Signs and symptoms

Postmenopausal bleeding is the most common complaint in women in whom endometrial cancer is diagnosed. Around 90% of women are diagnosed after the age of 50 years and postmenopausal bleeding is associated with an underlying carcinoma in up to 10% of women. While commonly associated with older women, endometrial cancer can occur in younger women and may present with irregular or intermenstrual bleeding. Such women often experience a delay in diagnosis, as management may initially be via a menstrual disorders clinic and characteristic findings at hysteroscopy may be lacking. Because of the strong aetiological association with estrogenic stimulation, the diagnosis should be considered in symptomatic younger women with polycystic ovary syndrome, those with irregular bleeding on hormone replacement therapy or those taking tamoxifen. Tamoxifen stimulates ovarian estrogen biosynthesis and elevates plasma estrogen levels, increasing the risk of endometrial cancer.

Endometrial hyperplasia can be termed a premalignant condition of the endometrium. Occurring as a result of estrogenic stimulation of the endometrium, endometrial hyperplasia is classified as simple or complex – in the absence of cytological atypia the risk of malignancy is low (1–4%) but the risk of co-existing or rapidly developing malignancy with a histological finding of complex endometrial hyperplasia with atypia may be as high as 43%.

Two distinct forms of endometrial cancer were described by Bohkman in 1983 and these distinct types are recognised when planning clinical management. Type 1 endometrial cancer is the most common, with over 80% of cases. The common risk factors are often found in women who are over-weight who develop grade 1–2, often superficially, invasive cancers. Type 1 endometrial cancer often arises in association with atypical endometrial hyperplasia. Such cases are usually associated with a 5-year survival of around 85%.

Type 2 endometrial cancers are not associated with estrogenic stimulation and include variants such as serous, clear-cell, small-cell,
carcinosarcoma and other rare subtypes. Such cases metastasise early and carry a much poorer prognosis, with a 50% 5-year survival.

In addition to these subtypes, a variety of smooth-muscle tumours can arise in the uterus. These range from the very common and benign leiomyoma (fibroid), through to malignant tumours such as carcinosarcoma or leiomyosarcoma. Carcinosarcomas are also known as malignant mixed müllerian tumours. Malignant smooth-muscle tumours of the uterus are uncommon, accounting for less than 5% of uterine tumours. It is estimated that the risk of malignant change in a fibroid is of the order of 1%, with rapid increase in the size of a fibroid a worrying sign that malignant transformation of a fibroid may be occurring.

While hysterectomy and bilateral salpingo-oophorectomy remains the mainstay of treatment, significant challenges remain to individualise staging and adjuvant therapy to improve the outcomes particularly for the poor prognostic subtypes, where a high risk of distant metastases and recurrence exists.

**Investigation**

Women presenting with postmenopausal bleeding are at risk of having endometrial cancer and investigations to confirm or exclude such a possibility should be performed (see also Chapter 4). As the risk of having cancer is approximately 10%, these women should be referred for gynaecological assessment at a local cancer unit, where there is a gynaecologist with a special interest in gynaecological oncology.

Many women with postmenopausal bleeding will not require an urgent assessment but they should be given an early appointment. Those at increased risk of cancer should be seen within 2 weeks of their general practitioner’s referral.

Clinical history is important in putting into context the result of triage investigations. These are often performed on an outpatient basis and, in many units, dedicated rapid access clinics have been established to investigate postmenopausal bleeding. Transvaginal ultrasound is commonly used as a screening tool to assess the endometrial thickness. If the overall thickness of the endometrium is 4 mm or less and the ovaries appear normal on the scan, the probability of endometrial cancer is low. The pre-test risk of endometrial cancer for those with postmenopausal bleeding is reduced from 10% to 1% in those with a normal transvaginal scan. In cases of a single light bleed in the presence of negative cervical pathology, this may be the only investigation undertaken.\(^1\,^2\)

Endometrial biopsies can be obtained as an outpatient using a variety of sampling devices. Some units use outpatient hysteroscopy as the screening investigation, combined with endometrial biopsy if indicated. In cases
where pathology is suspected or if the outpatient biopsy is unsatisfactory, inpatient hysteroscopy combined with dilatation and curettage is performed.\textsuperscript{3,4}

Once the histological diagnosis is confirmed, minimum further investigations include a chest X-ray, full blood count and biochemical profile. Staging of endometrial cancer is based on surgicopathological findings rather than preoperative staging by examination under anaesthesia in contrast to cervical carcinoma. The role of cross-sectional imaging with magnetic resonance imaging (MRI) or computed tomography (CT) scanning remains controversial. The potential benefits of MRI are in the prediction of depth of myometrial invasion, the presence of cervical involvement or extraterine disease and identification of pelvic or para-aortic lymphadenopathy. (Figure 10.1) CT imaging allows greater assessment of possible distant metastases as well as identifying pelvic and para-aortic lymphadenopathy. It could be argued that hysteroscopy is a better method of assessing the endocervix and clinical impression of an endometrial rather than cervical primary cancer a more accurate

\textbf{Figure 10.1} MRI of the uterus showing an anterior fundal tumour with deep myometrial extension (loss of the junctional zone)
discriminator. While MRI may allow identification of women with deep myometrial invasion, this may prove more difficult with high-grade tumours or in the presence of benign pathology, such as fibroids, in causing distortion of the junctional zone. The other important issue continues to be the additional interventional decisions that such information allows. The preoperative identification of pelvic or para-aortic lymphadenopathy is potentially useful in allowing selective node sampling, which would impact on the decisions around adjuvant therapy. For laparoscopic management, it is also helpful to have an accurate indication of uterine size.

The original staging system introduced by FIGO in 1988 has been revised to focus on factors likely to change adjuvant management decisions and influence outcomes (see Appendix 1).

**Surgical management**

The standard surgical procedure for the management of endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy by a method that allows evaluation of the peritoneal cavity. Traditionally, this would be performed by laparotomy via a lower midline incision. However, with large studies demonstrating comparable outcomes and enhanced recovery, best practice would now be via laparoscopically assisted or total laparoscopic hysterectomy. This allows direct inspection of the peritoneum, omentum and liver and can be combined with pelvic lymphadenectomy or sampling, depending on the preoperative management decision. Even in women who have asymptomatic distant disease identified on preoperative imaging, a decision to proceed with hysterectomy and bilateral salpingo-oophorectomy may be made for local control and management of vaginal bleeding.

The role of lymphadenectomy in the management of endometrial cancer has been the subject of much debate with differing standard practices internationally and significant variations with UK gynaecological cancer centres. While full surgical staging by performing pelvic and para-aortic lymphadenectomy improves knowledge of extent of disease and thus the options for adjuvant therapy, it cannot be performed without consideration of the additional therapeutic benefit that any such interventions allow.

The risk of locoregional pelvic nodal recurrence and distant recurrence can be estimated from knowledge of the grade and depth of myometrial invasion. Well-differentiated cancers with superficial invasion only may have a rate of pelvic node involvement of 5% or less. However, in those women with poorly differentiated tumours and deep myometrial invasion studies have shown a 30% rate of pelvic nodal disease and a 30% rate of distant recurrence at 5 years, even after adjuvant pelvic radiotherapy at initial treatment. Supporters of extended surgical staging by including para-aortic lymphadenectomy would point to recurrence in the para-
aortic nodes that had not been adequately staged at initial surgery. The extent of para-aortic lymphadenectomy required is not well defined and evidence is lacking to show improved survival with currently available adjuvant therapy in patients who are node positive.\textsuperscript{11,12}

Large retrospective non-randomised historical trials from the USA have suggested some survival benefit in pelvic lymph-node sampling which was further enhanced by systematic lymphadenectomy.\textsuperscript{13} Such trials, however, contained multiple selection and treatment inconsistencies. The role of extended surgical staging and adjuvant pelvic radiotherapy was addressed by the ASTEC trial with a double randomisation to pelvic lymphadenectomy and pelvic radiotherapy possible in patients with a high risk of disease.\textsuperscript{14} The study results were criticised for variations in surgical technique and in the extent of lymphadenectomy but no positive benefit was seen in life expectancy for those patients undergoing extending surgical staging as a therapeutic procedure or when combined with adjuvant pelvic radio-therapy. The theory that removal of microscopic disease present in pelvic nodes would have therapeutic benefit (extrapolated from lymphadenectomy in cervical cancer as part of radical hysterectomy) was not supported by the ASTEC findings. Moreover, those who had a more extensive lymphadenectomy did not show any difference in outcome but had more significant complications. Similar findings were reported in a further prospective randomised trial by Panici.\textsuperscript{15}

Equally important is avoidance of adverse effects from surgical treatment and radiotherapy in patients at low risk of recurrence. Pelvic lymphadenectomy is associated with lower limb lymphoedema in 5–10\% and vascular injury in 0.5–1.0\%. The risk of lymphoedema increases with postoperative radiotherapy.\textsuperscript{16}

Radiotherapy and chemotherapy

Women with endometrial cancer should be treated by surgery whenever possible. However, in those who are medically unfit with locally advanced disease, palliative radiotherapy to control vaginal bleeding is an option. The main role of radiotherapy is as adjuvant therapy. This may include external-beam pelvic treatment combined with vaginal brachytherapy. Despite initial evidence to the contrary,\textsuperscript{17} it is now generally accepted that radiotherapy does not improve life expectancy and that its main role is in reducing the incidence of local recurrence. The most common site for local recurrence is at the vaginal vault and, overall, the risk is 15–20\%. This risk may be halved by adjuvant brachytherapy.\textsuperscript{18} If, however, a close observation policy is followed and local vault recurrence is detected early then salvage rates of 80\% have been reported.

There is wide variability between centres in the use of adjuvant
radiotherapy and no consensus on which patients should receive this type of treatment or on the type of radiotherapy (external beam, vault brachytherapy or both) that should be given. The majority of UK practice is to base decisions on the need for radiotherapy on the grade and depth of myometrial invasion with factors such as the presence of adverse factors (for example, lymphovascular invasion) taken into account. This is independent of histological assessment of the pelvic or para-aortic nodes.

While radiotherapy has not shown any survival benefit, it has been shown to have lasting adverse effects, including damage to the vagina, bowel and urinary tract. The combination of radiotherapy and surgery (particularly lymphadenectomy) may cause lymphoedema of the legs and lower abdomen. Disease-related deaths are often associated with failure to control recurrent distal disease, which, in most instances, is not related to pelvic disease control.

No evidence has been identified to suggest that primary or adjuvant chemotherapy improves survival for women with endometrial cancer. Systemic chemotherapy has typically been reserved for women with disseminated primary disease or extrapelvic recurrence. The use of chemotherapy is increasing particularly in non-endometrioid forms of endometrial cancer, particularly clear-cell and papillary serous, by extrapolation of evidence from treatment of ovarian carcinoma. There is no standard regimen but platinum–taxane combinations are most frequently used. The spread patterns are often different, with a higher incidence of extraterine and distant disease. This needs to be balanced against the recorded potentially severe adverse effects. Patients with clear-cell or papillary serous tumours may receive pelvic radiotherapy and adjuvant chemotherapy to try to impact on the possibility of extrapelvic relapse. There may be a place for lymphadenectomy in such patients to be able to omit external beam therapy and consider adjuvant chemotherapy alone. However, there are no large trials to support this approach. It is hoped that trials such as PORTEC3, investigating the role of radiotherapy with chemotherapy, will address these issues.

Given the association with estrogen in the development of the more common variants of endometrial cancer, progestogens have traditionally been used as adjuvant therapy. However, a meta-analysis of the results of seven randomised controlled trials has shown that adjuvant progestogen therapy confers no survival benefit. Progestogens should not therefore be used routinely for adjuvant treatment for endometrial cancer. In some women with progestogen receptor-positive recurrent tumours, there may be a role for a trial of therapy. Likewise, tamoxifen and other oral chemotherapy drugs commonly used for breast cancer hormone manipulations have shown disappointing results. The role of estrogen replacement remains controversial. In early-stage disease, there is probably no increased risk...
of relapse and therefore estrogen replacement could be considered in selected cases.

**Palliative treatment and care**

As with any cancer, women with advanced endometrial cancer, whether in hospital or in the community, should have access to specialist palliative care on a 24-hour basis and there should be local arrangements to ensure continuity of care. The aim of palliative care is to maintain and improve quality of life and the whole person should always be considered. It is important to provide both optimum relief from symptoms and to maintain the social and psychological wellbeing of the woman. Particular attention should be given to adequate pain control, for which effective interventions should be readily available. A variety of interventions, ranging from surgery to supportive care, may be necessary to improve quality of life for women going through the late stages of cancer. Patients and their relatives should be given realistic information about potential benefits, limitations and adverse effects of interventions and their views should always be respected. Most women with advancing cancer are likely to wish to remain at home for much of the duration of their illness. Women should be helped to remain in the place they prefer, whether this is their home, hospital or hospice, and should, whenever possible, be allowed to choose where they wish to die. Palliative aspects of care are addressed in more detail in Chapter 14.

**Post-treatment support and follow-up**

At present, there is no evidence to support routine follow-up for women whose cancer is in remission. However, these women are likely to need aftercare and support during recovery following primary treatment and should have continuing access to appropriate services. Care following primary treatment aims to identify and manage physical and psychological morbidity and to detect recurrent disease and initiate treatment as early as possible. Women should be informed about specific problems that may develop some time after treatment.

**Organisation and provision of services**

The optimum management of endometrial cancers requires close coordination between the primary healthcare team, the treatment teams at the cancer unit and cancer centre, the palliative care team and patients and their families. Effective communication is essential between all care settings. Decisions about management should follow local clinical policy, which should be demonstrably evidence based. All members of teams should be involved in discussions on local policy decisions and auditing.
adherence to them. Teams should be jointly responsible for audit and participation in clinical trials.

For endometrial cancer, the cancer unit should provide a rapid and appropriate assessment service at the local level for women presenting with postmenopausal bleeding. The designated lead gynaecologist should normally carry out surgery for early (stage Ia or Ib, grade 1 or 2) cancers of the endometrium. Specialist support from a cancer centre should be available, if needed. Women with late-stage endometrial cancers should be referred to the cancer centre following initial assessment at the cancer unit, since these are relatively uncommon and may present particular challenges. It is crucial to have mutually agreed criteria for rapid referral and effective channels of communication between primary care, cancer units and cancer centres.

References


