Endometrial cancer – an update

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Abstract

Endometrial cancer incidence rates are continuing to rise and approximately 40 % of all cases being preventable. A major contributing factor to this is the current obesity epidemic. Surgery remains the cornerstone of treatment and minimal access techniques have established themselves as the gold-standard. Routine lymphadenectomy for all disease stages has not been demonstrated to benefit overall survival. Risk stratification and personalized approaches to patient treatment are becoming more of a necessity, especially in younger women who may wish to preserve their fertility. Genomic profiling is starting to change the way we consider endometrial cancer, which may help direct treatment modalities in the future. Priority setting the research agenda will help guide future research and allow us to further tackle this common gynaecological malignancy.

Keywords endometrial cancer; genomic profiling; hereditary endometrial cancer; lymphadenectomy; minimally invasive surgery; obesity

Introduction

Endometrial cancer (EC) is the most common gynaecological malignancy in the developed world and the fourth most common cancer to affect UK women. Incidence rates are rising, with approximately 8500 new cases reported in the UK in 2015. Most EC cases occur in postmenopausal women; and the age-specific incidence increases steeply from 50 years. However, up to 25% of women are pre-menopausal at the time of diagnosis. A major contributing risk factor to this increase in incidence is the current obesity epidemic and EC ranks highest amongst all cancers in its association with obesity. If diagnosed and treated at an early stage whilst confined to the uterus, EC carries an excellent prognosis with high curability. A recent integrated molecular classification drawing on proteomic, genomic and transcriptomic analyses performed by The Cancer Genome Atlas (TCGA) resulted in new insights into EC subtypes. This molecular classification represents a paradigm shift in the understanding of ECs and heralds a move towards a more targeted and personalized approach to patient management. This review provides a current update on endometrial cancer, building on the work of previous articles.

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Comparison of the typical characteristic features of 'type 1' and 'type 2' endometrial cancers

Characteristic features	Type I	Type II
Histological type	Endometrioid, mucinous	Serous, clear-cell
Typical histological grade	Low-grade	High-grade
Precursor lesion	Atypical hyperplasia/EIN	Atrophy, SEIC
Unopposed oestrogen effect	Present	Absent
Typical growth pattern	Slow	Rapid
Depth of invasion	Usually superficial	Often deep
Clinical course	Indolent	Aggressive
Average 5-year survival	85 %	43 %
Age	Younger, perimenopausal	Older
Predominant molecular & genetic changes	*PTEN* or *KRAS* gene mutation and MSI	p53 mutation

EIN = Endometrioid endometrial neoplasia, SEIC = serous endometrial intraepithelial carcinoma, *PTEN* = Phosphatase and tensin homologue, *KRAS* = Kirsten RAt Sarcoma virus oncogene, p53 = Tumour protein 53, MSI = Microsatellite instability.

Table 1

Endometrial cancer pathology

The majority of EC arise from endometrial epithelial cells and are adenocarcinomas. ECs have traditionally been classified into Type 1 and Type 2 cancers based upon their clinical, metabolic and histological features (Table 1).

Type 1 ECs incorporate most of tumours seen and include the endometrioid adenocarcinomas, which account for >80 % of all ECs. These tumours are oestrogen-dependant and are frequently associated with endometrial hyperplasia (EH). EH represents a spectrum of morphological endometrial alterations, whereby abnormal proliferation of the endometrial glands results in an increase in the endometrial gland-to-stroma ratio. The presence of cytological atypia is associated with a high risk of progression to malignancy, such that atypical endometrial hyperplasia (synonymously known as Endometrioid Intraepithelial Neoplasia, EIN) carries a 40–60 % risk of future EC. Endometrial biopsy samples reported as EIN carry a significant risk of a co-existing underlying associated EC that has not been detected by endometrial sampling. Type 1 ECs are strongly associated with conditions contributing to unopposed oestrogen exposure (e.g. obesity, polycystic ovarian syndrome (PCOS), oestrogen only hormone replacement therapy (HRT), chronic anovulation, tamoxifen therapy, granulosa cell ovarian tumours, etc.), in addition to nulliparity, hypertension and insulin resistance. Furthermore, emerging evidence suggests a role for endocrine disrupting chemicals (EDCs) in EC development. At a molecular level, type 1 ECs frequently harbour mutations in the genes *PTEN, KRAS, CTNNB1 and PIK3CA*. Type 1 ECs are assigned a grade (1–3) depending on the degree of differentiation and nuclear features. G1 are slow growing tumours with low metastatic

potential whilst G3 represent tumours with poor differentiation and an aggressive phenotype and are therefore sometimes considered like Type 2 tumours (Figure 1).

Type 2 ECs tend to be oestrogen-independent and include the serous', 'clear cell' and 'mixed-cell' histological subtypes and other rare sub-types. Type 2 ECs are high-grade by definition. Type 2 ECs are not associated with the same risk factors as type 1 ECs and are more often associated with endometrial atrophy in the postmenopausal woman rather than with EH. They are associated with a poorer clinical prognosis and have a high tendency for extra-uterine spread. At a molecular level type 2 ECs are associated with *HER2* amplification and recurrent *TP53* mutations.

The division into type 1 and type 2 ECs is not rigid and it is recognized that many ECs have overlapping features of both tumour types, such that 10–19 % of endometrioid ECs are deemed high-grade and have clinical, histopathological and molecular features that are more akin to Type 2 ECs. Rarer subtypes of EC also exist and include; endometrial carcinosarcomas (previously known as Malignant Mixed Müllerian tumours (MMT)), neuroendocrine tumours and dedifferentiated tumours (Figure 1 demonstrates representative histopathological examples of the various EC types).

It is increasingly recognized that endometrial cancer is a heterogeneous disease due to a range of diverse molecular alterations in the tumours. In 2013, an integrated molecular classification drawing on proteomic, genomic and transcriptomic analyses of over 370 ECs performed by The Cancer Genome Atlas (TCGA) resulted in new insights and classification of EC subtypes. By employing array-based and sequencing methodologies, four novel EC groups were characterized:

i) Ultra-mutated cancers with DNA polymerase epsilon (*POLE*) mutations (7%)
ii) Hypermutated cancers with microsatellite instability (28%)
iii) ECs with low mutation rate and low frequency of DNA copy-number alterations (CNA, 39%)
iv) ECs with low mutation rate but high-frequency DNA CNA (26%)

The TCGA data is clinically relevant as it has been found to be associated with prognostic significance. EC patients in the ultramutated group harbouring *POLE* mutations (more commonly seen in grade 3 endometrioid ECs in their cohort) have a less clinically aggressive course and improved progression-free survival when compared with patients in the other the three groups (Figure 2). Since adjuvant treatment would routinely be offered to women in this group, it is unclear whether this group may be overtreated with adjuvant treatment and would do well regardless (due to their *POLE* status) or whether the favourable outcomes are secondary to their tumours being more susceptible to the adjuvant treatment. All four TCGA groups contained some low-grade endometrioid ECs, suggesting that the genomic profiles of ECs can be markedly different even

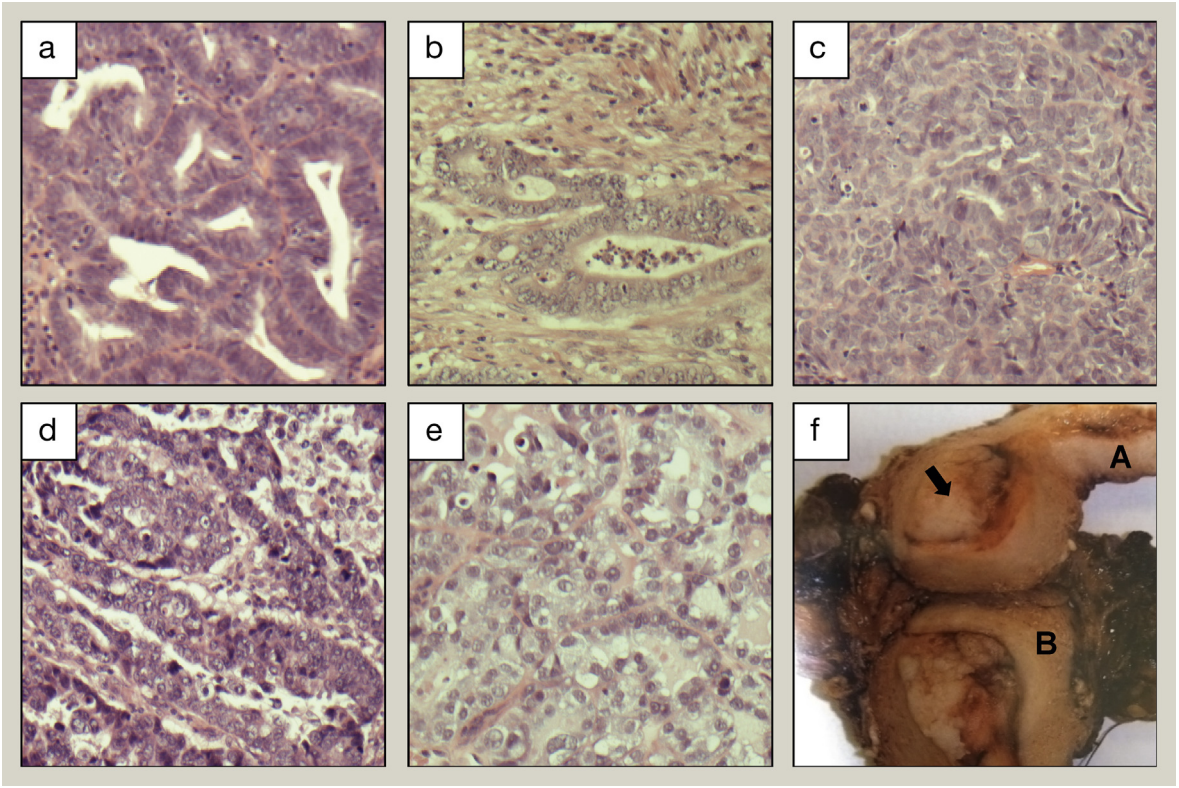


Figure 1 Representative pathology images of endometrial cancer types. Haematoxylin and eosin (H&E) stained diagnostic images and a tumour macroscopy image. (**a**) H&E image of grade 1 endometrioid endometrial cancer, (**b**) H&E image of grade 2 endometrioid endometrial cancer, (**c**) H&E image of grade 3 endometrioid endometrial cancer. (**d**) H&E image of high-grade serous endometrial cancer. (**e**) H&E image of clear cell endometrial carcinoma. (**f**) Macroscopy image of a bisected uterine specimen. Black arrow = tumour tissue filling the endometrial cavity, A = uterine cervix, B = uterine body/myometrial layer. Histology images at 20x magnification. (All images courtesy of Dr A. Moulla, Royal Infirmary of Edinburgh.)

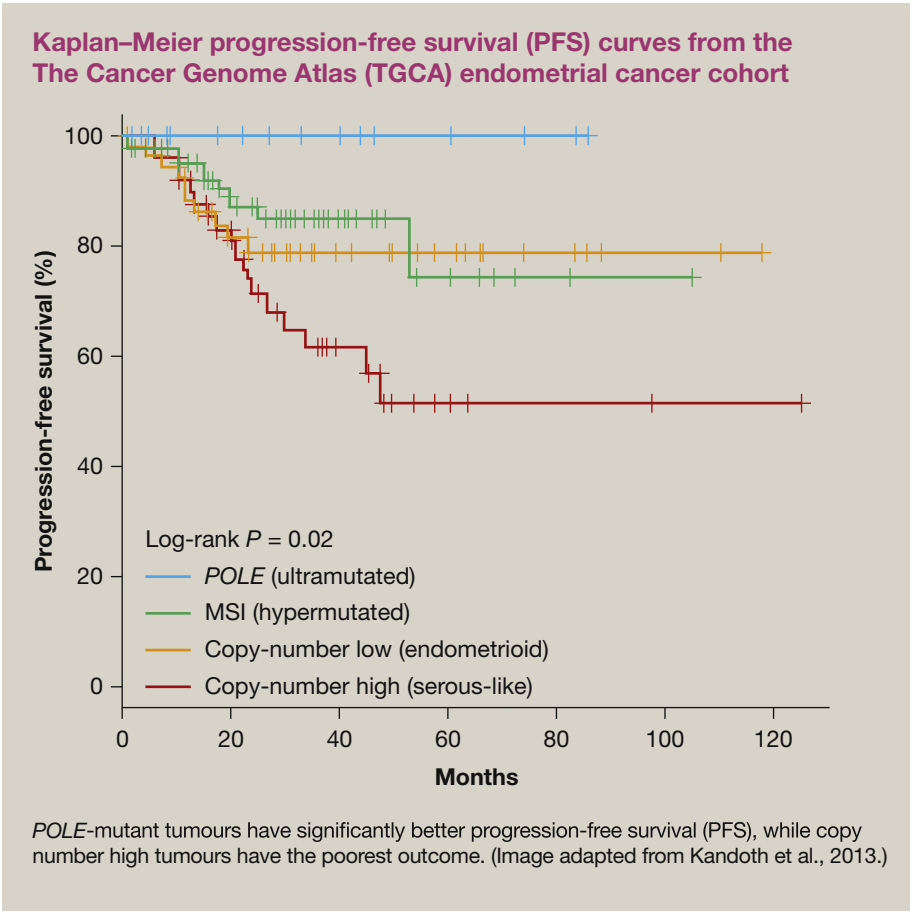
in tumours which have similar histological appearances. Furthermore, many of the grade 3 endometrioid ECs within the TCGA cohort had genomic profiles similar to serous carcinomas (i.e. *p53* mutations and high copy number alterations (CNAs)), extending the existing argument as to whether high grade endometrioid ECs should be grouped with other high grade serous ECs and considered as a 'type 2' tumour.

In the future it is likely that molecular analysis of endometrial tumours will improve risk stratification and ultimately contribute precision-based treatment of EC.

EC normally presents as a primary tumour, however in very rare cases it may be metastatic from another malignancy (e.g. breast, ovary, lung, stomach, colorectal, and melanoma). ECs usually spread by direct extension into surrounding structures (myometrium, cervix and vagina), with deeper infiltration eventually leading to a breach of the uterine serosa and invasion of the parametria. Haematogenous and trans-tubal spread may also occur, with the lungs being the most common site for distant metastasis. Lymph node involvement is related to the size and depth of tumour invasion into the myometrium, and the grade of the tumour. Lymphatic spread usually follows an anatomical distribution with involvement of the pelvic lymph nodes (internal and external iliac, obturator nodes) and the para-aortic nodal chain.

Hereditary endometrial cancer

The hereditary syndromes associated with EC include Lynch Syndrome (hereditary non-polyposis colorectal cancer (HNPCC) syndrome), Cowden's Syndrome and Hereditary breast–ovarian cancer syndrome (HBOC). Lynch Syndrome is an autosomal dominant condition caused by a germline mutation in DNA mismatch repair genes. Those affected have up to an ~80 % lifetime risk of developing colon cancer, followed by an ~60 % lifetime risk of developing EC and an ~10 % risk of developing other cancers (including but not exhaustive of; ovarian, renal, skin, brain and hepato-biliary tumours). This autosomal dominant syndrome is caused by a germline (inheritable, i.e. present in gametes) mutation in one or more of the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). The role of the DNA mismatch repair (MMR) system is to correct for 'mismatches' (i.e. base-pair substitutions and small insertions/deletions) that are caused by errors during DNA replication. DNA mismatches usually occur in regions of repetitive nucleotide sequences called microsatellites, leading to an expansion or reduction of those regions within tumour tissue compared to normal tissue. This is referred to as microsatellite instability (MSI) and is a characteristic feature of Lynch associated cancers. Although germline deficiencies in the mismatch repair system and MSI are a feature



POLE-mutant tumours have significantly better progression-free survival (PFS), while copy number high tumours have the poorest outcome. (Image adapted from Kandoth et al., 2013.)

Figure 2

of Lynch syndrome, they can also occur spontaneously (i.e. as somatic mutations) out-with Lynch syndrome and are reported in ~25–30 % of EC cases. Several criteria have been developed to identify individuals at risk of Lynch Syndrome, namely the Amsterdam II criteria and the Bethesda criteria for MSI tumour testing.

Cowden's syndrome is less common and is an autosomal dominant syndrome caused by a germline mutation in the *PTEN* gene which has life-time risk of ~20–30 % for developing EC and other cancers as well as hamartomas. Hereditary breast–ovarian cancer syndrome (HBOC) is due to inherited pathogenic mutations in the *BRCA1* and *BRCA2* genes, and confers high risks of breast carcinoma, ovarian serous cancer, as well as other cancers including serous carcinoma of the endometrium.

Prophylactic hysterectomy and bilateral salpingo-oophorectomy is usually recommended for women with hereditary syndromes who have completed their family. Endometrial surveillance with annual imaging and endometrial biopsy can offered to women who wish to retain fertility, although this has not yet been proven to be an effective prevention strategy.

Risk factors, initial investigations and diagnosis

EC most commonly presents as postmenopausal bleeding (PMB) (90 %), although only 10 % of women with PMB will have EC. Prompt referral for gynaecological assessment is mandatory for any episode of PMB. EC can also present as persistent post-menopausal discharge due to pyometra, abnormal uterine bleeding (AUB) in peri- and pre-menopausal women (especially those with established risk factors). Occasionally it may be detected by identifying abnormal endometrial cells on cervical cytology samples or even as an incidental finding. The British Gynaecological Cancer Society (BGCS) recommend that women with AUB over 45-years-old, or those with irregular bleeding or failure of treatment over 45 years of age, require endometrial sampling. Risk factors for EC are listed in Table 2.

Initial assessment of women suspected to have EC should take place within rapid-access clinics, with a targeted history taken to identify risk factors and co-morbidities. A pelvic examination should be performed to exclude lower genital tracts cancers or other causes of bleeding. A transvaginal ultrasound scan (TVUSS) is recommended to measure the endometrial thickness (ET) and identify any potential ovarian masses. TVUSS measurement of ET should be performed by scanning the uterus in a sagittal view. The measurement reported should be the double layer ET measured in an anteroposterior dimension from one basal layer to the other and excluding any fluid within the cavity.

There is no standard ET measurement threshold for pre-menopausal women, although TVUSS is recommended to be performed early in the proliferative phase of the menstrual cycle (days 4–6) when the endometrium would be expected to be at its thinnest. Ultrasound is less helpful in women taking tamoxifen or hormone replacement therapy (HRT) because typical morphological changes often result higher ET measurements and false positive ultrasound findings. A tissue biopsy is usually always

Established risk factors for the development of endometrial cancers

Risk factor category	Risk factor	Comments
Non-modifiable	Age	Incidence highest in females aged 75 to 79[1]
	Family history	Suggested higher risk if first degree relative affected by EC
Menstrual	Postmenopausal status	
	Early menarche	11 % higher in parous women aged under 13 at menarche[1]
	Late menopause	34 % higher in nulliparous women aged 50–54 at menopause[1]
	Prolonged perimenopause	
	Null parity	35–42 % higher in nulliparous women[1]
Co-morbid conditions	Obesity	34 % higher in overweight (BMI 25–30) women, and 2.5 times higher in obese (BMI 30+) women[1]
	Diabetes mellitus	40–81 % higher in diabetics compared with non-diabetics[1]
	Polycystic ovarian syndrome (PCOS)	2.8 times higher[1]
	Oestrogen secreting tumours	
Iatrogenic	Oestrogen only HRT	2.3 times higher[1]
	Tamoxifen therapy	Risk higher in postmenopausal women and is dose and duration dependant
	Exogenous oestrogen exposure	2.1–2.7 times higher in women with the high circulating oestrogen levels[1]
Others	Physical inactivity	Likely related to obesity
	Hereditary	Lynch and Cowden's Syndromes

Table 2

warranted in women taking tamoxifen or with recurrent unscheduled bleeding whilst taking HRT regardless of TVUSS findings.

The BCGS recommend that endometrial sampling should be performed where TVUSS measures an ET $\geq$ 4 mm, or if the scan cannot give a clear view of the endometrium. Some units may use lower thresholds, accepting the potential higher rate of unnecessary sampling in order to achieve greater detection sensitivity. The Pipelle® device is accepted as the optimal endometrial sampling device, with reported detection rates for EC in postmenopausal and pre-menopausal women of 99.6 % and 91 %, respectively. Hysteroscopy is the gold standard investigation and should be carried out if outpatient endometrial biopsy is not feasible, fails or for women with ultrasound irregularities and at high risk of EC. Where possible hysteroscopy should be performed in the outpatient setting. Recurrent PMB should be investigated with hysteroscopy and endometrial biopsy, and further evaluation is always warranted in cases of persistent AUB despite a negative endometrial biopsy. There is no evidence to support routine screening for endometrial cancer in asymptomatic women in the general population.

Further investigations and staging

Following a diagnosis of EC, UK practice is for immediate referral to a gynaecological oncology multidisciplinary team (MDT) meeting. The British Gynaecological Cancer Society (BGCS) recommended that women should have an identified key worker and a responsible clinician throughout their EC treatment journey. The aim of pre-operative imaging is to detect distant metastases and to help plan surgical treatment. Chest imaging, either in the form of a plain radiograph or computerized tomography (CT) should be performed to investigate for pulmonary metastases. CT is preferable with high-risk histological subtypes, e.g. carcinosarcomas. In many centres, all patients with histologically proven EC undergo magnetic resonance imaging (MRI) to identify deep myometrial invasion orcervical stroma involvement. At present, indications for MRI of the endometrium are not firmly established due to differing surgical practice with respect to lymphadenectomy. There is consensus that all patients with histological high-grade tumours should undergo MRI preoperatively. There is no indication for routine evaluation of cancer antigen 125 (CA125) since there are limited data regarding the efficacy of this tumour marker for detecting extrauterine disease.

Staging of EC is surgical and currently utilizes the 2009 International Federation of Gynaecology and Obstetrics (FIGO) system (Table 3).

International Federation of Gynaecology and Obstetrics (FIGO) endometrial cancer staging system 2009

Stage I	**Tumour contained to the corpus uteri**
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
Stage II	**Tumour invades the cervical stroma but does not spread beyond the uterus**[a]
Stage III	**Local and/or regional spread of tumour**
IIIA	Tumour invades the serosa of the corpus uteri and/or adenexas
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to the pelvis and/or para-aortic lymph nodes
IIIC1	Positive pelvic lymph nodes
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	**Tumour invasion of bladder and/or bowel mucosa and/or distant metastases**
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and or inguinal lymph nodes

Grading is reported addition to stage: either G1, G2 or G3.
Positive cytology to be reported separately without changing the stage.
[a] Endocervical glandular involvement should only be considered as stage I and no longer stage II.

Table 3

Management of endometrial cancer

Surgical

Surgery is the mainstay of treatment for EC and is usually total hysterectomy with bilateral salpingo-oophorectomy. There has been a progressive move towards the use of minimally invasive surgical (MIS) techniques. It is now accepted that for women with grades 1–2 EC apparently confined to the uterus (based on physical examination, with or without pelvic imaging), MIS techniques (laparoscopic or robotic) should be considered the optimal approach. MIS is associated with a lower rate of severe post-operative morbidity and shorter hospital length of stay compared with laparotomy and it is more cost-effective with comparable oncologic outcomes. Laparoscopic surgery is not inferior to open surgery in terms of overall survival. Robotic surgery has been shown in the short term to be non-inferior to laparoscopy. It appears to be associated with lower conversion to laparotomy rates in high-BMI patients, although overall it has a higher cost association.

The role of lymphadenectomy

Staging lymphadenectomy is sometimes offered in the surgical management of selected 'high risk' endometrial cancers, although practice varies widely between different institutions as the benefits are debated in the literature. Removal of the lymph nodes that drain the uterus is not in itself therapeutic as lymphadenectomy does not improve oncological outcomes. The rationale for removing lymph nodes is for accurate surgical staging and this information can be used to select those patients who are likely to benefit from adjuvant treatment, and spare those who will not. Pathological lymph node involvement upstages endometrial cancer to stage 3.

Consequently, different lymph node management approaches will be associated with different rates (and modalities) of adjuvant therapy.

Several randomized controlled trials (RCTs) have been conducted to evaluate the role of lymphadenectomy, however challenges in trial design and quality control have dampened the

conclusions that can be drawn. Additionally there is no consensus definition of what constitutes 'high-risk' factors for nodal disease, although, the incidence of pelvic lymph node metastases has been does increase with grade of tumour and degree of myometrial invasion In 2015 a Cochrane review identified two large RCTs of women with pre-operative clinical stage 1 disease, including the multinational ASTEC trial. The meta-analysis demonstrated no statistically significant difference in the risk of death or disease recurrence in women undergoing lymphadenectomy compared to those who had not, after adjusting for age and tumour stage. Indeed, the data suggested women who had lymphadenectomy performed were more likely to suffer from surgically related systemic morbidity, i.e. lymphoedema and lymphocysts. The authors of the review also concluded that no current RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.

Given the on-going uncertainties surrounding lymph node evaluation in women with EC confined to the uterus the decision to proceed is practically dependant on a number of factors including:

1) the probability of lymph node metastasis (e.g. pre-operative biopsy tumour type and grade, pre-operative imaging to suggest deep myometrial invasion or the presence of suspicious lymph nodes on imaging)
2) the technical feasibility of surgically assessing the lymph nodes (e.g. in high-BMI patients, the risks of surgical morbidity may be unacceptable)
3) the risk and patient acceptance of surgical morbidity (i.e. lymphoedema)
4) the acceptability and suitability of the patient for adjuvant therapies, including long term morbidity

When deciding to proceed with lymph node assessment patients should be counselled about their options and engage with their surgical team in shared decision-making.

The role for sentinel lymph node biopsy (SLNB) is starting to gain more interest, potentially providing a balance between achieving adequate staging whilst minimising morbidity. Prospective studies have assessed practicality of this technique and found a low false-negative rate for recognition of positive lymph nodes. However, at present due to the lack of robust trial data more evidence is required to support its use in routine management. There are no randomized controlled trials to compare pelvic and para-aortic lymphadenectomy with either pelvic lymphadenectomy alone or no lymphadenectomy.

It is likely that practice will continue to vary with respect to lymphadenctomy until further studies are published to guide best practice.

Radiotherapy

Pelvic radiotherapy can be administered as external beam radiotherapy (EBRT) or vaginal brachytherapy (BT). It plays a significant role in the adjuvant treatment of EC after surgery and can also be used for the minority of women who are unsuitable for surgical intervention, and to treat localized disease recurrence. The suitability for adjuvant radiotherapy treatment is usually determined following pathology review. Adjuvant radiotherapy is not recommended for low-risk endometrioid EC since there is no conferred increase in survival from it and additional morbidity and mortality may be caused.

Chemotherapy

The use of adjuvant chemotherapy remains controversial and it has been the subject of investigation in several clinical trials for both intermittent-risk and high-risk ECs, as a single therapy and in combination with radiotherapy. In high-risk ECs, post-operative platinum-based chemotherapy may be associated with a small benefit in progression-free survival and overall survival irrespective of radiotherapy treatment, for those women acknowledging the possibility for toxicity and small potential survival advantage. The PORTEC-3 trial was initiated to investigate the benefit of adjuvant chemotherapy during and after radiotherapy (chemoradiotherapy) *versus* pelvic radiotherapy alone for women with high-risk EC. The trial reported data to suggest that chemoradiotherapy was of no benefit for those with stage 1 or 2 ECs. In stage 3 ECs, although no significant difference was found in overall survival, chemoradiotherapy did help to reduce the risk of disease recurrence. Two further clinical trials (GOG-249 and GOG-258) have not yet been fully published, however abstract summaries are provided by Dowdy and Glaser in their 2018 commentary. GOG-249 compared pelvic radiotherapy with a combination of three cycles of carboplatin-paclitaxel chemotherapy and vaginal brachytherapy. Chemotherapy did not improve failure-free survival, overall survival, or the incidence of distant recurrence, but resulted in twice the incidence of nodal recurrence and more adverse events than radiotherapy alone. The GOG-258 trial compared chemoradiotherapy (the same schedule as used in the PORTEC-3 trial) with six cycles of carboplatin—paclitaxel chemotherapy alone. No differences in overall or recurrence-free survival were reported, but significantly more vaginal and pelvic or para-aortic recurrences were reported in the chemotherapy group.

Special considerations

Advanced and recurrent disease or unfit patients

Advanced EC at presentation or recurrent disease requires special consideration in order to balance the goals of any treatment against a patient's performance status, quality of life and personal wishes. Patients with advanced EC may be suitable for surgical resection with/without neoadjuvant chemotherapy, although chemotherapy in this context has not been formally assessed in RCTs. Complete surgical resection of all visible disease in advanced EC can be offered to patients who are fit to undergo surgery as there is some evidence to suggest that this may prolong survival. In addition, debulking palliative surgery has a role in providing symptomatic relief, especially from vaginal bleeding which can often be significant and difficult to control. Primary radiotherapy is often the treatment of choice for advanced disease with significant vaginal extension. Where advanced (stage III or IV) disease is diagnosed following surgery, multimodal treatment is employed.

Patients with isolated vaginal vault recurrence can be treated with further surgery or radiotherapy, although careful patient selection is key and will depend on the type of primary treatment received. For women previously treated with radiotherapy and who are surgical candidates (i.e. where complete resection is

technically feasible), pelvic exenteration can be offered. Alternatively, a radical resection of the recurrent disease (e.g., vaginectomy) may be an alternative, provided the chance for complete resection is not compromized. Other pelvic recurrences are generally treated with radiotherapy (which is especially helpful in palliating pain from bony metastases) and for more distant metastases, chemotherapy can be considered.

In those patients who are medically unfit for standard treatment regimens (i.e. morbid obesity and/or comorbidities) a highly individualized approach is required. Consideration should be given to vaginal hysterectomy, definitive pelvic radiotherapy or medical management with progestogens/aromatase inhibitors. The choice of treatment will be influenced by patient preferences and following MDT review. There is minimal evidence available in the published literature to inform on the outcome of medical management as a primary treatment. The delivery of progestins is challenging due to the short half-life and the high doses that are required. The levonorgestrel-releasing intra-uterine system (IUS) has higher rates of compliance and reduced side effects compared to oral alternatives. Aromatase inhibitors (e.g. Letrazole) may be an alternative. The comparative efficacy of progestogens and aromatase inhibitors has not yet been investigated in a RCT.

Obesity

Obesity is a major contributing risk factor to the current increase in EC incidence, with reports that for every 5 kg/m^2 increase in body mass index, a 1.6-fold increased risk of EC is conferred. Novel research is on-going surrounding the provision of bariatric surgery to obese women diagnosed with obesity-related precancerous endometrial lesions, with exploration of non-surgical treatments for early ECs in selected patients.

Management of obese patients can often be problematic, since an elevated BMI increases the risk of perioperative and postoperative complications, particularly in the presence of comorbid conditions such as diabetes, hypertension and coronary artery disease. Perioperative technical challenges can also arise, with higher rates of failed laparoscopic entry, impeded tissue manipulation and poor visualization of the operative field. Obesity may limit the extent of Trendelenburg positioning due to excessively high ventilatory pressures. MIS procedures should always be considered for the obese woman since they have fewer reported postoperative complications, including; wound infections, paralytic ileus and incidences of venous thromboembolism.

Fertility sparing treatments

Age-specific incidence rates of EC rise steeply from around age 45 −49 and every year in the UK ∼120 women present with EC before the age of 45 years. Women of reproductive age who are diagnosed with EC are being seen more frequently, and these women often wish to retain their fertility. For women who are candidates for fertility preservation, the most common approach is progestin therapy (to counteract oestrogenic stimulation and cellular proliferation) and deferral of surgical treatment until after their family is complete. Current evidence suggests that conservative management of EC may be safe in the short-term in selected women with grade 1 EC and with superficial myometrial invasion. Various progestogenic regimens have been suggested with the most common being Medroxyprogesterone acetate 400 −800 mg in divided daily doses or megestrol 160 mg daily. The levonorgestrol containing intrauterine system may be useful for maintenance therapy. There is no consensus on the appropriate duration of treatment and most researchers advocate sampling the endometrium at 3-monthly intervals during the first year. Synchronous ovarian cancers have been reported and judicious evaluation of ovarian cysts found on imaging need to be assessed by expert review and require cautious management. These patients should also be referred to the fertility clinic to receive appropriate counselling and discussion of assisted reproduction, if appropriate.

Prognosis and follow-up

Overall prognosis for EC is determined by histology and disease stage. Many women will have a favourable prognosis, since most will have an endometrioid histology which tends to present early. The prognosis for early stage EC is excellent. If diagnosed and

The top-ten unanswered research questions in endometrial cancer research as set by the James Lind Alliance

1	Is it possible to develop a personalized risk score which reflects a woman's individual risk of developing endometrial cancer?
2	Which women with abnormal vaginal bleeding should be referred for specialist review?
3	What are the most effective treatments currently available for advanced endometrial cancer and what key molecular pathways should be targeted when developing new treatments?
4	Can we predict which women will benefit from adjuvant chemotherapy or radiotherapy and avoid ineffective treatments?
5	Are blood tests, including markers like CA125, useful in predicting duration of survivorship and/or recurrent disease?
6	What ways of raising public awareness about endometrial cancer are the most effective and cost-effective?
7	What are the psychological issues surrounding diagnosis and treatment of endometrial cancer and what interventions might be helpful?
8	What are the underlying causes of different types of endometrial cancer and how do they develop?
9	Can we predict at the time of diagnosis which endometrial cancers and precancerous lesions will respond to hormone treatments?
10	Do changes in lifestyle, including weight loss, reduce the risk of recurrent and improve survival in women who have been treated for endometrial cancer?

Adapted from (Wan et al., 2016)

Table 4

treated at stage I or II, EC 5-year survival figures stand at ~92% and 75%, respectively. Women diagnosed with advanced EC, FIGO stages III and IV, have 5-year survival figures reported at 57–66% and 20–26%. Factors that adversely affect prognosis include non-endometrioid pathology, stage and the presence of lymphovascular space invasion (LVSI).

Recurrences are most likely to happen within the first 3 years after treatment, and the most common sites of recurrent disease are the vaginal vault, pelvis, abdomen and the lungs. Signs and symptoms of recurrence may include: vaginal bleeding, pelvic pain, backache or significant weight loss. Post-treatment follow-up should take the form of a detailed history of symptoms followed by clinical examination, including a pelvic examination. Only ~70 % of women with recurrence will have symptoms and so a high index of suspicion should be maintained. Routine radiological investigation for recurrence in asymptomatic women is not evidence based. Frequency of follow-up will vary between institution; a standard regimen would be 3–4 monthly for the first 2 years and 6–12 monthly thereafter to complete 5 years before discharge to primary care. However, there is a move towards patient-initiated follow-up for patients with low risk disease. This requires careful selection of appropriate patients, provision of adequate information about signs and symptoms of recurrence, and a robust care system to ensure patients can be seen quickly and easily if they do experience symptoms.

Future directions

The recent genomic classification of ECs by TCGA heralds' new opportunities for EC risk stratification and personalized patient management. What has previously been considered a predominantly postmenopausal disease is becoming an increasing issue for women of childbearing age, obese individuals and those with polycystic ovarian syndrome (PCOS). As many cases of the disease may be prevented by tackling obesity, Public Health programs need to do more to encourage maintenance of a normal BMI in the population. Despite the relative frequency of EC, awareness amongst the general public of EC is low and EC research is somewhat underfunded relative to its societal burden. With this in mind, work from the James Lind Alliance, a priority setting partnership incorporating patients, carers, physicians and researchers has published the top-ten unanswered questions in EC research (Table 4). By focusing on these priority areas, we are in an excellent position to reduce the burden of this disease in the future. ◆

FURTHER READING

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Practice Points

- Endometrial cancer ranks highest of all cancers in its association with obesity
- If diagnosed and treated whilst confined to the uterus, endometrial cancer carries an excellent prognosis
- Atypical hyperplasia/endometrial intraepithelial neoplasia (EIN) carries a 40–60 % risk of future endometrial cancer
- Surgery is the mainstay of treatment and minimally invasive techniques should be the gold-standard approach
- Adjuvant radiotherapy is not recommended for low-risk endometrioid endometrial cancer since there is no increase in survival from it
- In clinical FIGO stage 1 disease routine lymphadenectomy does not reduce the risk of death or disease recurrence
- Genomic profiling is providing new insights into the pathology of endometrial cancers