The Cervix

1. **Shape and Dimensions**
   a. Is the lower, narrow portion of the uterus, connected to the uterine fundus by the uterine isthmus.
      i. upper limit is considered to be the internal os,
      ii. cervix protrudes through the upper anterior vaginal wall.
      iii. Approximately half its length is visible; the remainder lies above the vagina beyond view.
   b. The portion projecting into the vagina is referred to as the portio vaginalis.
      i. The portio vaginalis averages 3 cm long and 2.5 cm wide.
      ii. The size and shape of the cervix varies widely with age, hormonal state, and parity.
      1. In parous women, the cervix is bulkier and the external os appears to be more slit-like and gaping than in nulliparous women.
      2. Before childbearing, the external os is a small, circular opening at the center of the cervix.
   c. The portion of the cervix exterior to the external os is called the ectocervix.
   d. The endocervical canal is the passageway between the external os and the endometrial cavity.
      i. Its upper limit is the internal os.
      ii. Flattened anterior to posterior, the endocervical canal measures 7 to 8 mm at its widest in reproductive-aged women.
      iii. The canal is a complex configuration of mucosal folds or plicae.
      iv. These make cytologic screening and colposcopy of the endocervical tissues technically more difficult and less reliable than for the smoother and more accessible squamous epithelium of the ectocervix.

2. **Lymphatics / mucosal immunity**
   a. The lymphatic drainage of the cervix includes common, internal, and external iliac nodes, the obturator and parametrial nodes.
   b. The primary route of spread of cervical cancers is through the lymphatics of the pelvis.
   c. Radical hysterectomy for invasive cancer of the cervix includes removal of as much of the pelvic lymphatics as possible.

3. **Support and Innervation**
   a. The main support structures of the cervix are the cardinal and uterosacral ligaments.
   b. Sensory, sympathetic, and parasympathetic fibers are present in the cervix.
   c. Instrumentation of the endocervical canal (dilatation and / or curettage) may result in a vasovagal reaction with reflex bradycardia in some patients.
   d. The endocervix also has a plentiful supply of sensory nerve endings, while the ectocervix is relatively lacking in these. This allows procedures such as small cervical biopsies and cryotherapy to be well tolerated in most patients without the use of anesthesia.

4. **Histology of the Normal Cervix**
   a. The stroma of the cervix, which accounts for most of its mass and shape, is composed of dense, fibromuscular tissue made up of collagenous connective tissue (smooth muscle and elastic tissue) and ground substance (mucopolysaccharide).
      i. Through the stroma course the vascular, lymphatic, and nervous supplies of the cervix.
      ii. The stroma plays little role in cervical neoplasia.
   b. The epithelium of the cervix gives rise to cervical neoplasia.
   c. The cervix is covered by both columnar and stratified non-keratinising squamous epithelia.
   d. The squamocolumnar junction (SCJ), where these two meet, is the most important cytologic and colposcopic landmark.
i. The SCJ is where over 90% of lower genital tract neoplasia arises.
ii. The SCJ is thought to be the embryologic junction of the Müllerian and urogenital sinus epithelia.

5. **Squamous Epithelium**
   a. The squamous epithelium of the cervical portio is similar to that of the vagina, except that it is generally smooth
      i. Colposcopically, it appears featureless except for a fine network of vessels which is sometimes visible.
      ii. The relative opacity and pale pink coloration of the squamous epithelium derives from its multi-layered histology
   b. The maturation and glycogenation of the squamous epithelia of the vagina and cervix are influenced by **ovarian hormones**.
      i. Estradiol promotes maturation, glycogenation, and desquamation.
      ii. Progesterone inhibits superficial maturation.
      iii. This explains why the squamous epithelium appears atrophic after loss of ovarian function, with pallor and subepithelial point-hemorrhages from increased vulnerability of the underlying vessels.
      iv. Atrophic changes may also be seen, albeit less dramatically, with prolonged exposure to **progestins**, as with injectable progestin-only contraceptives.
      v. Glycogenation of the mature squamous epithelium of the vagina and cervix under the influence of estrogen cause strong uptake of *Lugol's* iodine solution.
         1. **Schiller's test is** used to help distinguish normal tissue from abnormal.
   c. *Dysplastic* or HPV-infected squamous epithelium show arrested maturation with incomplete or absent glycogenation and will reject iodine staining. It may also show abnormal deposition of keratin in the upper layers of the epithelium.

6. **Glandular Epithelium**
   a. The “glandular” or **columnar epithelium** of the cervix is located cephalad to the squamo-columnar junction.
      i. It covers a variable amount of the *ectocervix* and lines the *endocervical canal*.
      ii. It is comprised of a single layer of *mucin-secreting cells*.
   b. The epithelium is thrown into longitudinal folds and invaginations that make up the so-called **endocervical glands** (they are not true glands).
      i. The infolding crypts and channels make the cytologic and colposcopic detection of neoplasia less reliable and more problematic.
      ii. The complex architecture of the endocervical glands gives the columnar epithelium a papillary appearance through the colposcope and a grainy appearance upon gross visual inspection.
      iii. The single cell layer allows the coloration of the underlying vasculature to be seen more easily. Therefore, the columnar epithelium appears redder in comparison with the more opaque squamous epithelium.
iv. Endocervical canal – a single layer of columnar cells with a basal layer.

7. **Mucosal Immunity**
   a. Both the secretory (IgA mediated) and cellular immune systems are active
      i. macrophages, including some Langerhans cells, -lymphocytes are present.
   b. Local immunity is suspected to play an important role in the wide variety of outcomes seen among individuals following HPV infection and in the susceptibility to the development of neoplasia.

8. **Squamocolumnar Junction**
   a. The squamocolumnar junction (SCJ) is the junction between the squamous epithelium and the glandular epithelium.
   b. It is often marked by a line of metaplasia and its location is variable.
   c. Age and hormonal status are the most important factors influencing its location.
      i. During the perimenarche, the SCJ is located at or very close to the **external os**.
      ii. The SCJ is generally located on the **ectocervix** at variable distances from the os in reproductive-aged women due to the effect of estrogen on length of the endocervical canal,
      iii. high estrogen levels of pregnancy and oral contraceptive use promote further eversion of the SCJ.
   iv. Eversion is usually more pronounced on the anterior and posterior lips of the ectocervix and less so at the 3 and 9 o’clock positions.
   v. Eversion of the columnar epithelium onto the ectocervix may not be symmetrical.
      1. The resulting asymmetric appearance may cause confusion and prompt a referral for a possible cervical lesion.
      2. An eversion of the SCJ onto the ectocervix is sometimes referred to as an “ectropion” or “erosion.”
      3. “Erosion” is a misnomer and should not be used.
vi. Occasionally, the SCJ is located in part or entirely on the vaginal fornices.

1. The process of squamous epithelialization of the vaginal tube begins at the dorsal urogenital sinus and vaginal plate, spreading upwards along the vaginal tube.
2. If the epithelialization proceeds normally, the SCJ is located at near the external os of the cervix.

3. If the epithelialization is arrested before completion, the SCJ will be located on the vaginal walls
   a. usually involving the anterior and posterior vaginal fornices, as epithelialization in these locations occurs later than laterally.
   b. This type of variant in SCJ location are most striking in in-utero DES-exposed women.
   c. In some cases the entire cervical portio will be covered with columnar epithelium.
   d. From the perimenopause on, or with prolonged exposure to strong progestational agents which cause atrophy, the SCJ recedes up the endocervical canal. This makes cytologic sampling less reliable and colposcopic examination of the SCJ impossible in many cases.
   e. Identifying the location of the SCJ is important for the optimal collection of cytologic samples.
   f. The acquisition of cells should be modified from patient to patient to insure that the area at risk for neoplasia is targeted.
      i. The location of the SCJ also determines in large part the efficacy of colposcopy in ruling out the presence of neoplasia.
      ii. If the SCJ cannot be visualized in its entirety, the colposcopy is deemed “unsatisfactory.”
   f. Finally, the location of the SCJ influences the choice of treatment modality if neoplasia is present.

9. Transformation Zone
   a. The transformation Zone (TZ) is essential to the identification and management of cervical intraepithelial neoplasia.
   b. It lies between the “original” and “new” squamocolumnar junctions.
   c. The SCJ discussed above is the visible border between the squamous and columnar epithelia of the cervix and represents the new squamocolumnar junction.
   d. It is adjacent to the new SCJ that the dynamic process of squamous metaplasia occurs throughout the reproductive years.
   e. Squamous metaplasia is a normal process during which columnar epithelium is replaced by squamous.
   f. The trigger for this process is thought to be the eversion of the columnar epithelium under the influence of estrogen and its subsequent exposure to the acidic vaginal pH.
   g. In response to the “insult” of vaginal acidity, the process of metaplasia replaces the more fragile columnar epithelium with the more sturdy squamous type.
   h. This process is thought to occur by two mechanisms.
      i. Reserve cell hyperplasia.
         1. Reserve cells proliferate around the exposed endocervical glands and eventually obliterate and replace them.
         2. The columnar epithelium is replaced, not changed into another type of epithelium.
ii. Some metaplasia occurs by the ingrowth of squamous epithelium centripetally from the squamous epithelium of the ectocervix.
   1. This ingrowth undermines and replaces the overlying columnar epithelium.
   2. The net result is a zone of squamous metaplasia of variable width distal (caudal) to the columnar epithelium and proximal (cephalad) to the “original squamous epithelium” laid down during embyogenesis.

i. The border between the metaplastic epithelium arising during the reproductive years and the original squamous epithelium is called the “original SCJ.”

j. The TZ is the area of metaplastic epithelium between the original and new SCJs.

   i. During the process of metaplasia, still-functioning endocervical glands may become covered and blocked, giving rise to Nabothian cysts.

ii. The metaplastic epithelium adjacent to the new SCJ is the newest and the least mature squamous epithelium on the cervix.

iii. As new metaplastic epithelium arises, the older metaplastic epithelium is moved outward toward the original SCJ.

iv. The newest and least mature metaplasia is adjacent to the new SCJ.

v. With time, the metaplastic epithelium matures to the point where its thickness and glycogenation is indistinguishable from the original squamous epithelium.
   1. This makes the colposcopic identification of the original SCJ, and therefore the outer limits of the TZ, impossible in many cases.
   2. The location of Nabothian cysts, always formed within the TZ, is useful in identifying its limits.
k. Essentially all cervical neoplasia arises within the transformation zone.
l. Metaplasia is particularly active during the peripubertal years and during the first pregnancy.
1. Perhaps this accounts for the fact that early first sexual intercourse and early age at first pregnancy are risk factors for cervical cancer.

2. It is hypothesized that the reserve cells in adolescent and young women are especially vulnerable to the oncogenic potential of human papillomavirus infection.

3. The size and location of the TZ will influence selection of treat modality if neoplasia is present.

4. Nearly all cervical neoplasia occurs in the TZ.

5. This is even true of the adenocarcinomas, which are often associated with adjacent high-grade squamous disease.

6. The reserve cells undergoing metaplasia that are vulnerable to various carcinogens such as HPV.

7. Since metaplasia is at peak activity during adolescence and first pregnancy, it is understandable that early age on sexual activity and first pregnancy are known risk factors for cervical cancer.

8. The importance of the TZ to cervical neoplasia explains why it is desirable to see both columnar (endocervical) and squamous metaplastic cells on Pap smears. Their presence indicates that the area at risk has indeed been sampled.
11. **Pregnancy-related Changes**
   a. The cervix in pregnancy shows stromal edema, increased vascularity, enlargement of glandular structures, and acute inflammatory response.
   b. Stromal decidualization may occur in the second and third trimesters; these changes may appear suspicious to the inexperienced observer.

**Invasive Cancer of the Cervix**

1. Cervical cancer is a relatively uncommon finding in comparison to the number of cases of CIN diagnosed annually in the US.
2. In 2000, the incidence of invasive cervical cancer was estimated at 12,800 cases, and there were 4,600 cervical cancer related deaths.
3. In other parts of the world that lack screening programs, cervical cancer is still the most common cancer among women.
4. **Characteristic features of cervical cancer**
   a. Atypical vessels-non branching (comas, corkscrew, sausage shaped, hairpin)
      i. As a cancer of the cervix develops, neovascularization occurs as the result of tumor angiogenic factor released by the cancer cells.
      ii. These vessels do not follow the normal regular arborizing vessel pattern, but instead the new vessels have irregular course and caliber.
      iii. They can run parallel to the surface of the cervical epithelium and form non-branching patterns such as corkscrews, squiggles and comma shaped vessels.
   b. Abnormal vaginal bleeding or discharge
   c. Ulcerations
   d. Raised, irregular surface
   e. Yellow color to epithelium
   f. Firmness to palpation
5. **Diagnosis**
   a. Cervical cancer can be squamous, glandular or mixed type.
   b. Invasion is diagnosed when there is a breach in the basement membrane.
      i. If the invasion extends 3 mm or
less, it is referred to as microinvasive disease.

ii. If invasion is greater than 3mm, it is frankly invasive cancer.

C. If biopsy or endocervical curettage reveals invasive cancer, a cone biopsy is not needed.

6. Epidemiology
   a. There are approximately 12,800 new cases/year and around 4600 deaths/year in the United States.
   b. There are 50,000 new cases carcinoma in situ/year.
   c. There are 2 major histological types of cervical cancer.
      i. 93% are squamous cell cancers and contain HPV DNA;
         1. 90% are subtypes 16/18, which are most virulent.
      ii. 7% of cases are adenocarcinomas -- but these are on the rise.
      iii. Adenocarcinomas are associated with HPV type 18.
   d. When considering preinvasive disease, the classic theory holds that SIL leads to squamous carcinoma.
      i. When SIL progress to invasive squamous cervical cancer, ISCC usually develops from an area of SIL located adjacent to the SCJ.
      ii. Oncogenic HPV serves as initiators.
      iii. Other factors relating to immune status such as cigarette smoking, nutrition, or chlamydia infections may be promoters.
   e. Adenocarcinoma develops from glandular atypia and may be preceded by an Atypical Glandular Cells of Uncertain Significance (AGUS) Pap smear.
      i. The only preinvasive stage we usually find is adenocarcinoma in situ (AIS)
   f. The median age to develop cervical cancer is 45 to 50 years.
   g. Older women are often more susceptible due to lack of screening.
   h. Younger women have more problems with rapidly progressing disease.
      i. 50% of women diagnosed with invasive cancer have never had a Pap smear.
      i. 10% have not had a Pap smear in last 5 years.

See this article on new tests to detect cervical cancer
7. **Staging of Cervical Cancer**

Stage 0 -- carcinoma-in-situ

Stage I -- the tumor is confined to the cervix

- **IA** -- microinvasive disease, with the lesion not grossly visible: no deeper than 5 mm and no wider than 7 mm
  - **IA1** -- invasion <3 mm and no wider than 7 mm
  - **IA2** -- invasion >3 mm but <5 mm and no wider than 7 mm
- **IB** -- larger tumor than in IA or grossly visible, confined to cervix
  - **IB1** -- clinical lesion no greater than 4 cm
  - **IB2** -- clinical lesion greater than 4 cm

Stage II -- extends beyond the cervix, but does not involve the pelvic side wall or lowest third of the vagina

- **IIA** -- involvement of the upper 2/3 of vagina, without lateral extension into the parametrium
- **IIB** -- lateral extension into parametrial tissue

Stage III -- involves the lowest third of the vagina or pelvic side wall, or causes hydronephrosis

- **IIIA** -- involvement of the lowest third of the vagina
- **IIIB** -- involvement of pelvic side wall or hydronephrosis

Stage IV -- extensive local infiltration or has spread to a distant site

- **IVA** -- involvement of bladder or rectal mucosa
- **IVB** -- distant metastases

8. **Treatment and Survival**

a. Treatment of frankly invasive cancer usually consists of a radical hysterectomy with lymph node dissection, or radiation therapy with advanced disease.

b. If the biopsy reveals microinvasive disease, a cone biopsy is required, since a biopsy alone is insufficient to rule out frankly invasive cancer, which may be adjacent to the biopsy site.

c. If a cold cone or loop excision reveals microinvasive cervical cancer with clear margins, treatment can include a simple hysterectomy or, if the patient desires to maintain her fertility, observation with careful follow-up.

Stage IA -- 5-year survival 95%

- simple hysterectomy or careful observation after cone biopsy (With clear margins).

Stage IB or IIA -- 5-year survival 70% to 85%
radical hysterectomy with pelvic-node dissection, or
even external beam and intracavitary radiotherapy (equally effective)

Stage IIB, III, IVA--5-year survival 65%, 40%, 20% respectively

- pelvic radiotherapy
- Treatment with cisplatin-based chemotherapy should strongly be considered for patients receiving radiotherapy

Stage IVB--5year survival 10%

- chemotherapy with or without pelvic radiotherapy