Cervical cancer

Epidemiology

- Significant downtrend in the incidence
- Current lifetime risk in developed countries is 0.7%
- More common in developing countries
- Average age of diagnosis is 50

Risk factors

- **HPV-related**: in almost all cases, cervical Ca due to persistent HPV, risk factors that are associated with HPV-related cancers:
  - Early onset of sexual activity
  - Multiple sexual partners
  - A high-risk sexual partner (partner with multiple sexual partners)
  - History of STIs
  - Increasing parity / early age at first birth
  - Immunosppression

- **Non HPV-related:**
  - Lower socioeconomic status
  - Cigarette smoking
  - Estrogen (COCs): especially adenocarcinoma rather than SCC

Pathogenesis

- HPV plays a central role (detected in 99.7%) of cervical cancer.
- More than 40 genital HPV types identified, some are oncogenic.
- Subtypes HPV 16 and 18 found in over 77% of all cervical cancers

- Major steps in cervical cancer development:

1. Oncogenic HPV infection of the metaplastic epithelium
2. Persistence of HPV infection
3. Progression of a clone of epithelial cells from persistance to precancer
4. Invasion of basement cells and development of carcinoma

- Most women readily clear HPV
- In general, progression from infection to invasive cancer require several years (average 15 years)

Histopathology

- Most common histologic types of cervical cancer are: SCC and adenocarcinoma.
- **SCC:** account for 70%, affects the ectocervix, divided into keratinizing and nonkeratinizing, mostly due to HPV.
- **Adenocarcinoma:** account of 25%, affects the endocervix (mucus-producing columnar cells), usully occult and diagnosed at advanced stage, more than 80%% due to HPV

Diagnosis

- Early cervical cancer is frequently asymptomatic (importance of screening)
- The most common symptoms: Irregular or heavy vaginal bleeding, or postcoital bleeding.
- Some patients have mucoid or watery vaginal discharge
- Patients with advanced disease have pressure symptoms or back pain, ususally have advanced disease

Physical examination

- Most women have normal general physical examination
- Pelvic examination should be done in any woman with suspected cervical cancer
- Cervix can appear grossly normal, Genital warts should be sought
- Visible cervical disease displays varied appearance (exophytic, endophytic, polypoid or papillary growth, ulceration, granular mass …)

- **With advanced disease**:
- Enlarged uterus on bimanual exam, extension into vagina, mass palpated on rectovaginal exam.
- Lower limb edema may reflect compression of lymphatics.
- Hydronephrosis due to compression of ureters leading to renal angle tenderness and sigs of uremia

Investigations

- CBC: anemia
- Urinalysis: heamturia
- Creatinine: obstruction
- LFT: liver metastasis
- Cystoscopy
- Proctoscopy
- Cervical biopsy when lesion visible or symptomatic, not pap smear.

Imaging

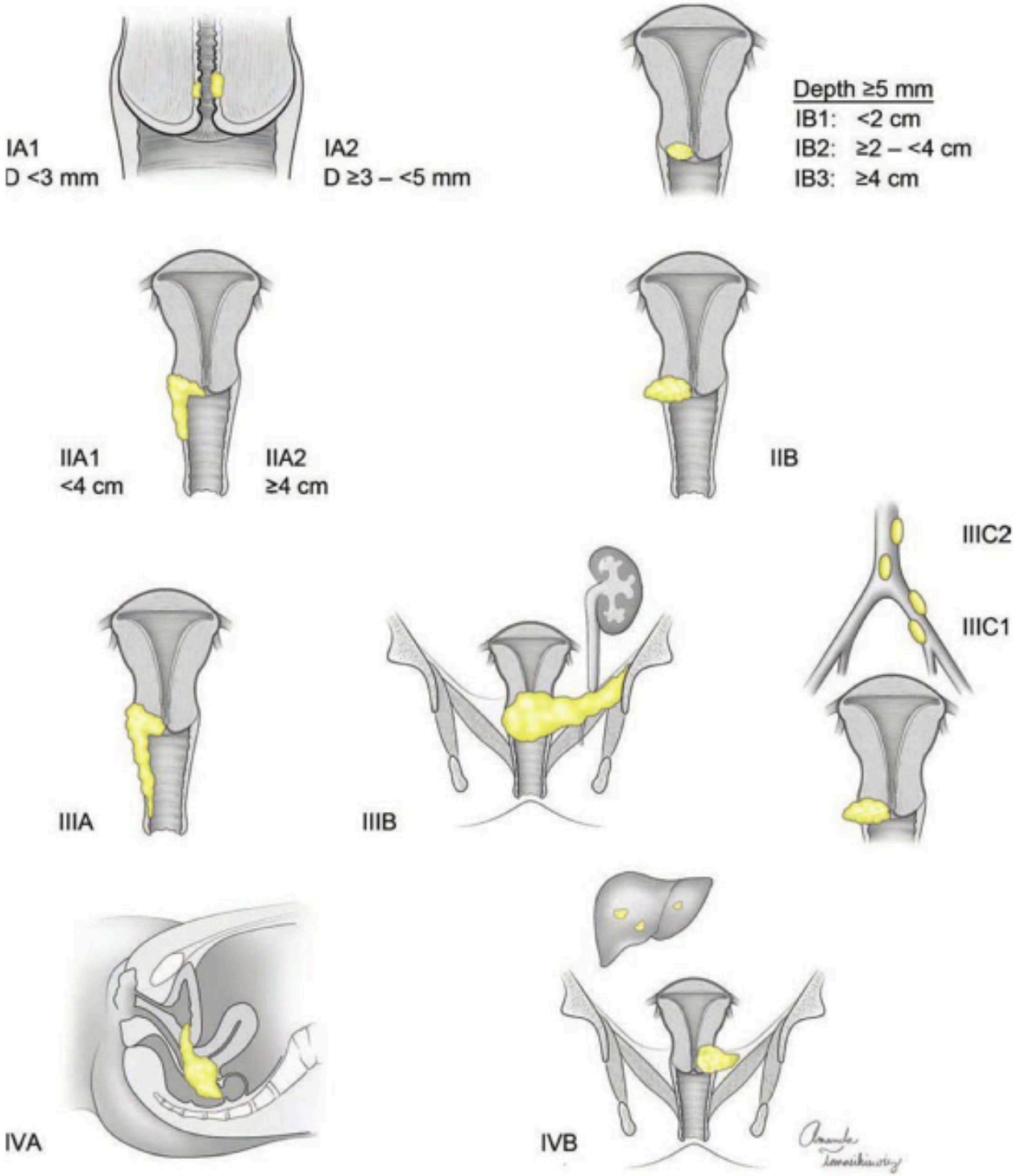
- Imaging is incorporated into FIGO staging
- MRI to measure tumor size, local parametrial invasion
- CT used to exclude metastaic disease, to lymph nodes or distant organs
- Chest radiograph
- IVP

Staging

- Currently, staging is Surgical and Radiological
- Traditionally used to be clinical
- Ususally early stage disease describes stages IB2 and lower
- LVSI (lymphovascular space invasion)is poor indicator especially in early stage
- Lymph node evaluation is important during surgical staging (pelvic and paraaortic lymph nodes)

TABLE 30-3. Clinical Stages of Cervical Cancer (FIGO, Revised 2018)

Stage	Characteristics[a]
0	**Carcinoma in situ, cervical intraepithelial lesion (CIN) 3**
I	**Carcinoma is strictly confined to cervix (extension to corpus should be disregarded)**
IA	Microscopic lesion, invasion is limited to measured stromal invasion with a maximum depth <5 mm
IA1	Measured invasion of stroma <3 mm in depth
IA2	Measured invasion of stroma ≥3 mm and <5 mm in depth
IB	Clinical lesions confined to the cervix or preclinical lesions greater than IA
IB1	Invasive carcinoma <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive ≥4 cm in greatest dimension
II	**Carcinoma extends beyond uterus but has not extended to pelvic wall; it involves vagina, but not as far as the lower third**
IIA	No obvious parametrial invasion
IIA1	Invasive carcinoma <4 cm in size
IIA2	Invasive carcinoma ≥4 cm in size
IIB	Obvious parametrial involvement
III	**Carcinoma has extended to the pelvic wall; on rectal examination there is no cancer-free space between tumor and pelvic wall; tumor involves lower third of vagina; all cases with hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to another cause; involves pelvic and/or para-aortic lymph nodes[b]**
IIIA	No extension to pelvic wall, but involvement of lower third of vagina
IIIB	Extension to pelvic wall, or hydronephrosis or nonfunctioning kidney due to tumor
IIIC1	Pelvic lymph node metastasis only
IIIC2	Paraaortic lymph node metastasis
IV	**Carcinoma has extended beyond true pelvis or has clinically involved mucosa of bladder or rectum**
IVA	Spread of growth to adjacent pelvic organs
IVB	Spread to distant organs


IA1
D <3 mm
IA2
D ≥3 – <5 mm
Depth ≥5 mm
IB1: <2 cm
IB2: ≥2 – <4 cm
IB3: ≥4 cm
IIA1
<4 cm
IIA2
≥4 cm
IIB
IIIA
IIIB
IIIC2
IIIC1
IVA
IVB

Management

- For early stage disease surgery is preferred over radiation
- Stage IA1 (without LVSI): Simple hysterectomy or Conization (according to fertility desires)
- Stage IA1 (with LVSI): Modified radical hysterectomy with PLND or radical trachelectomy with PLND
- Stage IA2: Radical hysterectomy with PLND or radical trachelectomy with PLND

- Stage IB1, IB2, IIA1: Radical hysterectomy with PLND or Radical trachelectomy with PLND (Chemoraidation considered for specific cases)
- Ovarian transposition should be considered if ovaries are preserved and EBRT is anticipated
- Stage IB3 and IIA2: **Chemoradiation,** adjuvant hysterectomy can be considered
- Stage IIB and above: Chemoradiation (Paliative CCRT in IVB)

Procedure[b]	Type[c]	Involved Tissues[a]			
		Parametria & Paracolpos	Uterine Vessels	Uterosacral Ligament	Vagina
Simple hysterectomy	I	Preserve	Ligate at uterine isthmus	Transect at uterine insertion	Preserve
Modified radical hysterectomy	II	Removed medial to ureter	Ligate at level of ureter	Transect midway between uterus & rectum	Remove 1–2 cm
Radical abdominal hysterectomy	III	Removed medial to uterine vessel origin	Ligate at origin from internal iliac vessels	Transect near rectum[d]	Remove ≥2 cm
Type	IV[e]	Removed medial to uterine vessel origin	Ligate at origin from internal iliac vessels; ligate superior vesical artery	Transect near rectum	Remove 3/4ths
Type	V[e,f]	Removed medial to uterine vessel origin	Ligate at origin from internal iliac vessels; ligate superior vesical artery	Transect near rectum	Remove 3/4ths

- The most common complication of radical hysterectomy is urinary dysfunction as a result of partial denervation of the detrusor muscle.
- Other complications include shortened vagina, hemorrhage, infection, bowel obstruction, **rectovaginal fistulas**

Chemoradiation

- Evidence indicates chemotherapy given concurrently with radiation improves survival rate compared with radiation alone
- Cisplatin-base chemotherapy considered
- For certain patients Pembrolizumab has been approved to be given with CCRT

Prevention

- Vaccination: Gardasil-9, against HPV 6, 11, 16, 18, 31, 35, 45, 52 and 58
- Given to girls and boys aged 9 -14 years (before onset of sexual activity), 2 doses
- Catch up can be given between ages 15 -26, 3 doses schedule
- May be given to adults aged 27-45, some benefit

Thank you