**
- Nearly 20-30% (most common tumor in females)

**Age**
- Range 30-40 (reproductive period)

**High risk factors**
- Low parity, nullipara, infertile, nuns, black, familial.
- Chromosome defects: translocations & deletions most often in chromosome 12.

**Regulation of leiomyoma growth**

1. **Estrogen**: evidences:
   - never before puberty,
   - never starts after menopause,
   - stop growing or even regress after menopause,
   - increase in size during pregnancy & with oral pills containing estrogen,
   - it is rich in estrogen receptors
   - GnRH-a causes significant reduction in tumor size.

2. **Progesterone**: evidences:
   - Mitotic index of leiomyoma is increased in the luteal phase of the cycle.
   - Levels of progesterone receptors in leiomyoma are high.
   - Anti-progesterone reduces its growth.

3. **Growth factors**: *IGF-I* (an intrauterine mediator of estrogen).

**Macroscopic**

- **site**:
  1. uterus 99% (corpus 92-96% + cervix 2-8%). Stump leiomyoma is rare.
  2. extra uterine 1% (broad ligament, round ligament, vagina, vulva, tubes)

- **appearance**:
  1. site: intramural (interstitial) the commonest, sub serous or submucous,
  2. number: single or multiple.
  3. size: mm to cm. It has a slow growth rate (may take 3 years to reach the size of an orange).
  4. shape: pedunculated or sessile
  5. consistency: firm
  6. color: pinkish white
  7. cut surface: whorl-like appearance
  8. The capsule:
     - outer is compressed uterine muscle (*pseudocapsule*);
     - intermediate is connective tissue and blood vessels ramify in it;
     - inner is part of the tumor.
  9. blood supply: single main artery enters the capsule and ramify in the middle layer and gives branches that enter the tumor at right angle → rich peripheral blood supply (liable to
calcification) & poor central blood supply (liable to degeneration). The sub serous leiomyoma is the one with the least blood supply. In the submucous polyp, the artery enters through the pedicle & so the least vascular area is the tip.

**Microscopic**

- Type: It is formed of interlacing smooth muscles (nuclei are short fat rods with rounded ends) & fibrous tissue (nuclei are thinner and spindle shaped). Small tumors (≤1 cm) are formed only of muscle tissue.

<table>
<thead>
<tr>
<th>Rare types</th>
<th>mitotic figures/10 HPF</th>
<th>cellular atypia</th>
</tr>
</thead>
<tbody>
<tr>
<td>cellular leiomyoma</td>
<td>0-4</td>
<td></td>
</tr>
<tr>
<td>atypical leiomyoma</td>
<td>0-4</td>
<td>+</td>
</tr>
<tr>
<td>uncertain malignant potential</td>
<td>5-9</td>
<td></td>
</tr>
<tr>
<td>leiomyomatosis intravenous disseminata</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>leiomyomatosis peritonei disseminata</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Complications**

- pathological changes in the tumor:
  1. atrophy: after menopause
  2. hyaline change: is the most common. There is loss of whorl appearance in the center.
  3. cystic change: secondary to hyaline degeneration due to liquefaction of the areas of hyaline change.
  4. fatty degeneration.
  5. calcification: It includes a thin rim of calcium on the periphery (egg shell pattern), a diffuse honeycomb pattern, a series of concentric rings, and a solid calcific mass (womb stone).
  6. Red degeneration (necrobiosis): a reversible change starting in the center at 1st then all the tumor which becomes soft with raw meat cut surface. It is common in pregnancy. There is acute abdomen, fever, tenderness, ↑ TLC & ESR. Treatment is conservative
  7. Torsion: in cases of pedunculated subserous myoma
    a. acute: → necrosis
    b. chronic: obstruct veins → congestion & edema → adhesions to surrounding structures & further torsion → obstruct arteries so the tumor takes its blood supply from the surrounding structures e.g. omentum. This is parasitic myoma
  8. hemorrhage: due to torsion or rupture of a vein on the surface
  9. infection: commonly ascending after abortion, labor, D&C, IUCD insertion, ulcerated tip of submucous polyp
  10. Malignant change: *leiomyosarcoma* (0.54%)
    a. rapid increase in size in short time
    b. recurrence after removal
    c. appearance or persistent growth after menopause
    d. postmenopausal bleeding
    e. macroscopic:
      1. ill defined, homogenous (fish flesh), areas of hemorrhage & necrosis
      2. no whorly appearance
    f. microscopic:
      1. mitotic figures ≥ 10 per 10 HPF
mitotic figures 5-10 per 10 HPF + cytologic atypia
g. treatment: TAH + BSO
h. prognosis: depends on the number of mitotic figures

• Effects on surrounding structures:
  1. uterus:
     a. enlargement, distortion of uterine cavity, increase endometrial surface area,
     b. increase vascularity,
     c. endometrial hyperplasia,
     d. displacement: prolapse, RVF, chronic inversion
  2. tubes: displacement, obstruction, associated salpingitis
  3. ovaries: associated follicular cysts
  4. pressure symptoms:
     a. cervical tumors which grow extraperitoneal & remain fixed in the pelvis (→ frequency of micturition, retention of urine, constipation, hydroureter)
     b. huge subserous tumors (→ dyspepsia, palpitation, intestinal obstruction)
  5. blood: iron deficiency anemia due to chronic blood loss. Polycythemia ??? (very rare).
  6. Hypoglycemia especially with retroperitoneal tumors with unusual cellular activity.
  7. reproduction:
     a. infertility: due to
        (1) cervical block, cornual block, tubal displacement,
        (2) associated disorders e.g. endometrial hyperplasia, bilateral salpingitis, endometriosis.
     b. ectopic pregnancy
     c. recurrent pregnancy loss
     d. preterm labor
     e. malpresentation
     f. non engagement
     g. prolonged labor:
        (1) soft tissue obstruction
        (2) incoordinate uterine action
     h. postpartum hemorrhage:
        (1) primary: atonic,
        (2) secondary: subinvolution

Diagnosis

• history:
  1. asymptomatic the majority of small myomas & some large ones are accidentally discovered during routine examination. The nearer the myoma to the endometrial cavity the most likely it is to cause symptoms especially menstrual symptoms
  2. menorrhagia heaviest on the second & third days (flooding).
  3. metrorrhagia: myoma does not cause metrorrhagia unless it is
     a. complicated by:
        (1) infected ulcerated submucous polyp,
        (2) sarcomatous change,
b. associated with:
   (1) endometrial carcinoma,
   (2) complications of pregnancy
4. It **NEVER** causes amenorrhea.
5. pain: myoma does not cause pain unless it is
   a. complicated by torsion, infection, red degeneration, sarcomatous change
   b. associated with: endometriosis or salpingitis
6. Dysmenorrhea: congestive or **spasmodic (with a submucous polyp)**.
7. pelviabdominal swelling
8. subfertility

- signs:
  1. general examination: anemia
  2. abdominal examination: pelviabdominal mass
  3. PV examination:
     a. **enlarged uterus**: either asymmetrical (subserous or intramural) or symmetrical
        (submucous or small intramural)
     b. mass in Douglas pouch, or in utervesical pouch,
     c. Broad ligamentary or adnexal mass
     d. polyp protruding from the cervix.
- investigations:
  1. laboratory: CBC
  2. radiology:
     a. Ultrasound (TAS or TVS)
     b. IVP (broad ligamentary or cervical tumors),
  3. endoscopy: hysteroscopy or laparoscopy
  4. biopsy: D&C in cases of metrorrhagia

### Treatment

- general:
  1. correct iron deficiency anemia
  2. counsel for operative treatment
- specific:
  1. no treatment: if asymptomatic (No data to support hysterectomy or myomectomy in women
     with asymptomatic LM, but there is clear evidence that both are associated with the risk of
     complications) particularly with a small uterus (<12 weeks) and age near menopause
  2. Hysterectomy: is the only definitive therapy.
     a. Based on age, fertility requirement, and wish to spare the uterus
     b. Route: Vaginal or abdominal
     c. If abdominal: total or subtotal techniques may be used
  3. Uterus sparing interventions: **All uterus-sparing treatments for symptomatic LM leave some risk of persistent or recurrent LM resulting in the need for additional therapy.**
     a. Myomectomy:
        (1) indications: a young patient, wish to retain fertility, wish to spare the uterus (refusing
            hysterectomy)
operative:
(a) to reduce blood loss:
   (i) Evidence is limited from a few RCTs that misoprostol, vasopressin, bupivacaine
       plus epinephrine, tranexamic acid, tourniquet, and mesna (mercaptoethane
       sulfonate) may reduce bleeding during myomectomy.
   (ii) There is no evidence that morcellation or laser dissection have an effect on
        intraoperative blood loss.
(b) to decrease adhesions: interceed (oxidized regenerated cellulose) or Goretex
    surgical membrane.
(3) postoperative complications:
(a) immediate: (as compared with hysterectomy) more hemorrhage ??
(b) remote:
   (i) persistent or recurrent menorrhagia
   (ii) persistent infertility
   (iii) recurrent, persistent or new LM
   (iv) higher CS rate
b. Laparoscopic myomectomy: pedunculated subserous myomas are resected by
   coagulating the base using thermocoagulation or cautery. The myoma is transected from
   its base & morcellated or cut if necessary.
(1) non fertility benefits of removal via laparoscopy including shorter hospital stay, less
    febrile illness and a smaller drop in pre-operative HB (compared to laparotomy)
(2) insufficient evidence of a difference in clinical pregnancy rate and live birth rate when
    fibroids were removed via laparotomy or laparoscopy
c. Hysteroscopic resection of a single submucous polyp.
   (1) a resectoscope: by progressive shaving.
   (2) Nd:YAG laser.
d. Polypectomy in single submucous polyp
e. Hormonal
   (1) GnRH analogues
      (a) As a primary conservative therapy: insufficient evidence
      (b) Adjuvant: for 4 months before surgery (hysterectomy or myomectomy)
         (i) correction of pre-operative iron deficiency anemia, if present,
         (ii) uterine volume, uterine size and fibroid volume were all reduced.
         (iii) reduce intra-operative blood loss.
         (iv) reduced operating time
         (v) reduced Duration of hospital stay.
   (2) Insufficient evidence for Danazol, gestrinone, SERMs, tibolone, Antiprogesterone
f. Uterine artery Embolization
   (1) Advantages
      (a) improves LM-related symptoms e.g. heavy menstrual loss
      (b) decreases mean LM volume.
(c) reduces length of hospital stay compared to either hysterectomy or myomectomy.

(2) Disadvantages: a higher rate of minor complications:
   (a) vaginal discharge,
   (b) post puncture hematoma
   (c) post embolization syndrome (pain, fever, nausea, vomiting),
   (d) higher readmission rates after discharge
   (e) elevated FSH levels post UAE indicates possible ovarian dysfunction.

g. Myolysis: Cryotherapy, Electrocautery, Laser
Choriocarcinoma

Incidence

- In the far east: 1: 4000 and in UK & USA: 1: 40,000 pregnancies.

Age

- reproductive period (gestational choriocarcinoma)

High risk factors

- vesicular mole (50% of cases)
- abortion (25%)
- term preg (22.5%)
- ectopic (2.5%)

Macroscopic

- site: uterus 90% of cases
- appearance:
  1. uterus:
     a. localized hemorrhagic polyp or fungating mass
     b. diffuse
     c. intramural with an empty uterine cavity
  2. ovaries: theca lutein cysts (due to ↑ hCG)

Microscopic

- No villi + extensive hemorrhage + sheets of malig trophoblast. Rarely it is localized to syncytium only, called syncytioma

Spread

- local: myometrium
- blood: early:
  1. Site: genital (vulva, vagina, ovaries) or extrgenital (L, L, B, B).
  2. Secondaries are: multiple, hemorrhagic, large, may regress after treatment of primary tumor & may be symptomatic before the primary.
  3. lung: is the commonest site → hemoptysis.
  4. vagina is the second most common
- cause of death due to spread (genital & extragenital) → hemorrhage

Diagnosis

- Diagnosis
  1. History:
     a. a recent pregnancy (vesicular mole, abortion, term pregnancy) is followed by irregular uterine bleeding.
     b. Hemoptysis may be the presening symptom
  2. signs:
     a. symmetrically enlarged uterus,
     b. secondaries in vagina,
     c. ovarian mass (secondaries or theca lutein cysts).
  3. investigations:
a. to confirm diagnosis: biopsy (D&C): No villi + extensive hemorrhage + sheets of malignant trophoblast.

b. to assess stage: \( \beta \)-hCG, X-ray (chest & bone), CT scan brain & liver

4. to prepare the patient: CBC, liver & kidney functions

**Staging**

**FIGO staging & scoring:**

- Stage I: confined to the uterine corpus
- Stage II: extending outside the uterus but limited to genital structures (adnexa, vagina)
- Stage III: extending to lungs ± known genital tract involvement
- Stage IV: all other metastatic sites

**FIGO (WHO) scoring system**

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>&lt;40</td>
<td>≥40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
<td>Term</td>
<td></td>
</tr>
<tr>
<td>Interval in months</td>
<td>&lt;4</td>
<td>4-6</td>
<td>7-12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Pretreatment hCG (log)</td>
<td>&lt;3</td>
<td>3-4</td>
<td>&gt;4-5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Largest tumor size (cm)</td>
<td>3-4</td>
<td></td>
<td>≥5</td>
<td></td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Spleen, kidney</td>
<td>Gl</td>
<td>Brain, Liver</td>
<td></td>
</tr>
<tr>
<td>Number of metastases identified</td>
<td>1-4</td>
<td>5-8</td>
<td>&gt;8</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy failure</td>
<td>Single</td>
<td>2 or more</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Low risk:** ≤6; **High risk:** ≥7.

**Prognostic Group system**

- **Non Metastatic**
  - Low Risk
    - Duration < 4 months
    - NO prior chemotherapy
    - NOT after term preg
    - lungs or bone metastases
    - hCG < 100,000 IU/24 hours urine or <40,000 mIU/ml serum

- **Metastatic**
  - High Risk
    - duration > 4 months
    - failed prior chemotherapy
    - after term preg
    - brain or liver metastases
    - hCG > 100,000 IU/24 hours urine or >40,000 mIU/ml serum
Treatment

- chemotherapy:
  1. nonmetastatic & low risk metastatic:
     a. single agent chemotherapy: methotrexate (MTX) (a phase specific, antimetabolite, folate antagonist)
        (1) weekly doses of 30 to 50 mg/m² (intramuscular) or
        (2) 1 mg/kg on days 1, 3, 5, 7 + folinic acid 0.1 mg/kg on days 2, 4, 6, 8
     b. Side effects of MTX: Nausea & vomiting, stomatitis, GI ulceration
     c. repeated at 7-10 day intervals (depending on toxicity) provided that
        (1) WBC >3000/cu mm
        (2) polys >1500/cu mm
        (3) platelets >100,000/cu mm
        (4) BUN, SGOT, SGPT normal
     d. continue till remission (3 successive normal β-hCG done weekly)
     e. contraception begun (oral if not contraindicated)
  2. high risk metastatic: Multi Agent Chemotherapy:
     a. MAC: MTX + Actinomycin-D + Chlorambucil or Cyclophosphamide
     b. EMACO: Etoposide + MTX + Actinomycin-D + Cyclophosphamide + Oncovin (vincristine)

- surgery: hysterectomy may be done as adjuvant to chemotherapy to
  1. eradicate persistent chemotherapy-resistant disease in the uterus
  2. control local hemorrhage or infection

- radiotherapy: whole brain or whole liver irradiation with combination chemotherapy
Vesicular Mole

Incidence
- far east 1:100 & Europe 1:1500

Age
- reproductive period

High risk factors
- chromosomal:
  1. diploidy (all chromosomes are paternal) → complete mole.
  2. triploidy (dispermic fertilization) → partial mole.
- racial

Macroscopic
- site: uterus
- appearance: multiple grape like thin walled vesicles with stalks. Vesicular mole may either be partial or complete. Multiple theca lutein cysts can be seen in the ovaries (due to ↑ hCG) in 59%.

<table>
<thead>
<tr>
<th></th>
<th>complete</th>
<th>partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype</td>
<td>diploid</td>
<td>triploid</td>
</tr>
<tr>
<td>fetus, fetal RBC or membranes</td>
<td>_</td>
<td>abnormal fetus (may be alive or dead)</td>
</tr>
<tr>
<td>trophoblastic hyperplasia</td>
<td>Total</td>
<td>focal</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>more common</td>
<td>less common</td>
</tr>
</tbody>
</table>

Microscopic
- villi are
  1. avascular (no fetal blood vessels),
  2. edematous (edema of villous stroma),
  3. hyperplastic (both cyto & sycyto trophoblast)

Complications
1. Hemorrhage.
2. Choriocarcinoma: 5% of vesicular mole
3. Recurrent mole: 2% of cases & there is an increased risk of invasive mole & choriocarcinoma.
4. invasive mole: chorioadenoma destuens invades myometrium (15 % of vesicular mole). It undergoes spontaneous regression
5. metastatic mole: to distant organs (lungs & vagina)
6. DIC
7. Pulmonary embolism
8. Preeclampsia in the first half of pregnancy.
9. Thyrotoxicosis.
10. Hyperemesis gravidarum

Diagnosis
- history:
  1. symptoms of early pregnancy with bleeding,
  2. prune juice vaginal discharge,
3. passage of vesicles,
4. pain,
5. may be symptoms of PE, hyperemesis, thyrotoxicosis

- signs:
  1. Fundal level is higher than the period of amenorrhea
  3. Passage of vesicles during examination.
  4. Bilateral cystic ovaries.

- investigations:
  1. to confirm diagnosis:
     a. ultrasound: snow storm appearance
     b. histopathology after suction evacuation
  2. pre operative: baseline $\beta$- hCG, chest X ray, coagulation profile, prepare at least 2 units of blood

**Treatment**

- Suction evacuation followed by curettage + IV oxytocin drip after evacuation.
- anti-D gamma globulin must be given to Rh -ve patients with partial moles
- hysterectomy may be an option with an advanced maternal age and complete family
- prophylactic methotrexate may be considered after evacuation in high risk patients:
  1. age > 40 years
  2. uterine size > 20 weeks
  3. bilateral theca lutein cysts > 6 cm
  4. high serum hCG
  5. metastatic mole
  6. recurrent mole
  7. medical complications: PE, thyrotoxicosis

- follow up:
  1. serial quantitative $\beta$- hCG every 1-2 wk till 3 successive negative values then every 3 months for 1 year
  2. pelvic examination 2 & 4 weeks postoperatively & then monthly
  3. chest X ray at 4 & 8 weeks postoperatively
  4. effective contraception during follow up using COCP or barrier method.

- diagnostic curettage is done if
  1. the titer remains high or plateau in 3 consecutive measurements
  2. the titer increased after being negative or showed a 2-fold increase.
  3. irregular bleeding after evacuation
  4. uterine subinvolution
  5. persistent theca lutein cysts

- indications to initiate chemotherapy:
  1. evidence of choriocarcinoma by D&C
  2. evidence of metastasis
Ovarian Masses

Non neoplastic

- cystic:
  1. inflammatory
  2. endometriotic
  3. functional:
     a. the most common adnexal mass in the reproductive years
     b. they never occur before puberty or after menopause.
     c. usually small (< 7 cm)
     d. regress spontaneously or with COCP for 3 months
     e. include:
        (1) follicular cyst
        (2) corpus luteum cyst
        (3) theca lutein cyst: associated with
           (a) vesicular mole and choriocarcinoma.
           (b) multiple pregnancy.
           (c) normal pregnancy.
           (d) women receiving hCG.

- solid:
  1. Massive Edema
  2. Hyperthecosis
  3. Pregnancy Luteoma
     a. appears during the last trimester of pregnancy
     b. multiple, bilateral, orange yellow to greyish yellow solid nodules
     c. it may produce androgen leading to virilization of the mother & her female fetus
     d. it is commonly discovered during CS but may present as abdominal mass
     e. spontaneous regression occurs after labor.

GOLDEN RULE: Any Ovarian Mass that is more than 7 cm, pre menarche, post menopausal, or persistent MUST be considered NEOPLASTIC till proven otherwise

Neoplastic

- Primary: benign, borderline, malignant
- Secondary malignancy:
  1. The ovary is a common site for metastasis. The primary tumor may be:
     a. genital e.g. endometrial carcinoma, tubal carcinoma, the opposite ovary.
     b. extra genital e.g. breast (the most frequent), gall bladder, stomach, large intestine.
  2. Secondaries reach the ovary: trans-celomic, direct, lymphatic, blood.
  3. Macro: bilateral, large, solid or heterogeneous, may present before primary tumor.
  4. micro: may be either typical or atypical (Krukenberg - with intracellular (signet ring cell) & extra cellular mucin. The primary growth is in mucin secreting tissue usually the stomach or colon but sometimes the gall bladder or breast.
  5. Prognosis: patient dies within 1 year.
Primary Ovarian Tumors

Incidence

- ovarian neoplasm: 1.5%
- primary ovarian malignancy: is the second most common genital malignancy worldwide.
- age: any (according to the histological type)

High risk factors

- low parity, nullipara, infertile, nuns
- white,
- high social class
- Family history: breast ovarian cancer syndrome
- dysgenetic gonads
- trauma of ovulation.
- viral infection.
- X ray exposure.

Macroscopic

<table>
<thead>
<tr>
<th>benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Appearance</td>
<td>cystic</td>
</tr>
<tr>
<td></td>
<td>rare surface &amp; intracystic papilla</td>
</tr>
<tr>
<td></td>
<td>well defined borders</td>
</tr>
<tr>
<td></td>
<td>mobile</td>
</tr>
<tr>
<td></td>
<td>no spread</td>
</tr>
</tbody>
</table>

Microscopic

- FIGO & WHO classification according to the cell of origin
  1. epithelial tumor: 70-80% of primary ovarian tumors
  2. germ cell tumor: 5-15% of primary ovarian tumors
  3. Sex cord stromal tumor: 10% of primary ovarian tumors

Features of primary ovarian tumors

Surface epithelial tumors

- serous: most common ovarian tumor 50%
  1. benign:
    a. age: 30 years
    b. site: unilateral 90%
    c. appearance: cyst adenoma: unilocular, thin wall, filled with serous fluid & papillary cyst adenoma: with papillae
    d. microscopic: the cyst is lined with a single layer of flattened or cuboidal epithelium ± psammoma bodies (not diagnostic & not indicative of malignancy)
  2. borderline malignancy: diagnosis = histological findings
    a. age: 30-60 years
    b. site: unilateral 80%
    c. appearance: cyst adenoma & papillary cyst adenoma
d. microscopic: the cyst is lined with ≤ 3 layers, few mitotic figures, no stromal invasion

3. malignant:
   a. age: **45-70 years**
   b. site: bilateral 60%
   c. appearance: adenocarcinoma, papillary adenocarcinoma, papillary cyst adenocarcinoma
   d. microscopic: stratification >3 layers, atypia, loss of polarity, ↑ mitotic figures, invasion of the stroma.

- **mucinous:** 2nd most common ovarian tumor 30%
  1. benign:
     a. age: 30 years
     b. site: unilateral 95%
     c. appearance: cyst adenoma: multilocular, thick wall, filled with mucinous fluid & rarely papillary cyst adenoma: with papillae
     d. microscopic: the cyst is lined with a single layer of columnar epithelium with NO psammoma bodies
  2. borderline
  3. malignant:
     a. age: 45-70 years
     b. site: bilateral 20%
     c. appearance: adenocarcinoma, papillary adenocarcinoma, papillary cyst adenocarcinoma
     d. microscopic: stratification > 3 layers, atypia, loss of polarity, ↑ mitotic figures, invasion of the stroma.

- **endometrioid:**
  1. benign and borderline: rare
  2. malignant:
     a. adenocarcinoma
     b. associated with endometrial adenocarcinoma in 20-30% of cases
     c. associated with endometriosis in 10% of cases

- **clear cell (mesonephroid):**
  1. benign and borderline: rare
  2. malignant:
     a. adenocarcinoma with hobnail cells
     b. associated with endometrial adenocarcinoma & endometriosis

- **Brenner:**
  1. benign:
     a. solid small nodule, usually part of fibroma or the wall of mucinous cyst adenoma.
     b. stroma is fibrous tissue with transitional or squamous epithelium having coffee bean nuclei.
     c. It may produce estrogenic or androgenic activity due to ⊕ of theca cells
  2. Borderline and malignant: rare

**Germ cell tumors**

- **Dysgerminoma (Disgerminoma) (Germinoma):**
  1. Malignant, produces hCG
2. bilateral in 10%
3. extremely radiosensitive
4. in dysgenetic gonads with Y chromosome in the genotype
5. microscopically: cords of rounded cells & syncytiotrophoblastic giant cells in a stroma infiltrated with lymphocytes

- Endodermal sinus tumors (yolk sac tumors):
  1. Malignant, produces α fetoprotein
  2. microscopically: festoon (endodermal sinus) layers of germ cells with a central capillary (Schiller-Duval body)

- embryonal carcinoma:
  1. malignant, produces α fetoprotein & hCG
  2. solid sheets of anaplastic cells with glandular & papillary formation and syncytiotrophoblastic giant cells. It usually exists as a part of the mixed germ cell tumor.

- polyembryoma:
  1. malignant, produces α fetoprotein & hCG
  2. embryoid bodies at different stages of development

- choriocarcinoma:
  1. rare & malignant, produces hCG
  2. diagnosed with certainty only in pre menarchal girls & as a part of mixed germ cell tumors

- teratoma
  1. mature cystic teratoma (dermoid cyst): 20% of ovarian tumors
    a. age: 20 years
    b. bilateral in 20% of cases
    c. moderate size with a long pedicle
    d. contains:
       (1) ectodermal (skin, hair, keratin, sebaceous & sweat glands), endodermal (intestine), mesodermal (cartilage, bone) tissues
       (2) embryonic nodule (Rokitansky protuberance)
    e. if the tumor is composed of only ectodermal derivatives of skin & skin appendages, it is a true dermoid cyst
    f. malignant transformation: squamous cell carcinomas in most cases
  2. mature solid teratoma
  3. immature: grading depends on amount of immature tissue and neuroepithelium
  4. monodermal:
    a. struma ovarii: thyroid tissue → T3 & T4 → thyrotoxicosis
    b. carcinoid: argentaffin cells → serotonin → carcinoid syndrome

Sex cord stromal tumors

- Granulosa cell tumors:
  1. potentially malignant, produces estrogen, appears in adults usually postmenopausal. Juvenile (pre pubertal) may occur but rare.
  2. microscopic: coffee bean nuclei & Call Exner bodies

- Thecoma
  1. benign, produces estrogen, and appears after 30 years usually post menopausal
2. microscopic: spindle shaped cells with lipid rich vacuolated cytoplasm.

- **Fibroma**
  1. Benign, appears after 30 years, usually post menopausal.
  2. microscopic: spindle shaped cells.

- **Androblastoma (arrhenoblastoma): Sertoli-Leydig cell tumor:**
  1. Appears at \( \approx 25 \) years.
  2. malignant behavior is rare except with poorly differentiated type.
  3. microscopic:
     a. Sertoli cell tumors: estrogenic (70%), androgenic (20%). no activity (10%)
     b. Leydig cell tumors: androgenic
     c. Sertoli-Leydig cell tumors: androgenic
        1. well differentiated:
        2. of intermediate differentiation
        3. poorly differentiated (sarcomatoid)
        4. with heterologous elements

4. Gynandroblastoma: rare, benign, may be androgenic or estrogenic

5. lipid (lipoid) cell tumors: rare, usually virilizing, formed of large oval cells which resemble:

6. sex cord tumor with annular tubules

7. sclerosing stromal tumor

**Spread**

- Transcelomic: most common: omentum, intestine, diaphragm.
- Direct to adjacent organs: tubes, uterus, bladder & rectum.
- lymphatic: early: to pelvic, paraaortic, inguinal lymph nodes
- blood: distant organs

**Complications**

- rupture: spontaneous or traumatic \( \rightarrow \)
  1. hemorrhage.
  2. malignant tumors \( \rightarrow \) dissemination.
  3. teratoma \( \rightarrow \) aseptic peritonitis
  4. infected cyst \( \rightarrow \) septic peritonitis

- pseudomyxoma peritonei. This occurs in 5% of mucinous tumors especially the borderline group. There are pools of cellular mucin in the abdominal cavity. Refilling occurs even when the tumor is benign & the mucinous material removed. Theories:
  1. leakage from the cyst
  2. epithelial cells of the tumor invade the omentum & spread over the peritoneum
  3. mucinous metaplasia of the peritoneum

- Meigs' syndrome: large ovarian fibroma may be associated with ascites and right sided hydrothorax in 1% of cases. Removal of the tumor results in spontaneous & permanent cure.
  1. ascites may be due to:
     a. exudation from the peritoneum resulting from mechanical irritation
     b. degeneration of fibroma
     c. changes in the capsular veins of the fibroma
d. lymphorrhea due to lymphatic obstruction
2. hydrothorax may be due to communication between pleura and the peritoneum

- infection: usually ascending through tubes after labor or abortion
- Incarceration
- Torsion due to twisting of a pedunculated moderate size mobile tumor, common in pregnancy & puerperium. Torsion may be:
  1. acute → acute abdomen
  2. chronic → parasitic tumor
- Hemorrhage: due to trauma, torsion, rupture, incarceration, malignancy
- effect on reproductive function:
  1. before puberty: precocious puberty
  2. after puberty: abnormal uterine bleeding, infertility, virilism
  3. during pregnancy: preterm labor, pressure manifestation, malpresentation
  4. during labor: soft tissue dystocia (obstructed labor)
  5. rate of all complications of ovarian tumors ↑ e.g. torsion, infection
  6. the commonest ovarian neoplasm during pregnancy: mature cystic teratoma or serous cyst adenoma

Diagnosis

- history:
  1. asymptomatic: accidentally discovered
  2. abdominal distention, discomfort & dyspepsia (often first seen by internists)
  3. pelviabdominal mass: may be noticed by the patient or discovered during routine examination
  4. abnormal bleeding (metrorrhagia, postmenopausal bleeding)
    a. functioning tumors
    b. effect on the surrounding ovarian stroma
    c. secondaries in the uterus
  5. pain: malignancy or complications
  6. pressure manifestations
  7. symptoms of secondaries
  8. hormonal effects: virilization, precocious puberty, thyrotoxicosis, carcinoid syndrome
- signs:
  1. general: cachexia, secondaries, hormonal effects
  2. abdominal: 3 questions must be answered about the mass that is felt abdominally:
    a. Abdominal or pelviabdominal? if pelviabdominal: the examining hand can not get below the mass (can not define its lower border)
    b. Ovarian or uterine? if ovarian: the uterus can be felt apart from it, it does not move with cervix, a sharp cleft is felt between the uterus and the lower border of the tumor
    c. Benign or malignant?
  3. Pelvic examination:
    a. adnexal mass
    b. mass in the Douglas pouch
    c. nodules in the Douglas pouch
d. frozen pelvis  
e. mass in uterovesical pouch

**Investigations**

**Screening (early diagnosis)**

- **Bimanual examination:** a normal postmenopausal ovary is not palpable so any palpable ovary 3-5 years after menopause must be considered pathological. But a tumor volume of 1 cm\(^3\) contains a billion cancer cells

- **Ultrasound:** is very sensitive for detection of early asymptomatic ovarian cancer
  1. Malignancy features: multilocular cyst, bilateral lesions, solid areas, separate papillary growths, ascites, intra-abdominal metastases,
  2. TVS has a higher resolution but has some Disadvantages:
     a. frequencies used → \(\uparrow\) resolution but \(\downarrow\) penetration to 10 cm: ovaries high or lateral in the pelvis or greatly enlarged may not be seen
     b. post menopausal vaginal atrophy ↓ access
  3. Doppler Ultrasound to examine pattern of blood flow → ovarian tumor has a high peak velocity, increased mean velocities, decreased pulsatility index

- **Cytology:** only 20% of advanced cases have positive smears

- **Tumor Markers:**
  1. carcinoplacental antigen: alkaline phosphatase, hCG, HPL, LDH, SP1
  2. fetal antigen: CEA, AFP
  3. tumor associated antigen: are glycoprotein detected by monoclonal Antibody: **CA 125**.
     a. Its expression is a feature of cells derived from celomic epithelium & Mullerian duct
     b. causes of **elevated CA 125**:
        (1) ovarian cancer:
           a. levels > 35 u/ml in stage I (50%) & stages II-IV (90%)
           b. levels are increased prior to clinical diagnosis of ovarian cancer
           c. follow up: after cytoreduction and chemotherapy for 3 months: if CA 125 level becomes normal, there will be no evidence of disease at 2\(^{nd}\) look laparotomy
        (2) other cancer arising from celomic epithelium e.g. endometrium
        (3) pancreatic, breast, colon or lung cancer
        (4) endometriosis
        (5) PID
        (6) pancreatitis
        (7) peritonitis
        (8) renal failure
        (9) liver cirrhosis
        (10)in only 1% of normal females
**Work up for ovarian neoplasm**

- **laboratory:** blood chemistries, complete blood count (CBC), CA 125
- **radiological:**
  1. pelvic ultrasound: multilocular cyst, solid areas, bilateral lesions, ascites, intra-abdominal metastases
  2. Chest x ray, IVP, barium enema
  3. CT scan or MRI
- **Laparotomy:** surgery is used to *diagnose, stage and treat* ovarian cancer
- **Women with an RMI score >200** should be referred to ovarian cancer surgery center

RMI = ultrasound score x menopausal score x CA125 level in U/ml

**FIGO Staging**

- **Preoperative bowel preparation** where clinical findings and imaging reveal an advanced disease with bowel involvement.
- **Perioperative VTE prophylaxis:** Unfractionated heparin or low molecular weight heparins (LMWH) (Ovarian cancer patients are at significant risk of developing VTE)
- **Surgicopathological staging:** Rules of Exploratory laparotomy

1. adequate vertical incision (midline sub umbilical)
2. take a sample for cytology from ascites or peritoneal wash
3. inspection of the neoplasm (capsular rupture during surgery should be avoided).
4. intraoperative frozen section assessment can be used to diagnose malignancy and to exclude metastatic disease
5. inspection of the other ovary, uterus, tubes & other pelvic organs
6. inspection & palpation of peritoneal surfaces, omentum, under surface of the diaphragm
7. Perform TAH + BSO + lymph nodes sampling (pelvic & para aortic) + infracolic omentectomy.

<table>
<thead>
<tr>
<th>I. Stage I: limited to the ovaries:</th>
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<tbody>
<tr>
<td>A. one ovary</td>
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<tr>
<td>B. both ovaries</td>
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<tr>
<td>C. one or both ovaries with tumor on external surface, ruptured ovarian capsule, ascites or positive peritoneal wash for malignant cells</td>
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<th>II. Stage II: pelvic spread:</th>
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<tbody>
<tr>
<td>A. uterus &amp;/or tubes</td>
</tr>
<tr>
<td>B. other pelvic tissues</td>
</tr>
<tr>
<td>C. either a or b with tumor on external surface, ruptured ovarian capsule, ascites or positive peritoneal wash for malignant cells</td>
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<th>III. Stage III: abdominal spread: including superficial liver metastasis</th>
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<tbody>
<tr>
<td>A. microscopic seedings of abdominal peritoneal surfaces,</td>
</tr>
<tr>
<td>B. implants ≤ 2 cm of abdominal peritoneal surfaces,</td>
</tr>
<tr>
<td>C. implants &gt; 2 cm of abdominal peritoneal surfaces or positive retroperitoneal &amp;/or inguinal lymph nodes</td>
</tr>
</tbody>
</table>

| IV. Stage IV: distant metastasis, parenchymal liver disease, pleural effusion with positive cytology. |
Treatment

- **prophylactic:**
  1. screen all high risk groups
  2. routine pelvic examination in postmenopausal patients
  3. routine examination of both ovaries during laparotomy e.g. CS
  4. prophylactic oophorectomy during general or gynecological laparotomy in all menopausal patient

- **benign:**
  1. <40 years:
     a. ovarian cystectomy
     b. ovariectomy (ovariotomy): solid tumor, whole ovary is involved
  2. >40 years: TAH + BSO

- **Epithelial ovarian cancer (EOC):**
  1. stage I:
     a. TAH + BSO.
     b. Adjuvant chemotherpay for
        (1) Higher-risk early-stage disease includes
           a. Stage I.C.
           b. Histological Grade 2 and grade 3.
           c. Clear cell carcinomas
        (2) These patients should be treated with front-line chemotherapy: *paclitaxel (Taxol) and carboplatin* (Cisplatin can be substituted for carboplatin) *for a minimum of 3-6 courses*
  2. stage II: TAH + BSO + postoperative front-line chemotherapy: *paclitaxel and carboplatin* (Cisplatin can be substituted for carboplatin) *for 6-8 courses*
  3. stages III & IV: Debulking (*Cytoreductive Surgery*) to reduce residual cancer before adjuvant treatment + postoperative front-line chemotherapy: *paclitaxel and carboplatin* (Cisplatin can be substituted for carboplatin) *for 6-8 courses*
  4. Interval chemosurgical debulking: in patients with bulky, unresectable tumor
  5. follow up by
     a. Visits every 2-4 months for 2 y, then 3-6 months for 3 y, then annually after 5 y
     b. Physical exam including pelvic Examination
     c. CA-125 every visit if initially elevated
     d. Chest/abdominal/pelvic CT, MRI, PET-CT, or PET as clinically indicated
     e. CBC and chemistry profile as Indicated
     f. second look laparotomy (or laparoscopy): may be done for patients who are clinically and radiologically free of disease after primary surgery and first-line chemotherapy.
  7. Estrogen replacement therapy after treatment of EOC
     a. The benefits of ERT outweigh the risks.
     b. endometrioid ca are theoretically estrogen-sensitive. If estrogen is used in such patients, a progestogen should be given with it.
• **Malignant Germ cell tumors:**
  1. unilateral salingoophorectomy (conservative surgery) can be done **ONLY** if
     a. Young patient who wishes to preserve fertility
     b. Stage I A: staging laparotomy negative.
     c. Close follow up: examination, CT scan, tumor markers.
  2. postoperative chemotherapy:
     a. VBP (vinblastine, bleomycin, platinum)
     b. VAC (vincristine, actinomycin, cyclophosphamide)
  3. Although dysgerminoma is extremely radiosensitive but chemotherapy gives the same results with the advantage of preserving fertility

**Prognosis**

• **prognostic factors:**
  1. amount of residual tumor remaining after surgery
  2. the stage
  3. additional therapy after surgery

**Ovarian cancer has a bad prognosis (the overall 5-year survival rate is 31%):**
  1. early cases are asymptomatic
  2. no reliable screening
  3. usually diagnosed late stage (III C)
  4. early transcelomic (no peritoneal covering) & lymphatic spread
  5. no prophylaxis except bilateral oophorectomy

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