Gynaecological Malignancies: Uterine Cancer

Definition
An epithelial malignancy of the uterine corpus mucosa, usually an adenocarcinoma.[1]

Epidemiology
Endometrial cancer is the 4th most common cancer in women (see figure 1).[2]Endometrial cancer, predominantly affects post menopausal women (91% of cases in >50 years of age), peak incidence in the 55 – 65 year old age group.[3]

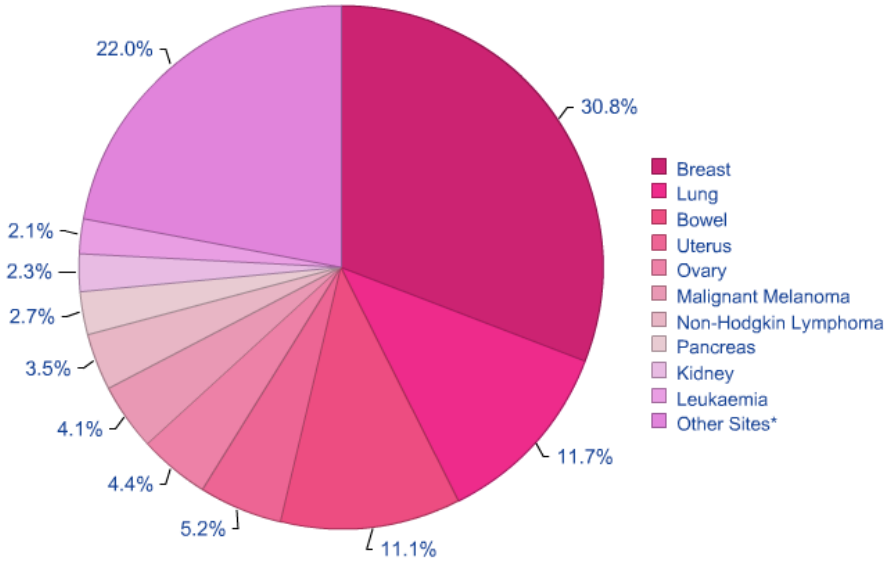

Figure 1: The most commonly diagnosed cancers in females within the UK in 2010[2]

Aetiology
Prolonged unopposed oestrogen stimulation due to endogenous or exogenous sources.[4]

Risk Factors:
The majority of endometrial cancers are associated with conditions in which there are relatively rather than absolutely high levels of oestrogen production.[4]

Other risk factors

- **Age >50 years** – average age at presentation is 60 years.[1]
- **Ethnicity** – of endometrial cancer is higher in white woman than black women; however black women more commonly have poor prognostic features.[5]

Endogenous sources of oestrogen:

- **Excessive body weight** – increased adipose tissue allows for more conversion of androstenedione to oestrone by aromatization in the adipose tissue.[4]
- **Oestrogen producing tumour** – sex cord stromal tumours of the ovary, such as granulosa cell tumours.[1 6]
- **Polycystic Ovarian Syndrome or long periods of anovulatory cycles**[1 4]
- **Late menopause** – with multiple anovulatory cycles in the climacteric phase[1]

Exogenous sources of oestrogen:

- **Oestrogen only HRT.**[1]
- **Tamoxifen** – causes an anti-oestrogenic effect on breast tissue but simultaneously causes an oestrogenic effect on the uterus.[4](Norwitz ER, 2010, Obstetrics and Gynecology at a Glance`, 3rd Edition)

Genetic risk factors:

- **Hereditary non-polyposis colorectal cancer/Lynch Syndrome II:** an autosomal dominant genetic condition which has a high risk of colon cancer as well as endometrial cancer.[1]
- **Gene mutation (MLH1, MSH2)** have a 40-60% lifetime risk of developing endometrial cancer.[1]
- **Family History of Breast, Ovarian or Endometrial cancer.**[1]
- **PTEN (phosphatise and tensin homologue protein gene)** tumour syndromes.[1]

Protective Factors:

- **Combined Oral Contraceptive Pill (COCP):** Endometrial cancer is less frequently seen in women who are/have been using the (COCP) as it administers progesterone in addition to the oestrogen.[6]
- **Smoking:** women who smoke are likely to have an early menopause and have a lower incidence of disease.[6]
- **Pregnancy:** high progesterone dose in pregnancy, and birth sometimes leads for addition shedding of lining of endometrium.[3]

Symptoms

The most common presenting symptom is abnormal uterine bleeding.[6] Intermenstrual, heavy and prolonged vaginal bleeding in premenopausal women and any postmenopausal vaginal bleeding (PVB) should be investigated.[6] Women who present with PVB should be regarded as having a malignancy until proven otherwise.[6] Approximately 5%-10% of women with (PVB) will have endometrial cancer.[7] Other less common symptoms are: uterine mass, pain and weight loss.[1]

Management and Treatment

The first step in the diagnostic pathway should be measurement of the endometrial thickness via

- **Pelvic ultrasound scans:** should show endometrial thickening greater than 3.5-4mm.[7]

Previously the principle method of investigation was dilatation and curettage (D&C), now the:

- **Pipelle device** (disposable, plastic tool)
- **Vabra device** (stainless steel) are used for endometrial sampling; both are highly reliable with sensitivities of over 99%.[8]

Hysteroscopy with a D&C is performed if a biopsy is not possible.[5 8]
All three of these investigations can be performed in the outpatient setting, or under general anaesthetic.

In conjunction prior to surgery a MRI is included, to assess the condition of the myometrium and determine the extent of the myometrium invasion.[8] In addition it will be able to determine whether the cervix has been invaded by the tumour.[6]

Treatment is dependent on FIGO staging determined by the results of the biopsies: Previously laparotomy was the standard treatment, however today they use of minimally invasive techniques is widely accepted.[8] Laparoscopy has additional benefits; shorter hospital stay, less use of pain killers, lower rate of complications and improved quality of life.[8]

Stage	Surgical Treatment	Adjuvant therapy
Stage IA	Hysterectomy with bilateral salpingo-oophorectomy	Observation or vaginal brachytherapy. IB grade 3 – pelvic radiotherapy If negative prognostic factors pelvic radiotherapy and/or adjunctive chemotherapy could be considered
Stage IB	Hysterectomy with bilateral salpingo-oophorectomy ± bilateral pelvic/para-aortic lymphadenectomy	
Stage II	Hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic/para-aortic lymphadenectomy	Pelvic radiotherapy and- vaginal brachytherapy If grade 1-2 tumour, myometrial invasion <50%, negative LVSI and complete surgical staging: brachytherapy alone If negative prognostic factors: chemotherapy ± radiation
Stage III	Maximal surgical cytoreduction with a good performance status	Chemotherapy If positive nodes: sequential radiotherapy If metastatic disease: chemotherapy-radiotherapy for palliative treatment
Stage IVA	Anterior and posterior pelvic exenteration	
Stage IVB	Systemic therapeutical approach with palliative surgery	

LVSI:lymphovascular space involvement

Table 1: Staging, treatment and adjuvant therapies[8]

Prognosis

Endometrial cancer is sometimes falsely regarded as a less aggressive tumour than other gynaecological malignancies however this is due to early presentation of symptoms in the course of the disease.[6] 70-75% of patients present with stage I disease. [4] There are a number of factors which affect prognosis; the most indicative is the stage of the disease (see Table 2):

Stage	Description	Stage at presentation	5 year survival

IA	Tumour confined to the uterus, no or < ½ myometrial invasion	**70%-75%**	**92%**
IB	Tumour confined to the uterus, > ½ myometrial invasion		
II	Cervical stromal invasion, but not beyond uterus	**10%-15%**	**87%**
IIIA	Tumour invades serosa or adnexa	**15%**	**74%**
IIIB	Vaginal and/or parametrial involvement		
IIIC 1	Pelvic node involvement		
IIIC 2	Para-aortic involvement		
IVA	Tumour invasion bladder and/or bowel mucosa		**10%**
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes		

Table 2: FIGO staging of endometrial cancer (table taken from Medscape[9] with added data) [10]

The histological type of endometrial cancer is also important:(Pecorelli, 2009, Revised FIGO staging for carcinoma of the vulva`, cervix`, and endometrium)

- **Endometrial adenocarcinoma** is the most common site and type of uterine cancer (data for prognosis is shown above)[6]
- **Uterine papillary serous carcinoma** this is more common in older women and spreads in a manner similar to cancer of the ovary, and is associated with a significantly poorer prognosis.[6]
- **Clear cell carcinomas**
- **Mixed cell types** – these are made up of the aforementioned 3 other types. These tumours tend to be high risk.[6]

Two main types of endometrial carcinoma have been recognized on the basis of clinical, pathological and molecular features.

Parameter	Type 1 (80%)	Type 2 (10-20%)
Age	50 – 60 years of age (around age of menopause)	60 – 70 years of age
Obesity	Common	Uncommon
Estrogenic stimulation	**Common**	Uncommon
Endometrial background	Anovulatory	Atrophic
Precursor lesion	EIN (endometrial intra-epithelial neoplasia)	EIC(endometrial intra-epithelial carcinoma)
Transition	Slow	Unknown
Type	**Endometrioid**	**Serous/Mixed/Grade 3 endometrioid/undifferentiated**
Molecular Genetics	MSI, PTEN, PAX2 loss	P53 mutation, 1p deletion, PAX2 loss
Receptors	Oestrogen & Progesterone	

Familial	HNPCC: hereditary non-polyposis colorectal cancer	
Spread	Lymph nodes	Peritoneum
Concurrent ovarian ca	Common	Uncommon
Prognosis	**Good**	**Poor**

Table 3: Differences between the two main types of endometrial carcinoma[6,8]

Recurrence

Of the endometrial adenocarcinoma cases which do reoccur, 85% of these will be within the first 2 years.[10] Recurrences are commonest in the vault of the vagina, but also in the lungs, bone, vagina, liver and inguinal and supraclavicular nodes.[6] Frequent follow-up is advised in these patients to look for signs of recurrence by use of a speculum examination.

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