

OBSTETRICS AND GYNECOLOGY

(9) : Malignant Uterine Tumors

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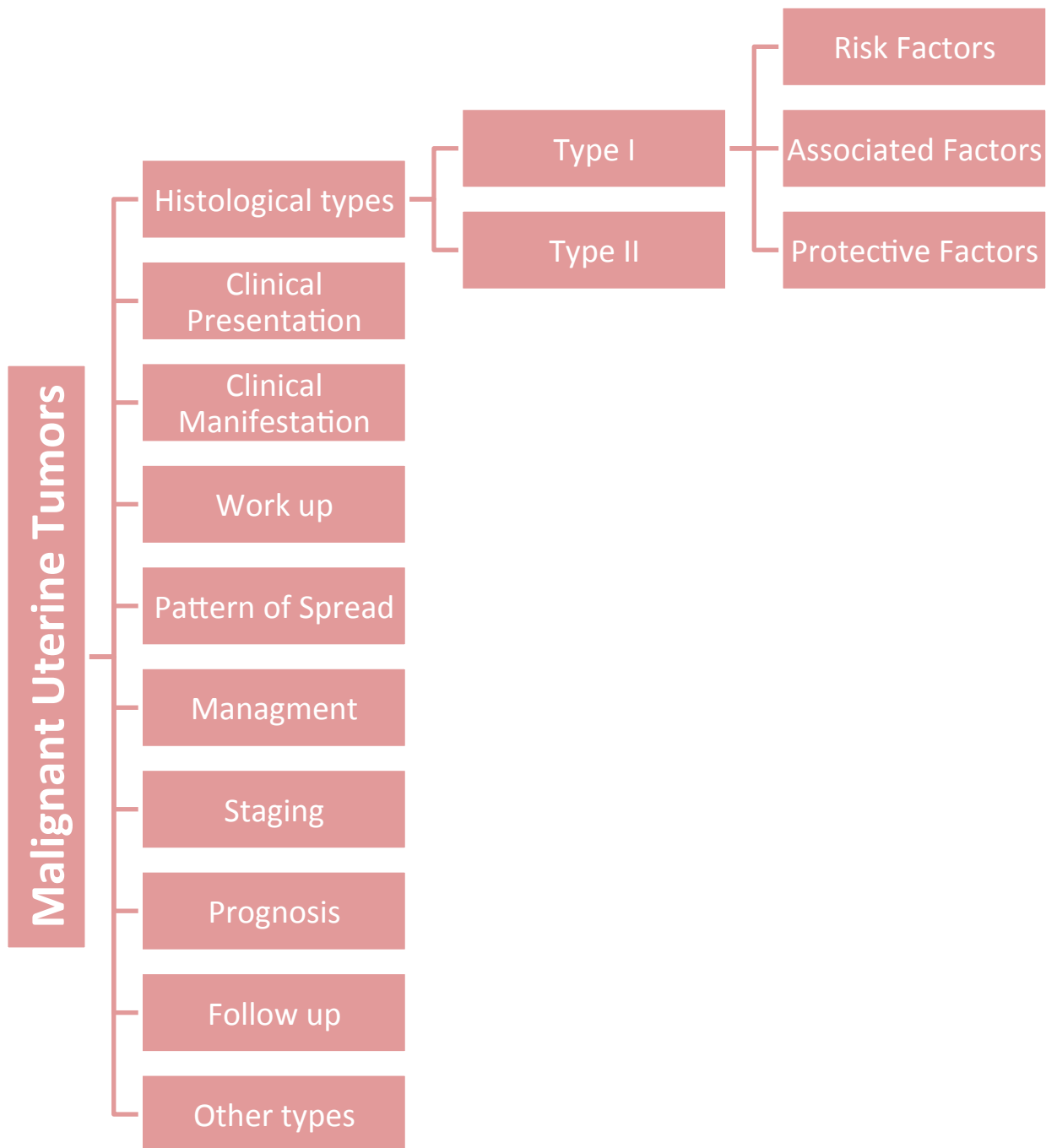
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Objectives:

Not given.



Epidemiology

- ✓ Most common gynecological cancer in the **developed countries**, with an incidence of 12.9 per 100,000 women and a mortality rate of 2.4 per 100,000. (Developing countries =cervical as most common)
- ✓ In developing countries, it is the **second most common** gynecologic malignancy, with an incidence of 5.9 per 100,000 and a mortality rate of 1.7 per 100,000.
- ✓ The average age of diagnosis of uterine cancer in the US is **61 years old**.
- ✓ From ages 50 to 70, women have a 1.4% risk of being diagnosed with uterine cancer.
- ✓ Women in the US have a 2.6% lifetime risk of developing uterine cancer.
- ✓ **Developed countries and age** are important factors in Endometrial cancer.

Histological types

Type I tumors Estrogen dependent (chronic unopposed estrogen exposure)	Type II tumors (non endometrioid – behave as ovarian CA. when papillary serous)
80 percent of endometrial carcinomas.	10 to 20 percent of endometrial carcinomas.
Grade 1 or 2.	Grade 3 endometrioid tumors & serous, clear cell, mucinous, squamous, transitional cell, mesonephric, and undifferentiated.
Endometrioid histology.	High-grade.
Favorable prognosis, are estrogen-responsive , and may be preceded by an intraepithelial neoplasm (atypical and/or complex endometrial hyperplasia) (precancerous lesions).	Poor prognosis, and are not clearly associated with estrogen stimulation . A precursor lesion is rarely identified.

Type I: Risk factors, Associated factors And Protective factors

Risk factors

Normally Estrogen causes chronic proliferation of the endometrium while Progesterin

counteracts that action. Incase of type 1 there's unopposed estrogen exposure.

Exogenous Estrogen

- Tamoxifen/Raloxifin : which is given to breast cancer patients. Its effect on the endometrium can be prevented by giving Minera)
- Unopposed systemic estrogen therapy: Its effect on the endometrium can be prevented by giving Minera or progesterone in the 2nd part of the cycle)
- Postmenopausal estrogen therapy
- Phytoestrogen

Endogenous estrogen

- Chronic anovulation like PCOS and nulliparity.
- Early menarche --- late menopause
- Obesity
- Estrogen secreting tumors such as Granulosa-theca cell tumors of the ovary.

Family history and genetics predisposition

1-Lynch syndrome (hereditary nonpolyposis colorectal cancer):

Autosomal dominant caused by a germline mutation in one of **several DNA mismatch repair genes**.

Develop the disease at **a young age**. About 15 years younger than the average age of patients presenting with endometrial cancer.

Accounts for two to five percent of all endometrial carcinomas.

Women with Lynch syndrome, the lifetime risk of endometrial carcinoma is 27 to 71 percent compared with 2.6 percent in the general population.

Mean age of diagnosis of endometrial cancer 46-54yrs.

Screen the family for colon , ovarian, prostate , breast CA.

2-BRCA I mutation

BRCA1 mutation carriers reported a significant increase in the risk of uterine cancer (RR 2.65, 95% CI 1.69-4.16).

Data from a prospective series suggested that the risk of endometrial carcinoma was significantly elevated only for **BRCA mutation carriers taking tamoxifen.**

Patients with BRCA I mutation present with **type II endometrial cancer.**

Associated factors

• Nulliparity and infertility

- ✓ The risk of endometrial carcinoma is inversely related to parity.
- ✓ Nulliparity and infertility do not appear to be independent risk factors for endometrial carcinoma; instead, the association is probably with **the high frequency of anovulatory cycles in infertile women.**
- ✓ Data are inconsistent regarding whether ovulation induction for treatment of infertility is associated with an increased risk of endometrial carcinoma.

• Diabetes and hypertension

- ✓ Women with diabetes mellitus and hypertension are at increased risk for endometrial carcinoma.
- ✓ Comorbid factors, primarily obesity, account for much of this risk, but some studies have found independent effects, as well.
- ✓ The risk of developing endometrial carcinoma is **higher in type 2** than type 1 diabetics. Diets high in carbohydrates and associated hyperinsulinemia, insulin resistance, and elevated levels of insulin-like growth factors may play a role in endometrial proliferation and development of endometrial carcinoma; this is an area of active investigation.

• Breast cancer

- ✓ A history of breast cancer is a risk factor for development of endometrial carcinoma, clearly in women treated with **tamoxifen and BRCA1+ve**

Protective factors

- **Hormonal contraceptives**

- ✓ The use of estrogen(**Ethinyl estradiol**)-progestin oral contraceptives (OCs) decreases the risk of endometrial carcinoma by 50 percent or higher.
- ✓ The benefit of hormonal contraceptives is likely due to the progestin component, which suppresses endometrial proliferation. **OCs have a low Estrogen dose so they don't usually cause an excess, and they are given to ovulating patients so they are already protected.**
- ✓ Studies have found that progestin-only contraceptives provide endometrial protection against development of endometrial neoplasia

- **Increasing age at last birth**

- ✓ Childbearing at an older age, independent of parity and other factors, was associated with a decreased risk of endometrial carcinoma. As an example, women who last gave birth at age 35 to 39 years had a 32 percent decrease in risk (95% CI 0.61-0.76).

- **Smoking**

- ✓ Cigarette smoking is associated with a decreased risk of developing endometrial carcinoma in postmenopausal women.

- **Physical activity**

- **Coffee and tea**

Clinical presentation

Abnormal uterine bleeding

- ✓ Suspicion of the presence of endometrial neoplasia (neoplastic endometrial hyperplasia or carcinoma) depends upon **symptoms, age, and the presence of risk factors.**
- ✓ Abnormal uterine bleeding is present in approximately 75 to 90 percent of women with endometrial carcinoma.
- ✓ The amount of bleeding does not correlate with the risk of cancer.
- ✓ **Post-Menopausal bleeding is the most common presentation of Endometrial cancer, while the most common cause of post-menopausal bleeding is vaginal atrophy due to lack of Estrogen (dryness).**

Clinical manifestation

Postmenopausal women

- ✓ Any bleeding, including spotting or staining. Three to 20 percent of women with postmenopausal bleeding are found to have endometrial carcinoma and another 5 to 15 percent have endometrial hyperplasia.

Age 45 to menopause

- ✓ Any abnormal uterine bleeding, among cases of endometrial carcinoma, 19 percent occur in women aged 45 to 54 years compared with 6 percent in those aged 35 to 44 years.

Younger than 45 years

- ✓ Abnormal uterine bleeding that is persistent, occurs in the setting of a history of unopposed estrogen exposure (obesity, chronic anovulation) or failed medical management of the bleeding, or in women at high risk of endometrial cancer (Lynch syndrome).
- ✓ If the patient is young, and doesn't have type II we have to investigate for any gene mutation unless she has a clear risk factor.
- ✓ If a patient in a reproductive age group presents with bleeding we have to rule out pregnancy.
- ✓ Any woman older than 35 yrs → consider doing as biopsy

Abnormal PAP smear

- ✓ If you do a pap smear of a patient for cervical cancer and the smear has abnormal endometrial cells it's important to have an endometrial biopsy to rule out endometrial cancer.
- ✓ Doctor skipped the rest
- ✓ Adenocarcinoma :is sometimes seen on cervical cytology. Since the malignant cells may arise from either the cervix or endometrium, further evaluation with cervical and endometrial biopsy is required.
- ✓ Atypical glandular cells : detected by cervical cytology should be investigated with an endometrial (and endocervical) biopsy to determine whether an endometrial neoplasm is the cause.
- ✓ Endometrial cells – The presence of endometrial cells on cervical cytology is reported in the results in women ≥ 40 years of age. The appearance of normal endometrial cells on cytology in **asymptomatic**

premenopausal women is rarely associated with pathology and **no further work-up is required.**

Incidental finding on imaging

- ✓ A thickened endometrial lining is sometimes found incidentally on ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) performed for another indication.
- ✓ Endometrial thickness is very informative for postmenopausal woman. Normal thickness is 3-5 mm(estrogen builds /progesterone thinning), if it's above you must investigate for endometrial cancer/hyperplasia.

Incidental finding at hysterectomy

- ✓ Endometrial carcinoma or hyperplasia is sometimes discovered incidentally when hysterectomy is performed for benign disease.
- ✓ Prior to hysterectomy, all women with abnormal uterine bleeding should have endometrial sampling.
- ✓ Woman older than 35yrs with abnormal uterine bleeding r/o hyperplasia

Work up

calm the patient , reassure , treat , protect:

- ✓ the first approach is HX and EX (BMI) and lab (CBC , HBA1C,RFT,ECG , CXR(standard for any above 40))

Endometrial sampling

- ✓ Office endometrial biopsy
- ✓ Can be performed without anesthesia.
- ✓ A Pipelle catheter is used for biopsy. Its sensitivity and specificity is 90-95% respectively
- ✓ Patients must be diagnosed histologically before planning for surgery.

D&C in some women

- ✓ Cannot tolerate an office biopsy

- ✓ Those with heavy bleeding (D&C is both a diagnostic and therapeutic procedure),
- ✓ Hysteroscopy with D&C to ensure that focal lesions are identified and biopsied.
- ✓ In postmenopausal bleeding patients who have an **inconclusive endometrial sample, Hysteroscopy is mandatory.**

Type II usually presents with late stage disease and metastasis and the patient would have a history of GI involvement in the form of nausea, vomiting, abdominal distention and ascites. Thus, we need to do more investigations (CT chest and abdomen) to rule out metastasis.

What about screening?

Routine screening is not advisable except for women known with **Lynch syndrome** and **is still bleeding**

Pattern of spread

Direct extension to adjacent structures

- ✓ **The most common:**
 - Invade through myometrium reaching the serosa.
 - Grow downward and involve **the cervix.**
- ✓ **Uncommon:**
- ✓ Vagina, parametrium, bladder and rectum.

Exfoliated cells may pass through the fallopian tube and implant on the:

- ✓ Ovaries.
- ✓ Viscera.
- ✓ Parietal peritoneum.
- ✓ Omentum.

Lymphatic spread

- ✓ **Pelvic lymph nodes:** External iliac, internal iliac and obturator lymph nodes.
- ✓ **Para-aortic lymph-nodes.**

Hematogenous spread

- ✓ **Less common**
 - Liver
 - Lung

Management

- ✓ Endometrial cancer is a **surgically staged disease** → so you don't have to do imaging , but some schools may do pelvic MR
- ✓ Further management depends on the stage
- ✓ **Basic surgery include:**
 - Total hysterectomy (uterus and cervix)
 - Bilateral salpingo-oophorectomy
 - Bilateral pelvic lymphadenectomy
 - Para-aortic lymphadenectomy
 - Omentectomy and peritoneal washing **in type II**
- ✓ Omentectomy is done in type II tumors because its aggressive and the mode of transmission is **transcoelomic (intraperitoneal)**.
- ✓ Peritoneal washing is **not a part of staging** but it **helps in prognosis** and its done if the patient doesn't have ascites in the abdomen, you wash with saline then aspirate it and send it for cytology.
- ✓ You can't operate without an Endometrial biopsy.
- ✓ Surgical resection is enough **to cure the patient in type I.**

Preoperative work up

In endometrial biopsy

- Tumor histology type
- Tumor grade

Risk of lymph node involvement:

- G1 3% Pelvic... 2% aortic

FIGO stage

- G2 9% pelvic...5% aortic
- G3 18% pelvic... 11% aortic

Stage I Tumor confined to the uterus	IA: Less than 50% myometrial invasion 85% of pts are here	
	IB: more than 50% myometrial invasion	
Stage II Invading cervical stroma but doesnot extend beyond the uterus		
Stage III Tumor extend beyond the uterus	IIIA: serosa of the uterus and or adnexa	
	IIIB: vagina or parametrial involvement	
	IIIc: lymph nodes	IIIc1: pelvic lymph nodes
		IIIc2: para-aortic lymph nodes
Stage IV	IVA: bladder or bowel mucosa	
	IVB: abdominal metastasis or inguinal lymph node	

- Doctor said that no one is going to ask about the staging but you have to know that early stage means stage I + II and Late stage is III + IV

When to give radiation?

As **adjuvant** therapy for **type I**

Types of radiation:

- ✓ External beam radiotherapy
- ✓ Brachytherapy (device goes into the vagina and then radiation is given)

When to give chemotherapy?

Type II tumor

In stage II and above using **Platinum-based chemotherapy**.

Hormonal treatment

- ✓ Hormonal treatment never cures, it only controls the disease.
- ✓ We use **Progesterone (medroxyprogesterone acetate)**
- ✓ Its used in three types of patients:
 - 1- Old and can't tolerate surgery
 - 2- Young and wants to preserve her fertility
 - 3- Not willing to go for surgery
- ✓ In case of patients who want to conceive they must have an **Endometrioid type, early stage, low-grade disease** so they can be treated temporarily (at least 1yr with 3 mn biopsies) by hormonal therapy until they get cured in their endometrial biopsy then they can get pregnant and after delivery they should get the surgery.

Prognosis and Survival

Stage	5 - year survival (%)
I	90 - 95
II	70 - 80
III	35 - 50
IV	15 - 20

Follow up

Follow-up examinations should be performed every 3 months for 2 years, every 6 months for 3 years, and then annually.

- Hacker & Moore's Essentials of Obstetrics and Gynecology, 5E

Other types

- ✓ Uterine sarcoma
- ✓ Endometrial stromal tumors
- ✓ Mixed mullerian tumor

Summary

Type I	Type II
Low grade	High-grade
Endometrioid histology	Endometrioid and non-endometrioid histology
Mode of transmission : direct or lymph	transcoelomic (intraperitoneal).
Good prognosis	Poor prognosis
Estrogen responsive	No association with estrogen
May be preceded by precancerous lesions	A precursor lesion is rarely identified

- a. - Developed countries and age are important factors in Endometrial cancer.
- b. - Ovarian cancer are worse with ovulation inducing therapy, because they already are due to multiple trauma from ovulation in its surface. In contrast, endometrial cancers are better with their therapies.
- c. - Post-Menopausal bleeding is the most common presentation of Endometrial cancer.
- d. - Endometrial cancer is a surgically staged disease.
 - Normal Endometrial thickness is 3-5 mm.
- e. - Radiotherapy is given as an adjuvant for type I and Platinum-based.
- f. - Chemotherapy is given to type II stage II and above.

BOX 41-1 *Risk Factors for Endometrial Cancer*

- Obesity
- Nulliparity
- Late menopause
- Diabetes mellitus
- Hypertension
- Family history of breast, colon, or ovarian cancer (HNPCC syndrome)
- Chronic unopposed estrogen stimulation
- Chronic tamoxifen use

HNPCC—hereditary nonpolyposis colon cancer syndrome.

MCQ's:

Women with postmenopausal bleeding need endometrial sampling if endometrium on US is thicker than:

- g. 1mm.
- h. 2mm.
- i. 5mm.
- j. 8mm.
- k. 10mm.

Answer: C

Endometrial thickness in menopause > 5 mm is suspicious for hyperplasia.

For mistakes or feedback

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