Endometrial cancer

Cathrine Holland

Abstract
Endometrial cancers are the most common gynaecological malignancies in the UK with approximately 4500 new cases occur each year and the incidence is rising. Increasingly there is evidence-based management and centralized specialist care of women with endometrial cancer. Women with high grade disease, deep myometrial invasion or lymphadenopathy should be managed by specialist gynaecological oncologists as part of a multi-disciplinary team (MDT). Results from important clinical trials now guide the application of surgical and non-surgical treatments. Surgery remains the cornerstone of management with a trend towards increased use of minimal access surgery. Radiotherapy-related morbidity can now be reduced by the more selective use of external beam radiotherapy. There remain several unresolved issues however and it is important that relevant clinical trials are offered to eligible women. Women must have multi-disciplinary input before treatment, so that up-to-date and evidence-based treatments and inclusion in clinical trials can be considered.

Keywords aetiology; chemotherapy; endometrial cancer; radiotherapy; surgery

Introduction
Factors contributing to the increased incidence of endometrial cancer include increasing life expectancy, increasing population obesity, fewer hysterectomies performed for benign disease and tamoxifen use. Most cases are diagnosed in women over 50, although 20–25% of women are pre-menopausal at diagnosis. Only 5% of women are diagnosed below 40 years. The overall lifetime risk of developing endometrial cancer is 2.5%. Early recognition contributes to generally high cure rates but approximately 25% of women will have poorer outcomes due to more aggressive histological types, later presentation and problems associated with co-morbid conditions such as cardiovascular disease. Expert multi-disciplinary care is therefore key in optimizing outcomes based on a good evidence base where this exists.

Pathology
Primary endometrial cancers arise from glandular epithelial elements within the endometrium. Different histological sub-types are classified based upon cell type. The great majority of primary endometrial cancers (>80%) are endometrioid adenocarcinomas. These usually arise on a background of atypical hyperplasia, a precursor lesion. Up to 50% of cases of severe atypical hyperplasia are upgraded to invasive endometrial cancer on the hysterectomy specimen. Endometrioid tumours are assigned a grade (1–3) depending on the degree of differentiation and nuclear features. Serous, clear cell, squamous and undifferentiated carcinomas are less common and have a poorer prognosis due to a tendency to early extra-uterine spread. Relatively little is known of the molecular events that precede a diagnosis of non-endometrioid carcinoma although a pre-cursor lesion for serous endometrial carcinoma Endometrial Intra-epithelial Carcinoma (EIC) has been identified. Other types of endometrial cancer including carcinosarcoma and endometrial stromal sarcoma (ESS) are less common still. Carcinosarcoma (previously known as Malignant Mixed Müllerian Tumour) is not a sarcoma as the name suggests, but is an aggressive epithelial tumour. The rare ESS, arises from stromal elements of the endometrium.

Endometrial cancers are rarely metastatic from other tumours. Breast carcinoma is the most likely to metastasize to the endometrium although metastases from ovary, lung, stomach, colorectal and melanoma are all reported.

Endometrial carcinomas spread by direct extension to the cervix, vagina and myometrium (Figure 1). Vaginal metastases can also occur as a result of haematogenous spread. Deeper myometrial invasion eventually leads to breach of the uterine serosa and parametrial involvement. Lymph node involvement in endometrial cancer is directly related to depth of myometrial invasion as well as grade. Lymphatic spread occurs to the external iliac, internal iliac and obturator nodes in the pelvis and to para-aortic nodes. Para-aortic node involvement is less common when the pelvic nodes are uninvolved although para-aortic spread can arise directly via lymphatic channels draining the upper uterus. Trans-tubal spread occurs via the fallopian tubes to the ovaries and peritoneal cavity. The lungs are the most common site for distant haematogenous metastasis. Non-endometrioid tumours have a tendency to early dissemination. Even minimal myometrial invasion in these tumours may be associated with extra-uterine disease. Expert histopathological assessment with accurate grading of disease, classification of histological sub-type and assessment of the final surgical specimen, is important in planning appropriate investigations and guiding treatment.

Aetiology
Based on molecular differences, endometrial cancers are now broadly classified into two main categories known as type 1 and type 2 cancers. The molecular differences between type 1 and 2 cancers, suggest different developmental pathways. Type 1 cancers are generally endometrioid cancers arising on a background of atypical hyperplasia. They are associated with obesity, nulliparity, insulin resistance and an oestrogenic environment e.g. use of unopposed oestrogens, 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 generally comprise serous and other non-endometrioid histology, e.g. clear cell carcinoma, and are not associated with the risk factors for type 1 cancers. Often these tumours occur in more elderly 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. Ongoing

Cathrine Holland PhD MRCOG is a Consultant in the Academic Unit of Obstetrics and Gynaecology at University of Manchester, School of Cancer and Enabling Sciences, St Mary’s Hospital, Manchester, UK.
Conflicts of interest: none declared.
translational research seeks to better understand and exploit molecular differences between type 1 and 2 cancers using targeted molecular therapies.

Tamoxifen
Tamoxifen is a common adjuvant treatment for women with breast cancer. Tamoxifen use is associated with a significantly higher incidence of endometrial pathology including endometrial cancers (2–5 times increased risk) than non-users. Both endometrioid and non-endometrioid endometrial cancers can develop. There is no evidence to support routine endometrial screening for asymptomatic women taking tamoxifen although bleeding on tamoxifen should be investigated promptly to exclude sinister pathology.

Hereditary endometrial cancer
Less than 5% of all endometrial cancers are heritable although endometrial cancer is one of the extra-colonic cancers caused by hereditary non-polyposis colon cancer syndrome (HNPCC). 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 (see Box 1). Prophylactic hysterectomy and bilateral salpingo-oophorectomy are recommended for those women who have completed their family.

Figure 1 A bisected hysterectomy specimen with attached fallopian tubes and ovaries containing an endometrial carcinosarcoma with myometrial invasion. The cervix has been separated from the main uterine specimen by the histopathologist revealing prolapse of the tumour into the endocervix and invasion into the cervical stroma.

“Red flags” for HNPCC in women with endometrial cancer
- Age <50 years
- Personal history of previous or current colorectal cancer
- Two or more HNPCC-related cancers in a family (small intestine; stomach; urinary tract; ovary; bile duct)

Box 1
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. Whilst heritable endometrial cancer is uncommon, recognition of cases is important. Despite the name of the syndrome, 50% of affected women will develop endometrial cancer as their index cancer rather than bowel cancer. Identifying these women enables them and their family to undergo genetic counselling, genetic testing and annual surveillance for bowel cancer. Different criteria have been developed to identify individuals at risk. Women needing referral for clinical genetics advice are shown in Table 1.

Diagnosis

Endometrial cancer can present as post-menopausal bleeding (PMB), persistent post-menopausal vaginal discharge due to pyometra, significant worsening in menstrual pattern or volume in pre-menopausal women or incidental finding of abnormal endometrial cells on routine cervical cytology. Presentation as in pre-menopausal women or incidental finding of abnormal pyometra, significant worsening in menstrual pattern or volume (PMB), persistent post-menopausal vaginal discharge due to endometrial cancer can present as post-menopausal bleeding (PMB). Approximately 10% of women with PMB will be diagnosed with endometrial cancer so awareness of PMB as a “red flag” symptom in general practice and prompt onward referral for investigation is important. Initial assessment should take place in rapid-access clinics where a relevant history can be taken to identify risk factors and co-morbidities. A pelvic examination should be conducted to exclude obvious vulval and cervical cancers. A suggested assessment algorithm is shown in Figure 2.

The recommended initial investigation is a trans-vaginal ultrasound scan for measurement of endometrial thickness and identification of ovarian masses. A thin endometrium (<5 mm) in the post-menopausal woman has a high negative predictive value for endometrial cancer and is reassuring. Further investigations (Figure 3a and b) can be safely performed in the outpatient setting in ~80% of women.

Ultrasound is less helpful in women taking tamoxifen because typical morphological changes seen with tamoxifen use often result in false positive ultrasound findings. Hysteroscopy can therefore provide prompt reassurance and provides a diagnosis in those cases where an endometrial abnormality is present. The serum tumour marker Ca125 is not indicated in the assessment of women with PMB nor those subsequently diagnosed with endometrial cancer.

Investigations

Once a diagnosis of endometrial cancer has been made, a blood count, renal biochemistry and liver function tests are performed and further imaging is undertaken to identify metastatic disease and aid treatment decisions. Discussion at a recognized specialist gynaecological cancer MDT should take place. 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 after discussion. Magnetic resonance imaging (MRI) is used in the pre-operative imaging of women with endometrial cancer to assess depth of myometrial invasion and to identify extension into the cervical stroma. MRI is more sensitive than both trans-vaginal ultrasound and CT for this purpose accurately predicting depth of invasion and cervical extension in 92% of cases. CT may be helpful in assessment of the upper abdomen if intra-abdominal metastases are suspected. On rare occasions where there is uncertainty regarding operability of a locally advanced tumour, examination under anaesthetic may be required.

Surgical management of endometrial cancer

Surgery for endometrial cancer has several different functions. The staging of endometrial cancer is based upon both findings at surgery and histopathological assessment of the surgical specimens and provides prognostic information. The staging system that is used is the International Federation of Gynecology and Obstetrics (FIGO) classification and this was revised in 2009 (Table 1). In addition surgery is therapeutic, surgery alone resulting in high cure rates for women with low grade disease confined to the endometrium or inner myometrium. Surgery can also be curative in cases of isolated disease recurrence although surgery in this scenario may involve more extensive procedures e.g. exenteration. Even in cases of advanced disease, hysterectomy, where possible, can provide good palliation of distressing and heavy vaginal bleeding although radiotherapy and/or chemotherapy are required thereafter.

Surgery comprises total hysterectomy and bilateral salpingo-oophorectomy (BSO) where disease appears to be confined to the uterus. The FIGO staging system includes pelvic and para-aortic lymphadenectomy in addition to hysterectomy although the need for lymphadenectomy has been questioned over a number of years. There is general agreement that lymphadenectomy is not

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Tumour confined to the corpus uteri</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>No or less than 50% myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Invasion ≥50% of myometrial thickness</td>
</tr>
</tbody>
</table>

| Stage II | Tumour invades cervical stroma but does not extend beyond the uterus* |

<table>
<thead>
<tr>
<th>Stage III</th>
<th>Local and or regional spread of the tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>Tumour invades the serosa of the corpus uteri and/or adnexae²</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal and/or parametral involvement</td>
</tr>
<tr>
<td>IIIC</td>
<td>Metastases to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Positive pelvic nodes</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Positive para-aortic lymph nodes with or without positive pelvic nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage IV</th>
<th>Tumour invades bladder and/or bowel mucosa and/or distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour invasion of bladder and/or bowel mucosa and/or distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes</td>
<td></td>
</tr>
</tbody>
</table>

* Endocervical glandular involvement only should be considered as stage I and no longer as stage II.

² Positive cytology has to be reported separately without changing the stage.

Table 1
required in women with grades 1 and 2 endometrioid type cancer, that appears to be confined to the inner myometrium or endometrium as the risk of lymph node metastasis is low. Large retrospective studies have suggested that lymphadenectomy is associated with improved survival in grade 3 tumours and where there is deep myometrial invasion. However, when pelvic lymphadenectomy was assessed in two large randomized controlled trials (RCTs) of stage I cancer, no survival advantage was seen in the lymphadenectomy groups. Survival for women with clinical stage I disease treated with hysterectomy and BSO alone is 85–89% compared to 88–90% for those women having lymphadenectomy (non-significant). These studies did, however, demonstrate higher morbidity in those women having lymphadenectomy. Despite the publication of RCTs in this area, controversy regarding the role of lymphadenectomy with more deeply invasive (outer half myometrium) or grade 3 tumours remains. Some gynaecological oncologists consider that the quality and extent of lymphadenectomy was too variable in the large A Study in the Treatment of Endometrial Cancer (ASTEC) trial for the results to be reliable. However, a further large RCT with thorough and extensive lymphadenectomy across all participating centres has confirmed the findings from ASTEC. Where enlarged or suspicious nodes are identified at surgery or on pre-operative imaging, nodal sampling (selective lymphadenectomy) is usually performed. Omental involvement is a feature of serous carcinomas and therefore omental biopsy forms part of the surgical procedure for serous disease. An unresolved issue is whether all patients with non-endometrioid tumours should undergo lymphadenectomy or not. This question has not been specifically addressed in large randomized trials. The therapeutic value of removing nodes that appear normal is unknown. With respect to guiding treatment decisions, whilst non-endometrioid tumours have greater risk of early nodal metastasis, knowledge of lymph node status does not necessarily influence decisions for adjuvant treatment after surgery. Operative or pathological findings of uterine serosa involvement or ovarian metastases, for example, require that additional treatment be given regardless of nodal status.

**Newer surgical approaches in endometrial cancer management**

Traditionally an open abdominal approach has been the treatment of choice with total hysterectomy and BSO with surgery being performed through either a low transverse or lower midline vertical incision. This may well change in future. Women with endometrial cancer increasingly present an increasing surgical and anaesthetic challenge. The high cure rates for endometrial cancer overall and the problems of major co-morbidity in this patient group have led to greater consideration of the need to reduce treatment-associated morbidity. An increasing number of cancer
centres in the UK, Europe and the USA now use minimal access surgery as the standard surgical approach for endometrial cancer thought to be confined to the uterine corpus. The two most commonly used techniques are the laparoscopically-assisted vaginal hysterectomy and BSO (LAVH) and the total laparoscopic hysterectomy and BSO (TLH). Both procedures are feasible in obese and elderly patients with endometrial cancer and where required, lymphadenectomy can also be performed with equally good lymph node yields when compared to open surgery. In meta-analyses of studies of laparoscopic hysterectomy for endometrial cancer, overall and disease-free survival rates appear similar for women treated with open surgery and laparoscopic surgery although length of follow-up varies between studies. The largest randomized study of laparoscopic surgery in this setting is the US Gynaecological Oncology Group (GOG) LAP2 study which randomized approximately 2600 women to either open hysterectomy and BSO or LAVH. Pelvic and para-aortic lymphadenectomy were planned for all women. Conversion to laparotomy was high at 26%, a very much higher rate of conversion than reported in other series. This almost certainly reflects the planned need for pelvic and para-aortic lymphadenectomy for all participants. As in other series, the rate of moderate and severe post-operative complications was significantly lower in women having laparoscopic surgery and 94% of women were discharged from hospital after 2 days. At 6 weeks, laparoscopic surgery was associated with less pain, earlier resumption of normal activity and quicker return to work. At 6 months, these quality of life measures were very similar in both groups although body image was better for women treated laparoscopically. Survival data from this trial are not yet mature but will be important in determining whether or not the standard surgical approach should change. Newer approaches to minimal access surgery in endometrial cancer include robotic hysterectomy. The benefits are similar to those of other minimal access techniques although currently the very high costs of implementing this surgery prevent widespread introduction.

Vaginal hysterectomy alone may be performed under regional anaesthesia in exceptional cases of women who have co-morbidities that preclude a general anaesthetic or abdominal approach. High cure rates can be achieved.

**HRT after surgery for endometrial cancer**

Following hysterectomy and BSO, pre-menopausal women with endometrial cancer will experience menopausal symptoms which can be severe for some women causing distress and impairing quality of life. There is currently no evidence that hormone replacement therapy with oestrogen alone has an adverse impact on survival in women who have had complete treatment for early (stage I) disease. Therefore women experiencing significant and distressing symptoms may be prescribed HRT after receiving appropriate information about risks and benefits. An alternative treatment is the anti-depressant drug, venlafaxine which can be very effective in reducing vasomotor symptoms. HRT should be avoided in women with more advanced disease or metastatic disease.

**Radiotherapy**

Radiotherapy is most commonly given as adjuvant treatment after surgery for early endometrial cancer in women at high risk of disease recurrence. Post-operative radiotherapy in all stage I endometrial cancer reduces pelvic recurrence from 14% to 10% but has no impact on overall survival and significantly increases treatment-related morbidity. A meta-analysis of trials does indicate a survival advantage of 10% for the sub-group of women with high risk disease i.e. grade 3 endometrioid cancer with >50% myometrial invasion. Therefore current practice is to select patients for adjuvant radiotherapy based on risk stratification. Patients are determined to be at differing degrees of risk of recurrence based upon depth of myometrial invasion, tumour grade and age (an independent prognostic factor) and assigned to radiotherapy or no radiotherapy accordingly. Radiotherapy may be given as external beam therapy to cover the pelvic lymphatics and/or vaginal vault brachytherapy to prevent central pelvic recurrence. Side-effects are common, occurring in 25% of women and include frequent bowel movements, diarrhoea and frequency of micturition. Severe toxicity e.g. bowel perforation or fistulae requiring surgery, occurs in approximately 2% of cases. Vaginal vault brachytherapy is as effective at preventing vaginal vault recurrence as external beam treatment but is associated with less gastrointestinal toxicity. Therefore, vault brachytherapy may be given alone if the risk of developing recurrence in the pelvic side walls is low.

Primary radical radiotherapy may be used where a patient cannot undergo surgery for medical reasons. Intra-cavitary radiotherapy combined with external beam treatment can achieve cure rates of approximately 70% in stage I disease although surgery to remove the uterus should be undertaken if at all possible.

**Chemotherapy**

Chemotherapy is mainly used as adjuvant treatment for more advanced disease (stage III and IV) following primary surgery, primary treatment of widely disseminated disease and palliation of recurrent extra-pelvic disease. Single agent or combination chemotherapy may be used, the choice depending on the aims of treatment, the performance status of the patient and the side effect profile. The most commonly used drugs are platinum-based drugs, anthracyclines and taxanes. The most common drug combinations used are cisplatin with doxorubicin and carboplatin with paclitaxel. Side-effects include nephropathy, cardiotoxicity, myelosuppression and peripheral neuropathy depending on the agents used. Whilst more intensive chemotherapy regimens improve disease-free survival and achieve a modest improvement in overall survival (3 months) in advanced, recurrent and metastatic disease, toxicity may be limiting in this patient group.

Chemotherapy is increasingly used in the adjuvant treatment of women with stage I disease deemed to be at high risk of distant recurrence e.g. serous or clear cell carcinoma although this is not well evidenced. A randomized controlled trial (PORTEC3) (now recruiting) will address the role of concurrent chemoradiation and adjuvant chemotherapy compared to pelvic radiotherapy alone in women with early disease at high risk of relapse. This important trial will help to determine the role of adjuvant chemotherapy for early stage endometrial cancer.

**Considerations in the treatment of advanced and recurrent disease**

Women with advanced or recurrent disease need careful consideration within the MDT in order to define the goals of
treatment and balance these against patient performance status and quality of life issues. Each case requires individual planning. Where disease is advanced at first presentation, it is generally preferable to remove the uterine tumour with surgery prior to radiotherapy or chemotherapy particularly where there is very troublesome and distressing vaginal bleeding and pelvic pain. Where disease involves the lower vagina at presentation, treatment is usually primary radiotherapy. Where advanced (stage III or IV) disease is diagnosed following surgery, multimodality treatment is used with adjuvant external beam radiotherapy to the pelvis and vaginal vault brachytherapy to treat residual disease and prevent local recurrence and adjuvant chemotherapy to prevent distant disease. Treatment for advanced disease with widespread nodal involvement at presentation is usually palliative and the sequence of treatments may be determined by the most troublesome symptoms. For example, chemotherapy may be given to treat systemic disease initially and external beam radiotherapy or surgery can be used, if necessary, to palliate vaginal bleeding. Treatment with high dose oral progestagens is useful for palliation in advanced disease and/or where the patient is unfit for other types of treatment. Good symptomatic relief can be achieved and tumour deposits may regress over a number of months although high grade tumours frequently lack progesterone receptors and may therefore respond less readily. Side-effects of hormonal therapy include weight gain, venous thromboembolism and hypertension.

Women who experience recurrence after treatment for early endometrial cancer are managed according to the pattern of recurrence and overall fitness. MRI is useful for initial evaluation of suspected pelvic recurrence although CT is required to assess the abdomen and thorax for other metastases in this setting. Isolated vaginal vault recurrence can be successfully salvaged with either surgery or radiotherapy with 3-year survival rates of approximately 70%. Other pelvic recurrences are usually treated with radiotherapy. Distant metastasis can be treated with chemotherapy, as discussed above, or high dose progestagens. Radiotherapy can also be used with good effect to treat isolated bony metastases which can cause pain and disability.

Prognosis and follow-up

The overall prognosis for endometrial cancer is generally good and reflects early presentation of the disease in most cases. The 5-year survival rate for all stages is approximately 80% but varies with tumour grade and depth of myometrial invasion. Survival in stage I disease is 85–90% but then falls to approximately 70–75% for stage II, 45% for stage III and <30% for stage IV disease. Other factors that adversely affect prognosis include non-endometrioid histological sub-type and lymphovascular space invasion.

Most endometrial cancer recurrences occur within the first 3 years after treatment. Follow-up is undertaken with the aim of detecting recurrence and identifying side-effects of treatment. A history of symptoms is taken and then clinical examination (including pelvic vaginal and rectal examination) is usually performed. Recurrence may be suggested by vaginal bleeding, new onset of persistent backache, significant weight loss or persistent pressure symptoms. The frequency and duration of follow-up visits varies between hospitals and usually follows guidelines developed locally within each cancer network. The role of the routine follow-up visit in detecting asymptomatic recurrence and improving survival from recurrence is unproven. It is also recognized that for some women, routine follow-up after a cancer diagnosis may be a stressful experience. The true value of routine hospital-based follow-up visits has yet to be properly determined.

FURTHER READING


Practice points

- Random endometrial biopsy or hysteroscopy, is as effective in diagnosing endometrial cancer as dilatation and curettage performed under anaesthetic in women with PMB.
- Clinical Genetics counselling should be considered for women diagnosed below 50 years or with a family history suggestive of HNPCC.
- Laparoscopic surgery for endometrial cancer reduces surgical morbidity and improves short-term quality of life scores and may be considered where the expertise exists.
- Systematic lymphadenectomy has no therapeutic benefit in clinical stage I disease.
- Adjuvant radiotherapy significantly reduces rates of pelvic recurrence but only improves survival in a small sub-group of women (grade 3, outer half myometrial invasion).