Endometrial Cancer

Epidemiology

- Lifetime risk is 3%.
- Most patients are diagnosed early (67% of affected women will have Stage I patients)
- Most common gynecologic malignancy worldwide
- Average of diagnosis is early 60s

Classification

- Dualistic model of pathogenesis:
- Type I: Endometrioid adenocarcinoma, 80 -90%, estrogen-dependent, low grade, derived from atypical endometrial hyperplasia.
- Type II: Serous or Clear Cell, not dependent on estrogen, no precursor lesions, and more aggressive clinical course.

Risk Factors

- Type I EC is associated with an excess-estrogen environment:
  - Obesity
  - PCOS
  - Unopposed estrogen therapy
  - Early menarche
  - Late menopause
  - Nullipairty
  - Tamoxifen use
  - Family history (HNPCC – 40-60% have EC)
  - DM, HTN (Association, not causal)

Protective factors

- COCs: due to progesterone
- Smoking: Hypo-estrogenic state

Signs and Symptoms

- Prolonged heavy menstruation or intermenstrual spotting in premenopausal women
- Postmenopausal bleeding (5-10% will have EC)
- Abnormal vaginal discharge in older women
- Pelvic pressure, pain, bloating, early satiety (advanced disease or Type II EC)

Imaging

- TVUS is the first-line imaging method for suspected EC
- In postmenopausal women, a threshold of 4mm has been proposed to triage patients:
- ≤ 4mm: low risk for EC
- > 4mm: further evaluation with biopsy needed
- In premenopausal women, there is no single “cutoff”, because of endometrial changes with the cycle

- CT scan can be used to assess lymph nodes or metastatic disease
- MRI can be used to assess cervical invasion (and distinguish from primary Cervical ca) and myometrial invasion (if fertility sparing management required)

Pap test

- Pap test is a screening test for cervical cancer.
- Some findings should prompt evaluation for EC
- Benign endometrial cells: in premenopausal women has limited importance, in postmenopausal women 3-5% of EC (1-2% if on HRT)
- So endometrial sampling is warranted in asymptomatic postmenopausal women with this finding.

- Atypical glandular cells on Pap test, have higher risk for underlying cervical or endometrial neoplasia.
- Thus, Colposcopy and endocervical currettage are done
- Endometrial sampling done in patients older than 35 years.
- In patients younger than 35 years, endometrial sampling done if AUB coexists, if has risk factors for EC, or cytology report specifies that cells are endometrial in origin

Endometrial Sampling

- Pipelle biopsy is preferred for the initial evaluation of women with suspected EC.
- If Pipelle fails to provide suffecient diagnostic information, D&C is required.
- Hysteroscopy is more sensitive for focal endometrial lesions, and less helpful in early EC.

Laboratory testing

- The only clinically useful marker is CA125.
- Elevated levels indicate possibility of more advanced disease.
- In practice, it is most useful in monitoring response to therapy in advanced disease or serous subtypes

Pathology

- Histologic grade: determined by the tumor's architectural growth pattern

1. Grade 1: indolent with little propensity to spread outside uterus.
2. Grade 2: intermediate prognosis.
3. Grade 3: increased potential for myometrial invasion and nodal metastasis.

Histologic type

- **Endometriod Adenocarcinoma**
  - the most common type (80% of cases)
  - Contains glands that resemble normal endometrium
  - When the glandular component decrease and replaced by solid nests of cells, the garde becomes higher.

- **Serous Carcinoma**:
  - 5-10% of EC,
  - highly aggressive, nuclear atypia, complex pattern of papillay growth
  - Histologic appearance resembles epithelial ovarian cancer
  - Has propensity for myometrial, lymphatic, and intraperitoneal spread

- Clear Cell Carcinoma
- Carcinosarcoma
- Mucinous Carcinoma
- Mixed carcinoma, undifferentiated carcinoma ..

Staging

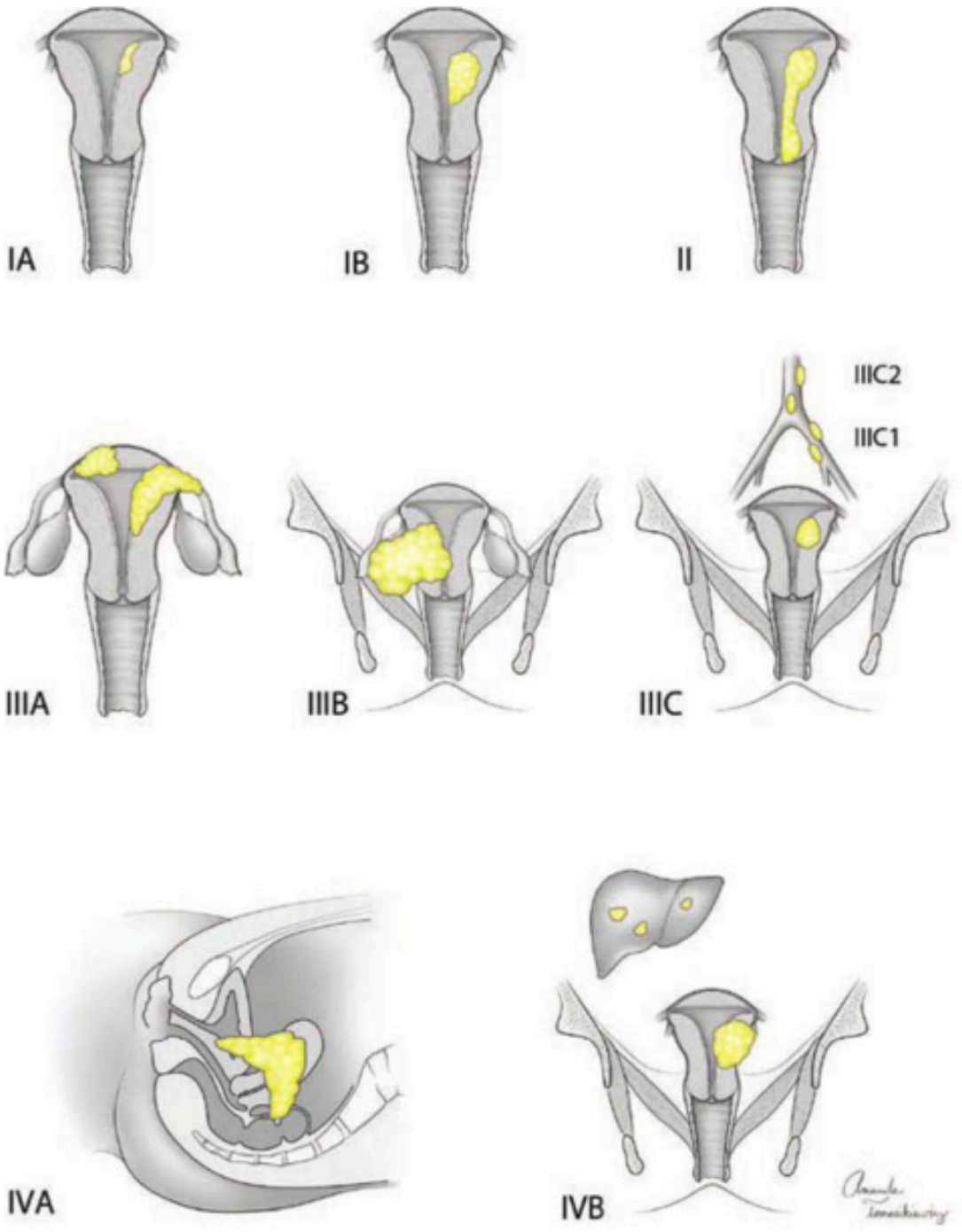
- Staging is surgical and pathological

FIGO Staging 2009

FIGO stage	Substage	Definition
I		Tumour confined to corpus uteri
	IA	Tumour limited to endometrium or invades less than one half of the myometrium
	IB	Tumour invades one half or more of the myometrium
II		Tumour invades stromal connective tissue of the cervix but does not extend beyond uterus
III		Local and/or regional spread
	IIIA	Tumour involves serosa and/or adnexae (direct extension or metastases)
	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
	IIIC	Metastases to pelvic and/or para-aortic lymph nodes
	IIIC1	Regional lymph node metastases to pelvic lymph nodes
	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
IV		Tumour invades bladder mucosa and/or bowel mucosa, and/or distant metastases
	IVA	Tumour invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumour as T4)
	IVB	Distant metastases (includes metastases to inguinal lymph nodes, intraperitoneal disease, or lung, liver, or bone metastases)

TABLE 1 2023 FIGO staging of cancer of the endometrium.[a,b]

Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIICii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone


IA
IB
II
IIIA
IIIB
IIIC
IIIC2
IIIC1
IVA
IVB

Management

- Most patients should undergo Hysterectomy and BSO
- Few circumstances contraindicate primary surgery such as massive obesity, high operative risk, desire for fertility
- In general, Simple (type I) hysterectomy is sufficient
- Radical hysterectomy (type II or III) may be preferred for patients with cervical extension

- Laparotomy had been standard approach.
- Laparoscopic and robotic are used for EC confined to uterus
- Lymphadenectomy not usually done, depending on myometrial invasion or grade of disease.
- Serous, Clear cell or Carcinosarcoma, requires more extensive surgery

Follow up

- Surgically treated patients simple followed up by **pelvic examination** every 3-6 months for 2 years, then 6-12 every 3 years.
- Imaging or CA12 measurments, usually for more advanced disease that requires radiation or chemotherapy

Chemotherapy

- Three classes of cytotoxic drugs with definite activity for EC:
- TAP chemotherapy: paclitaxel (Taxol), doxorubicin (Adriamycin), and cisplatin.
- Less toxic combination: paclitaxel and carboplatin.
- Frequently combined with radiotherapy

Radiotherapy

- Primary vs Adjuvant radiation therapy.
- Primary RT mainly for exceptionally poor surgical candiadates. (Intracvaitary bracytherapy or external beam radiation)
- Adjuvant RT reduces risk of recurrence in higher risk subgroups (high grade, LVSI, myometrial invasion, high age)
- The type of radiation for adjuvant RT is vaginal brachytherapy

Hormonal therapy

- EC is hormonal responsive
- Thus, women who are not surgical candidates, continous progestin (LNG-IUD) can be used
- Can act as adjuvant therapy in recurrent disease

Prevention

- Women with PCOS may benefit from weight loss and progestin therapy
- Women with Lynch (proved by genetic testing) benefit form screening, biopsy every 1-2 years at age 30-35 years.
- Prophylactic hysterectomy (usually with BSO) in early to mid 40s

Thank you