Endometrial cancer

Wendy MacNab

Mohamed K Mehasseb

Abstract

Endometrial cancer is the most common gynaecological malignancy, and an understanding of its presentation and management options is required for all gynaecologists. The surgical management of endometrial cancer has expanded to include laparoscopic surgery, and debate is ongoing regarding the merits of pelvic and para-aortic lymphadenectomy. Our understanding of the biology of endometrial cancer may help determine which women may benefit most from chemo- or hormonal therapy in an adjuvant setting. Pelvic radiation is associated with improved local control. Combination therapy with radiation and chemotherapy is under evaluation. The use of sentinel lymph node sampling is an area for further research and development.

Keywords chemotherapy; endometrial carcinoma; lymphadenectomy; obesity; radiotherapy

Introduction

Worldwide, endometrial carcinoma is only second to cervical cancer in frequency among female genital tract cancers. In the Western world, it is the commonest female genital tract malignancy, accounting for nearly 50% of all new gynaecologic cancers. Its incidence is rising due to increased life expectancy, obesity epidemic, and the fewer hysterectomies performed for benign diseases. Most cases (95%) occur in women over 40 years of age, mostly in the sixth and seventh decades of life (75–85%). The overall lifetime risk of developing endometrial carcinoma is 2.5%. Endometrial carcinoma is usually confined to the uterus at the time of diagnosis and as such, carries an excellent prognosis with high curability. However, women with high-risk factors (25%) including increased age, co-morbidities, higher tumour grade, aggressive histology, and advanced stage represent real challenges.

Pathology

Histologically and biologically, endometrial cancer is broadly classified into two main categories: type 1 and type 2. The vast majority (80%) of endometrial malignancies are type 1 i.e. endometrioid adenocarcinoma, arising from the glandular epithelium, usually on a background of atypical hyperplasia. Endometrial adenocarcinoma is found in up to 50% of cases of complex atypical hyperplasia. Endometrioid tumours are assigned a grade (1–3) depending on the degree of differentiation and nuclear features. They are associated with obesity, nulliparity, insulin resistance, and a hyper-oestrogenic environment e.g. the use of unopposed oestrogens or ovarian granulosa cell tumour. These tumours often exhibit mutations in the *PTEN* tumour suppressor gene; *k-ras* oncogene and mismatch repair genes and frequently stain positively for oestrogen and progesterone receptors.

Type 2 tumours i.e. serous, clear cell, squamous and undifferentiated carcinomas, carcinosarcoma (previously called Malignant Mixed Mullerian Tumour) and endometrial stromal sarcomas (ESS), are less common, more aggressive and have a poorer prognosis. They are not associated with the risk factors for type 1 cancers. Often these tumours occur in older women. At a molecular level, mutations of the *p53* tumour suppressor gene are common. Commonly, trans-peritoneal dissemination is seen with a pattern of spread that is reminiscent of ovarian cancers.

Endometrial cancer is usually primary, however in rare cases may be metastatic from other tumours (e.g. breast, ovary, lung, stomach, colorectal, and melanoma). Endometrial carcinomas spread by direct extension to the cervix, vagina and myometrium. Vaginal metastases (drop-lesions) can also occur as a result of haematogenous spread. Deeper myometrial invasion eventually leads to breach of the uterine serosa and parametrial involvement.

The risk of lymph node involvement in endometrial cancer is directly related to the depth of myometrial invasion as well as the grade. Lymphatic spread occurs to the external iliac, internal iliac and obturator lymph nodes in the pelvis, and to the para-aortic nodal chain. The latter is less common if the pelvic nodes are not involved, although direct spread via lymphatic channels draining the upper uterus can occur. Trans-tubal spread occurs via the fallopian tubes to the ovaries and peritoneal cavity.

The lungs are the most common sites for distant haematogenous metastasis. Non-endometrioid tumours have a tendency for early dissemination. Even minimal myometrial invasion in these tumours may be associated with extra-uterine disease.

Risk factors

i. Obesity

Obesity accounts for about 40%–50% of endometrial cancer cases in the developed world. Endometrial carcinoma was the first malignancy to be recognized as being linked to obesity. A linear increase in the risk of type 1 endometrial cancer with increasing weight and BMI has been observed (Table 1). Overweight and obese women have two to four times greater risk of developing endometrial cancer than do women of a healthy weight, regardless of their menopausal status. Obesity affects the production of peptides (e.g. insulin and IGF-1, SHBG) and steroid hormones (i.e. oestrogen, progesterone, and androgens). It is likely that prolonged exposure to high levels of oestrogen and insulin associated with obesity may contribute to the development of endometrial cancer.

Obesity in the menopause produces a state of excess oestrogen production. This is due to the peripheral conversion of androgens produced by the adrenal glands and ovaries into oestrone, by the enzyme aromatase, in the adipose tissue. Prolonged unopposed oestrogen exposure will lead to a continuous spectrum of endometrial changes from proliferative endometrium through hyperplasia/polyps to carcinoma (Figures 1 and 2). Avoiding weight gain lowers the risk of endometrial and postmenopausal breast

Wendy MacNab *MBChB MRCOG is a Subspecialty Trainee in Gynaecological Oncology at Glasgow Royal Infirmary, Glasgow, Scotland, UK. Conflicts of interest: none declared.*

Mohamed K Mehasseb *MBBCh MSc MD MRCOG PhD is a Consultant Gynaecological Surgeon and Oncologist at Department of Gynaecological Oncology, Glasgow Royal Infirmary, Glasgow, Scotland, UK. Conflicts of interest: none declared.*

Relative risk of endometrial cancer incidence and mortality in relation to body mass index (BMI)

	Body mass index			
	25–27.4	27.5–29.5	>30	Overall trend for overweight and obese
Incidence	+21%	+43%	+273%	+289%
Mortality	+9%	+21%	+228%	+246%

Table 1

cancers. However, there is limited evidence that intentional weight loss will lower cancer risk.

Obese women have a poorer outcome compared to lean women, probably reflecting a true biological effect of adiposity on survival, a delayed diagnosis in heavier women, and a higher rate of treatment-associated complications.

ii. Tamoxifen

Tamoxifen, used as an adjuvant treatment in breast cancer, is associated with a significantly increased (2–5 fold) incidence of endometrial pathology including endometrial cancers. Both endometrioid and non-endometrioid endometrial cancers can develop. There is no evidence to support routine endometrial screening for asymptomatic women using tamoxifen, although abnormal genital tract bleeding should be investigated promptly. This might become less of an issue over the next few years with a move to the use of aromatase inhibitors as a substitute for tamoxifen in the adjuvant treatment of breast cancer.

iii. Hereditary

Less than 5% of all endometrial cancers are hereditary. Compared to the expected rate of endometrial cancer in a general population, *BRCA* carriers who did not receive tamoxifen do not have a significant increase in risk of developing endometrial cancer. Thus, it seems that screening for endometrial cancer is not warranted in known *BRCA1* or *BRCA2* mutations carriers.

Conversely, endometrial cancer is one of the extra-colonic cancers caused by hereditary non-polyposis colon cancer syndrome (HNPCC) or Lynch II syndrome. This is an autosomal-dominant cancer susceptibility syndrome resulting of a germ-cell line mutation in one of the DNA mismatch repair genes (*MSH2*, *MLH1*, or *MSH6*). Despite the name of the syndrome, 50% of affected women will develop endometrial carcinoma as their index malignancy (rather than bowel cancer). Women with confirmed HNPCC have a 40–60% lifetime risk of developing endometrial cancer and a 10% risk of developing a number of other cancers. Strict criteria have been developed to identify these women at risk (the Amsterdam criteria). There is no uniform screening strategy, and risk-reducing hysterectomy and bilateral salpingo-oophorectomy are recommended for those women who have completed their family. Endometrial surveillance with annual endometrial imaging and biopsy is offered to women with HNPCC who wish to retain their uterus although this is not proven to be effective in prevention.

Screening

Although many endometrial cancers develop by way of a precursor lesion (i.e. atypical endometrial hyperplasia), routine mass screening of the population for endometrial cancer with pelvic ultrasound scans or endometrial biopsies is not practical due to the low prevalence of the precursor disease. Thus, management relies on the prompt assessment of symptomatic women, especially those at high risk. It is appropriate to evaluate individuals past their fourth decade of life if there is abnormal bleeding.

Diagnosis

Endometrial cancer most commonly presents as postmenopausal bleeding (PMB) (90%), although only 10% of women with PMB will have cancer. Other women can present with persistent postmenopausal vaginal discharge due to pyometra. Premenopausal women usually present with significant worsening in menstrual pattern, or with incidental finding of abnormal endometrial cells on routine cervical cytology. Malignant endometrial cells appear on cervical cytology screening smears in 25–50% of women with endometrial cancer. The significance of normal endometrial cells in cervical smears in postmenopausal women is less clear. Presentation as a result of metastatic disease is uncommon and pain is generally not a feature.

Prompt referral and initial assessment should take place in rapid-access clinics, identifying risk factors and co-morbidities. A pelvic examination should be conducted to exclude obvious lower genital tracts cancers. A transvaginal ultrasound scan is recommended to measure the endometrial thickness and identify any ovarian mass. A thin endometrium (<5 mm) in the postmenopausal woman has a high negative predictive value for endometrial cancer and is reassuring. Ultrasound is less helpful in women taking tamoxifen because typical morphological changes seen with tamoxifen use often result in false positive ultrasound findings. Hysteroscopy and endometrial sampling can be performed safely in the outpatient setting in >80% of women, providing prompt reassurance and a diagnosis in those cases where an endometrial abnormality is suggested on ultrasound scan. The pipelle is the best endometrial sampling device, with detection rates for endometrial cancer in postmenopausal and premenopausal women of 99.6% and 91%, respectively. The sensitivity for the detection of endometrial hyperplasia is 81%, with a specificity of 98%.

Investigations

Once a diagnosis of endometrial cancer has been made, discussion at a recognized specialist gynaecological cancer MDT should take place. A blood count, renal biochemistry and liver function tests are performed and further imaging is undertaken to identify metastatic disease and aid treatment decisions. A chest X-ray is done as a minimum to identify lung metastases. In some cases where the risk of lung metastases is higher e.g. carcinosarcoma, computed tomography scanning (CT) of the thorax may be used instead. CT may also be helpful in assessing suspected upper abdominal metastatic disease. Magnetic resonance imaging (MRI) is used to assess the depth of myometrial invasion and to identify extension into cervical stroma. MRI is sensitive for this purpose, accurately predicting depth of invasion and cervical extension in 92% of cases.