Endometrial cancer

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Endometrial cancer is the most common gynaecological cancer in high income countries and its incidence is rising globally. Although an ageing population and fewer benign hysterectomies have contributed to this trend, the growing prevalence of obesity is the major underlying cause. Obesity poses challenges for diagnosis and treatment and more research is needed to offer primary prevention to high-risk women and to optimise endometrial cancer survivorship. Early presentation with postmenopausal bleeding ensures most endometrial cancers are cured by hysterectomy but those with advanced disease have a poor prognosis. Minimally invasive surgical staging and sentinel-lymph-node biopsy provides a low morbidity alternative to historical surgical management without compromising oncological outcomes. Adjuvant radiotherapy reduces loco-regional recurrence in intermediate-risk and high-risk cases. Advances in our understanding of the molecular biology of endometrial cancer have paved the way for targeted chemotherapeutic strategies, and clinical trials will establish their benefit in adjuvant, advanced, and recurrent disease settings in the coming years.

Epidemiology

Endometrial cancer is the sixth most common cancer in women, with 417 000 new diagnoses made globally in 2020.[1] A woman's lifetime risk of endometrial cancer is approximately 3%, with a median age at diagnosis of 61 years. Overall incidence has risen by 132% in the last 30 years, reflecting a rise in the prevalence of risk factors; in particular, obesity and an ageing population.[2] The highest rate of endometrial cancer is currently observed in North America (86·6/100 000) followed by eastern (52·5/100 000) and central Europe (21·9/100 000; figure 1). Although diagnoses have increased across all age groups, there has been a doubling in cases in women under the age of 40 years, who now account for 4·2% of all low-grade endometrial cancers diagnosed in the USA.[3] The greatest upsurge in caseload has been in high-income countries (HICs); however, rising age-standardised incidence rates have been observed globally, including in sub-Saharan Africa.[2] By contrast, mortality rates have fallen over the same time period by 15% (estimated average percentage change –0·85, 95% CI –0·93 to –0·76), despite higher numbers of endometrial cancer-related deaths.[2] As a consequence, more women than ever are now both surviving and dying from endometrial cancer. An inverse relationship between endometrial cancer incidence to mortality ratio and socioeconomic index is of particular concern, with women from low-income and middle-income countries (LMICs) significantly more likely to die from endometrial cancer than those from HICs, reflecting poor access to timely, evidence-based medical care, and a higher proportion of aggressive, non-endometrioid tumour diagnoses. In the USA, Black women are more likely to develop aggressive and non-endometrioid tumours than White women, suggesting that racial differences in biology might contribute to disparate outcomes even in HICs.[4]

Search strategy and selection criteria

We searched PubMed, MEDLINE, and Embase with the terms "endometrial cancer", "epidemiology", "risk factors", "prevention", "survivorship", "follow-up", "screening", "presentation", "diagnosis", "fertility-sparing management", "pathology", "pathogenesis", "atypical endometrial hyperplasia", "molecular classification", "genetics", "prognostic factors", "survival", "surgery", "lymphadenectomy", "sentinel lymph node", "chemotherapy", "radiotherapy", "hormone therapy", and "targeted treatment" for articles published in English between Jan 1, 1995, and Oct 26, 2021. We also reviewed the reference list of articles identified by this search. We focused our search strategy on systematic reviews, meta-analyses, and randomised controlled trials and selected articles based on their relevance and scientific merit.

Clinical presentation

Endometrial cancer usually presents at an early stage with postmenopausal bleeding,[5] but only 5–10% of women with postmenopausal bleeding have sinister underlying pathology. The probability of endometrial cancer as a cause of postmenopausal bleeding is less than 1% in women younger than 50 years, rising to 3% in those aged 55 years and 24% in those older than 80 years.[6] The UK National Institute for Health and Care Excellence (NICE) therefore recommends urgent investigation for women with postmenopausal bleeding who are older than 55 years.[7] Around 15% of diagnoses are made pre-menopause, where heavy, prolonged, or intermenstrual bleeding are common presenting complaints, the latter being most predictive of endometrial cancer.[8] Such symptoms are extremely common and caused by endometrial cancer in just 0·3% of cases. Nevertheless, misattribution of symptoms to benign causes is responsible for diagnostic delays; patients with endometrial cancer aged 35–44 years were ten times less likely to be referred urgently than those aged 65–74 years in a review of suspected cancer referrals from primary care in England between 2006 and 2010 (odds ratio 0·09, 95% CI 0·07–0·12; p<0·001).[9] Decisions to investigate these younger women must be guided by risk factors, particularly the presence of an indicative family history, obesity, and polycystic ovary syndrome (PCOS). Symptomatic premenopausal women with a body-mass

index (BMI) greater than 30 kg/m² are five times more likely to be diagnosed with endometrial cancer than women with a healthy weight (BMI 18·5–25 kg/m²), in those with BMI greater than 40 kg/m² this likelihood is 20 times increased.[10] Locally advanced disease can occasionally present with abdominal distension, pain, and urinary or bowel dysfunction. Atypical glandular cells on cervical cytology samples are reported in up to 50% of endometrial cancer cases,[11] offering the potential for opportunistic detection during cervical screening, but a move towards primary human papillomavirus screening will limit diagnoses via this route.

Diagnosis

Diagnosis relies on histological examination of an endometrial tissue sample, but this invasive test is reserved for those who have endometrial pathology or a thickened endometrium on transvaginal ultrasound scan (figure 2).[12] In postmenopausal women, a threshold of 5 mm offers an endometrial cancer detection sensitivity of 96·2% and a negative predictive value of 99·3% according to a large systematic review of 44 studies including 1341 cases and 15 998 controls.[13] Poor specificity, of around 51·5% at an endometrial thickness of 5 mm in this postmenopausal age group, means that a large proportion of women require additional tests before significant endometrial pathology can be ruled out. In pre-menopausal women, transvaginal ultrasound is even less specific, since endometrial thickness fluctuates cyclically in healthy reproductive-aged women. Out-patient hysteroscopy enables direct sampling of suspicious lesions and is recommended when focal endometrial pathology is identified on an ultrasound scan and for women with recurrent symptoms. Blind endometrial sampling using an outpatient-based narrow bore suction device is extremely effective at making the diagnosis, although failure rates of around 11% are due to inadequate samples and cervical stenosis.[14] A one-stop clinic with sequential transvaginal ultrasound, hysteroscopy, and endometrial sampling as required during the same hospital visit is clinically effective and minimises delays for patients.[15] Lived experiences of intrauterine investigations range widely, from mildly unpleasant through to severely painful, and some women require general anaesthetic for their completion. Innovations in diagnostics, particularly non-invasive urogenital biomarkers, that identify high-risk women for invasive testing while safely reassuring low-risk women are in development, and their incorporation into diagnostic pathways will be transformative (figure 2).[16] Preoperative assessment of women with endometrial cancer can include an MRI scan, to estimate depth of myometrial invasion, assess pelvic lymph-node status and identify extrauterine disease. This information is important when considering fertility-sparing management[17] and might direct the place (local hospital or tertiary cancer centre) and extent of surgery, but is not clinically useful or cost effective for most women with low-grade histologies. A CT scan of the thorax, abdomen, and pelvis is used to identify extrauterine disesae or metastases in women with high grade histology. Anaesthetic assessment is important for safe surgery, particularly in the context of extreme obesity and associated comorbidities.

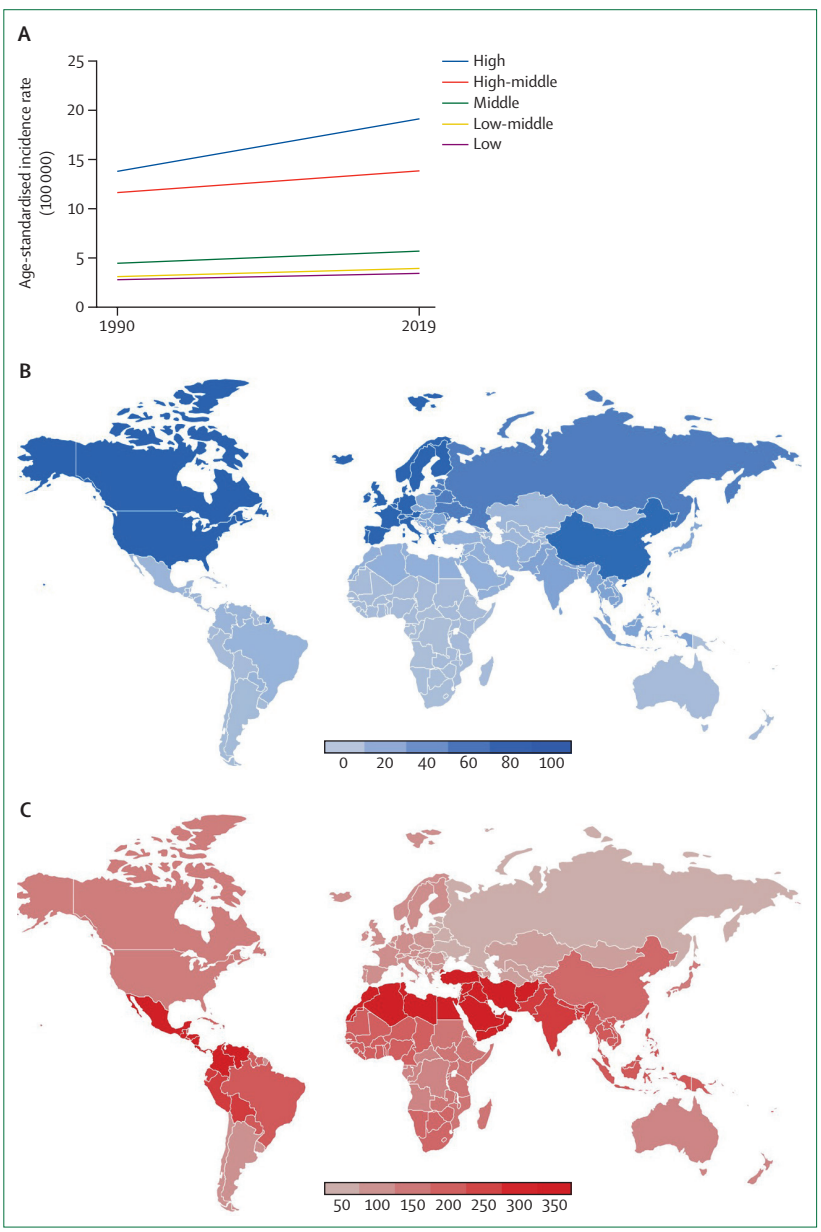
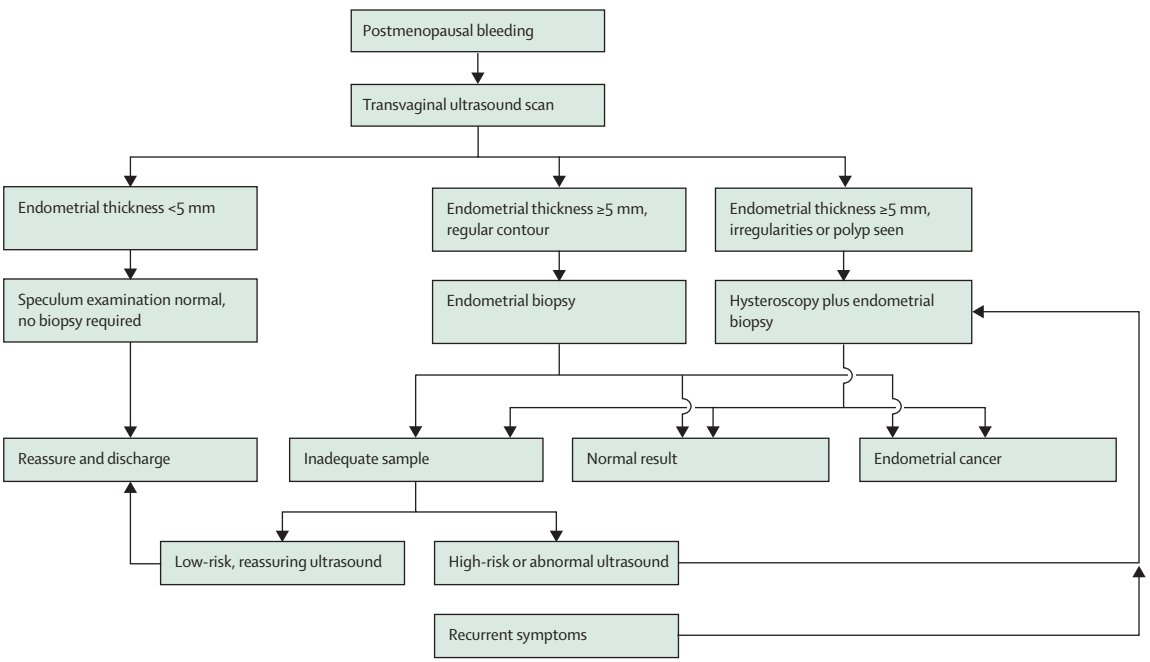


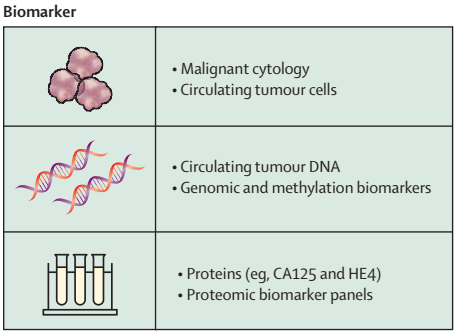
Figure 1: **Global burden of endometrial cancer[2]**
(A) Global trends in ASIR of endometrial cancer between 1990 and 2019 according to SDI. (B) ASIR of endometrial cancer 2019 (100 000 population) per GBD region. (C) Global increase in endometrial cancer incidence 1990–2019. The heat map represents percentage change in ASIR for each GBD region as calculated by the ASIR 2019 divided by the ASIR in 1990 multiplied by 100. There is a marked regional variation (>10 fold) in incidence rates globally, with a faster growing trend and birth cohort effect evident in many low-income and middle-income countries, reflecting a change in lifestyle and a higher prevalence of risk factors (obesity and inactivity levels) in younger generations. ASIR=age-standardised incidence rate. SDI=socio-demographic index. GBD=Global Burden of Disease.

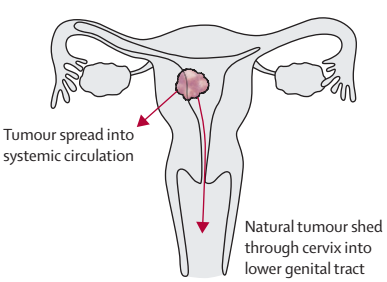
A Routine investigation of postmenopausal bleeding



B Novel diagnostic and screening tools in development

Biomarker





Biofluid	Source of biomarkers	Pros	Cons
Venous blood	Haematogenous spread	Good patient acceptability	• Tumour biomarkers at low concentration in early-stage disease
Uterine lavage	Lavage fluid in direct contact with tumour	Can be collected routinely during hysteroscopy	• Invasive sampling • Few advantages over current diagnostics
Cervico-vaginal fluid	Natural tumour shed through cervix into lower genital tract	• Minimally invasive sampling • Suitable for community care • Could be used to triage women for further diagnostic tests	• Speculum examination is needed to obtain a cervical sample • Vaginal tampons might be unacceptable method of biomarker collection for some women
Urine	• Renal excretion of systemic biomarkers • Contamination of urinary flow by natural tumour shed via lower genital tract	• Excellent patient acceptability • Suitable for community-based or home-based sampling • Could be useful as a screening tool in high-risk women	• Renally excreted biomarkers can be at low concentrations, whereas natural tumour shed can be unreliable, in early-stage disease • Proof-of-principle data only • More research is needed

***Figure 2*: Diagnostic pathway and innovations in diagnosis**
(A) Current diagnostic pathways for endometrial cancer involve sequential, invasive tests to assess the thickness of the endometrium by transvaginal ultrasound scan, visualise the endometrial cavity, or take a tissue sample for histological evaluation. (B) Innovations in endometrial cancer diagnostics include the identification and validation of cancer-specific biomarkers that can be reliably detected in non-invasive biofluids for community or home-based triage of symptomatic or asymptomatic high-risk women.

Risk factors

Obesity, metabolic, and reproductive factors

The risk of endometrial cancer increases with age and BMI. Of the 20 most common tumour types, endometrial cancer has the strongest link with obesity, with every 5 kg/m² increase in BMI associated with a 54% higher risk of cancer.[18,19] The lifetime risk of endometrial cancer in women with a BMI greater than 40 kg/m² is 10–15%, equivalent to the lifetime risk of lung cancer in smokers.[20] Whether weight gain during adulthood or body adipose distribution are more important than BMI in determining endometrial cancer risk is unclear.[18] Obesity creates a proinflammatory milieu dominated by high circulating levels of C-reactive protein, interleukin-6 and tumour necrosis factor-α, and a relative deficiency of protective immune cell types in the endometrium, which might contribute to endometrial cancer risk.[21,22] Obesity is a hyper-oestrogenic state due to the peripheral aromatisation of adrenal androgens to oestrogen by adipose tissue (figure 3).[23] Oestrogen stimulates the endometrium to proliferate, whereas cyclical progesterone and regular menstrual shedding maintains endometrial health during reproductive years. In postmenopausal women, natural progesterone deficiency contributes to an obesity-driven unopposed oestrogen excess, the leading theory behind endometrial carcinogenesis.[24] Reproductive risk factors that increase lifetime exposure to unopposed oestrogen, including early menarche (<12 years), late menopause (≥55 years), anovulation (eg, PCOS), and nulliparity also increase endometrial cancer risk, in keeping with this theory.[25] Tamoxifen is a selective oestrogen receptor modulator that inhibits breast but stimulates endometrial proliferation, and its long-term prescription for the prevention or treatment of hormone-sensitive breast cancer increases endometrial cancer risk four fold.[26] Insulin resistance and hyperinsulinaemia, features of obesity, type 2 diabetes, and PCOS, promote endometrial stimulation by increasing the bioavailability of both oestrogen and insulin-like growth factor(IGF)-1 through reduced levels of their respective circulating binding proteins, sex hormone binding globulin, and IGF-binding proteins. Activation of the pro-oncogenic PI3K–AKT–mTOR signalling pathway by direct (oestrogen) and indirect (IGF-1) routes increases endometrial proliferation and explains a higher incidence of the disease in type 2 diabetes and PCOS, independent of BMI.[27]

Genetic factors

Genetic predisposition to endometrial cancer is most commonly seen in Lynch syndrome, where inherited pathogenic variants involving one of the four mismatch repair (MMR) genes, *MLH1, MSH2, MSH6*, and *PMS2* portends a 13–49% lifetime risk of endometrial cancer, as well as elevated risks for colorectal, ovarian, and multiple other cancer types.[28] Several international groups,[29,30] including NICE,[31] recommend testing all endometrial cancers for MMR deficiency to identify the 3% that are caused by Lynch syndrome (figure 4).[32,33] Other hereditary causes of endometrial cancer include Cowden syndrome, where rare pathogenic variants in the *PTEN* tumour suppressor gene confer a 20–30% lifetime risk for endometrial cancer, and *BRCA1* and *BRCA2* pathogenic variant carrier status, which might marginally elevate risk for serous endometrial cancer, although reports are conflicting.[34,35] A first degree relative with endometrial cancer doubles a woman's risk of the disease even where a specific genetic variant is not implicated,[36] and a considerable part of this familial risk can be explained by common single nucleotide polymorphisms.[37,38]

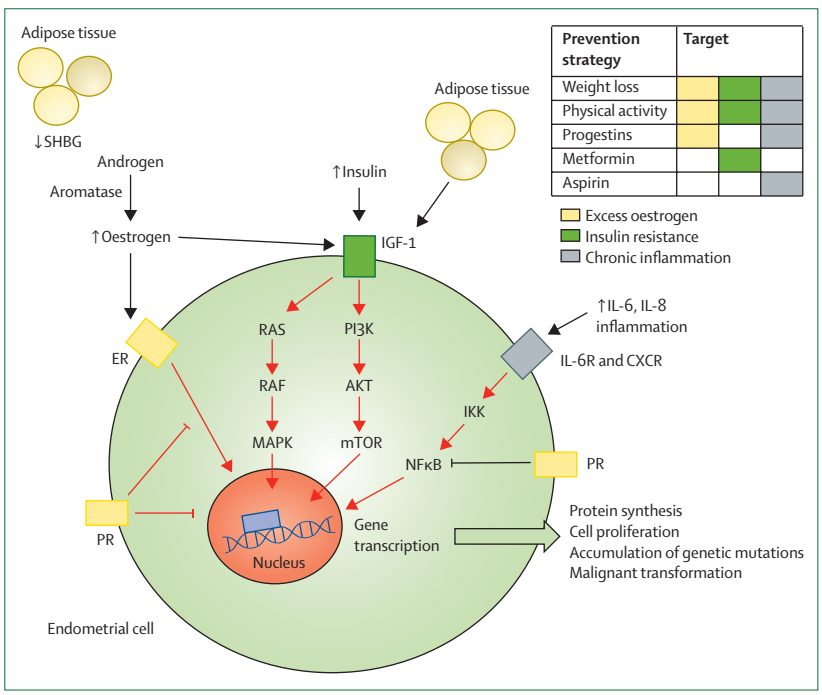


Figure 3: **Obesity-associated endometrial cancer: pathways to carcinogenesis and targets for prevention**
Obesity is a hyperoestrogenic, hyperinsulinaemic, pro-inflammatory state that promotes endometrial proliferation, the accumulation of unfavourable somatic genetic events, and subsequent malignant transformation. Risk-reducing interventions that target these pathways, including weight loss, physical activity, exogenous progestins, and anti-inflammatory and insulin-sensitising drugs can provide a strategy for primary endometrial cancer prevention in high-risk women. AKT=protein kinase B. CXCR=chemokine receptor. ER=oestrogen receptor. IKK=IκB kinase. IGF=insulin-like growth factor. IL=interleukin. IL-6R=IL-6 receptor. PR=progesterone receptor. mTOR=mammalian target of rapamycin. PI3K=phosphoinositide 3-kinase. SHBG=sex hormone binding globulin.

Pathogenesis

The endometrium has glandular and stromal components that proliferate, mature in anticipation of embryo implantation, and undergo shedding in a coordinated sequence over a monthly menstrual cycle, under the influence of oestrogen and progesterone.[39] Unopposed oestrogen results in unbalanced proliferation leading to a spectrum of changes characterised by preferential expansion of the glandular component at the expense of stroma.[40] A diffuse proliferation of the glandular component is termed endometrial hyperplasia without atypia, which

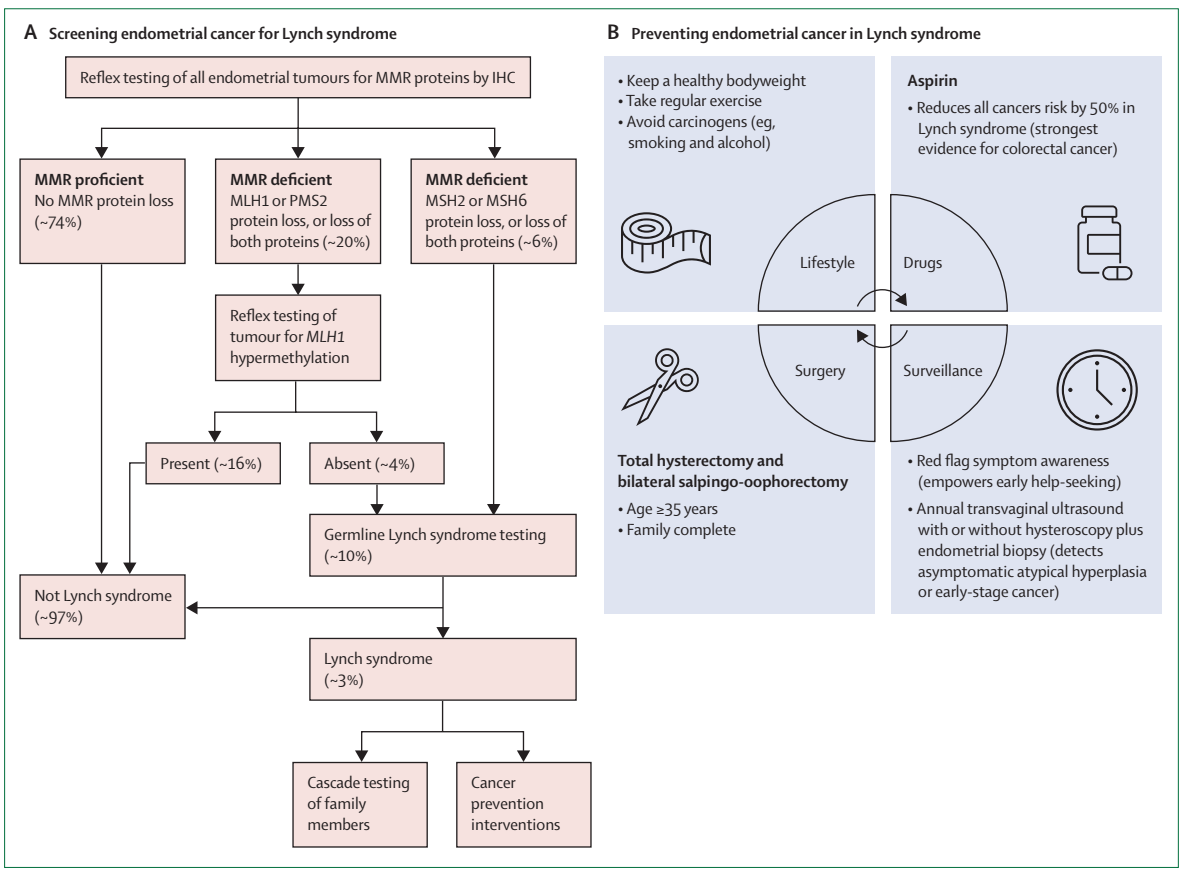


Figure 4: **Screening, diagnosis, and risk-reducing strategies for Lynch syndrome-associated endometrial cancer**
(A) International guidelines recommend the universal testing of all endometrial cancers for Lynch syndrome, using MMR IHC followed by reflex *MLH1* methylation testing and definitive germline Lynch syndrome testing, as appropriate. Women diagnosed with Lynch syndrome can reduce their risk of future cancers through adopting a healthy lifestyle, aspirin chemoprevention, and bowel cancer surveillance. Cascade testing identifies an average three family members with Lynch syndrome per index case, some of whom are healthy carriers. MMR-deficient tumours not caused by *MLH1* hypermethylation or Lynch syndrome can be explained by double somatic hits affecting the tumour MMR genes (around 70%). The remainder are called Lynch-like and might increase the patient's lifetime risk of future cancers, but an underlying genetic cause cannot be identified. (B) Healthy carriers of Lynch syndrome can reduce their endometrial cancer risk through knowledge of the red flag symptoms of endometrial cancer that should prompt urgent help-seeking, risk-reducing prophylactic hysterectomy when they have completed their family, and gynaecological surveillance to identify atypical hyperplasia or early-stage endometrial tumours. MMR=mismatch repair. IHC=immunohistochemistry.

carries a low (1–3%) risk of cancer.[41,42] Atypical endometrial hyperplasia, also known as endometrioid intraepithelial neoplasia, is a clonal glandular expansion that carries a 45-fold increased risk of cancer.[42] Diagnosis relies on glandular crowding relative to stroma showing cytological distinction from background glands, of sufficient size to be confident that differences are not artefactual, after exclusion of benign and malignant mimics. Molecular changes, including *PAX2*, *PTEN*, *PIK3CA*, and beta-catenin aberrations,[43,44] support the diagnosis and provide evidence for direct clonal progression from atypical hyperplasia to carcinoma.[45,46] The traditional division of endometrial cancers into two types with differing clinicopathological profiles translates in modern practice into low-grade endometrioid endometrial carcinomas that occur in younger women, and are relatively indolent, versus high-grade or non-endometrioid carcinomas that occur in older patients, and have poorer clinical outcomes.[47] The origins of non-endometrioid endometrial carcinomas are poorly understood.[48]

Pathology

WHO classifies endometrial cancer according to morphology.[42] The most common histotype, endometrioid, resembles normal endometrial glandular cells and arises on a background of hyperplasia. Endometrioid carcinomas are graded according to their architectural complexity, with low-grade tumours (grade 1 and 2) associated with better outcomes than high-grade (grade 3) tumours. Serous carcinomas arise on a background of endometrial atrophy and show extrauterine spread at presentation in 40–50% of adequately staged cases. These tumours show severe nuclear atypia and abnormal p53 staining in most cases. Clear cell carcinomas consist of atypical cells with water-clear cytoplasm arranged in a variety of

	FIGO stage	UICC TNM stage (TNM categories)	5-year survival (95% CI)
Tumour confined to the corpus uteri	Stage I	I (T1 N0 M0)	92% (91·3–93·0)
Tumour limited to endometrium or invading less than one half of myometrium	Stage IA	IA (T1a N0 M0)	..
Tumour invades one half or more of myometrium	Stage IB	IB (T1b N0 M0)	..
Tumour invades cervical stroma, but does not invade beyond uterine corpus	Stage II	II (T2 N0 M0)	74% (74·9–77·5)
Local or regional spread	Stage III	III (T1–T3b N1 M0 or T3a–3b N0 M0)	48% (45·4–50·3)
Tumour invades the serosa of the corps uteri or adnexae (direct extension or metastasis)	Stage IIIA	IIIA (T3a N0 M0)	..
Vaginal or parametrial involvement (direct extension or metastasis)	Stage IIIB	IIIB (T3b N0 M0)	..
Metastasis to pelvic or para-aortic lymph nodes	Stage IIIC	IIIC (T1–3 N1 M0)	..
Metastasis to pelvic lymph nodes	Stage IIIC1	IIIC1 (T1–3 N1 M0)	..
Metastasis to para-aortic lymph nodes with or without pelvic lymph node metastasis	Stage IIIC2	IIIC2 (T1–3 N2 M0)	..
Tumour invades bladder or bowel mucosa, or distant metastases, or any combination thereof	Stage IV	IV (T4 N_{any} M0 or T_{any} N_{any} M1)	15% (13·2–17·3)
Tumour invades bladder or bowel mucosa, or both	Stage IVA	IVA (T4 N_{any} M0)	..
Distant metastasis (excluding metastasis to vagina, pelvic serosa, or adnexa) including intra-abdominal metastases, inguinal nodes, or intra-abdominal nodes other than pelvic or para-aortic nodes, or any combination thereof	Stage IVB	IVB (T_{any} N_{any} M1*)	

FIGO=International Federation of Gynecology and Obstetrics. FIGO does not include stage 0. UICC=Union for International Cancer Control. TNM classification: N0 (no regional lymph node metastasis), M0 (no distant metastasis), N1–N3 (increasing involvement of regional lymph nodes), M1 (distant metastasis). *Microscopically confirmed distant metastasis.

Table 1: **FIGO and TNM classification of endometrial cancer defined by surgical and histological characteristics, and 5-year overall survival by stage**[49–51]

	Low risk	Intermediate risk	High-intermediate risk	High risk	Advanced or metastatic
Molecular classification unknown	Stage IA, endometrioid, low-grade, with negative or focal LVSI	Stage IB, endometrioid, low-grade, with negative or focal LVSI Stage IA, endometrioid high-grade, with negative or focal LVSI Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, or mixed) without myometrial invasion	Stage I endometrioid with substantial LVSI, regardless of grade or depth of invasion Stage IB, endometrioid high-grade, regardless of LVSI Stage II endometrioid	Stage III–IVA endometrioid with no residual disease Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, or mixed) with myometrial invasion and no residual disease	Stage II–IVA with residual disease Stage IVB
Molecular classification known*	Stage I–II *POLE*-mutant no residual disease Stage IA, MMRd or NSMP, endometrioid, low-grade, with negative or focal LVSI	Stage IB, MMRd or NSMP, endometrioid, low-grade, with negative or focal LVSI Stage IA, MMRd or NSMP, endometrioid, high-grade, with negative or focal LVSI Stage IA, p53-abnormal, or non-endometroid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, or mixed), or any combination thereof, without myometrial invasion	Stage I, MMRd or NSMP, endometrioid with substantial LVSI, regardless of grade or depth of invasion Stage IB, MMRd or NSMP, endometrioid high-grade regardless of LVSI Stage II, MMRd or NSMP, endometrioid	Stage III–IVA, MMRd or NSMP, endometrioid with no residual disease Stage I–IVA, MMRd or NSMP, serous, undifferentiated carcinoma, or carcinosarcoma with myometrial invasion and no residual disease Stage I–IVA, p53-abnormal, with myometrial invasion and no residual disease	Stage III–IVA with residual disease of any molecular type Stage IVB of any molecular type

ESGO=European Society of Gynaecological Oncology. ESP=European Society of Pathology. ESTRO=European Society for Radiotherapy and Oncology. LVSI=lymphovascular space invasion. MMRd=mismatch repair deficient. NSMP=non-specific molecular profile. *POLE*=polymerase epsilon. *Insufficient data are available for stage III–IVA *POLE*-mutated endometrial carcinoma and stage I–IVA MMRd or NSMP clear cell carcinoma with myometrial invasion to enable allocation of these patients to a prognostic risk group in the molecular classification. Prospective registries are recommended for these categories.

Table 2: **ESGO–ESP–ESTRO prognostic risk groups defined with and without molecular classification**[53]

patterns. Undifferentiated carcinomas show no lineage differentiation; their coexistence with another defined carcinoma type is termed dedifferentiated carcinoma, reflecting their clonal relationship and origin through progression from the better differentiated component. These carcinomas commonly show mismatch repair defects (50–75%) and mutations involving the SWI–SNF chromatin remodelling protein complex. Carcinosarcoma is a biphasic cancer with both epithelial (carcinomatous), typically serous, and mesenchymal (sarcomatous) components that share genomic alterations and arise from transdifferentiation of epithelial to sarcomatous components through epithelial–mesenchymal transition. Like serous carcinomas these are clinically aggressive tumours with a 45% likelihood of extrauterine spread at presentation. Mesonephric, mesonephric-like, squamous,

Panel: Molecular classification of endometrial carcinomas

Four molecular groups (TCGA pragmatic molecular classifier nomenclature):[42,55-59]

Ultramutated (POLE-mutant) endometrial carcinoma

- Characterised by pathogenic *POLE* mutations resulting in a markedly increased transversion mutation frequency; *POLE*-mutant tumours occur in relatively young women, in the absence of any metabolic associations, have outstandingly good clinical outcomes with very low rates of recurrence, regardless of other clinical–pathological factors, and have less than 1% disease-specific mortality.

Hypermutated (mismatch repair deficient [MMRd]) endometrial carcinoma

- Characterised by microsatellite instability as a result of defective mismatch repair, in turn resulting in a ten-fold higher mutation rate than microsatellite stable or MMR-proficient tumours; these have a wide age range. About 10% occur in the context of Lynch syndrome because of germline defects in MMR genes, with the remainder being somatic defects, largely caused by epigenetic *MLH1* silencing due to *MLH1* promoter hypermethylation. These tumours have intermediate, stage-dependent prognosis.

Copy number-high (p53-abnormal) endometrial carcinoma

- Characterised by mutations in TP53, extensive somatic copy number alterations, and low mutation rates. Although serous carcinoma and carcinosarcoma are the prototype p53-abnormal tumours, approximately 50% of cases demonstrate other histotypes, including some examples of low-grade endometrioid carcinoma. This group accounts for about 20% of all endometrial carcinomas but disproportionate (50–70%) disease-specific mortality.

Copy number-low (no specific molecular profile [NSMP]) endometrial carcinoma

- Composed of *TP53* wild-type and *POLE* wild-type, MMR-proficient tumours with relatively low somatic copy number alterations. This is a diagnosis of exclusion and consists largely of endometrioid carcinomas. This group shows intermediate to excellent stage-dependent and histomorphology-dependent prognosis.

and mucinous intestinal-type carcinomas are rare and relatively recently described entities. Serous or clear cell carcinomas occurring in combination with another histotype are termed mixed carcinomas.

Histopathological prognostic factors

Endometrial cancer is staged surgically and histological confirmation of the type, grade (if applicable) and extent of involvement are fundamental to staging.[49] Staging rules are defined by the International Federation of Gynaecology and Obstetrics (FIGO)[49] and tumour-node-metastasis (TNM)-based Union for International Cancer Control (UICC) criteria (table 1).[50,51] Lymphovascular space invasion (LVSI), the presence of tumour emboli within lymphatic, or capillary or venous channels, or both,[52,53] is associated with an increased likelihood of metastasis to lymph nodes and other sites[54] and is incorporated into risk stratification models that are used in clinical practice to direct adjuvant treatment (table 2).

Molecular classification of endometrial cancer

A new molecular classification system defined by the Cancer Genome Atlas (TCGA)[55] and subsequent pragmatic classification tools using clinically applicable methods[56–59] categorise endometrial cancer into four groups according to molecular profile (panel). The incorporation of molecular grouping into existing risk stratification models affords substantially better prediction of prognosis than either system alone.[42,56] This is because each of the four molecular groups is biologically distinct with clinical behaviour that is largely independent of histotype and grade. Further, the classification is based on objective findings allowing increased reproducibility between pathologists, between laboratories, and between biopsy and hysterectomy specimens. In routine clinical practice, molecular classification relies on accurate interpretation of immunohistochemistry (IHC) for MMR proteins,[60] IHC for p53 (the protein product of the oncogene *TP53*),[61] and sequencing for hotspot mutations with confirmed pathogenicity in the gene encoding the enzyme DNA polymerase epsilon (*POLE*).[62] Since 3·5–5·0% of cases are positive by more than one test,[63] interpretation follows a validated, WHO-endorsed algorithm (figure 5).[42] These additional tests add significant cost to histological interpretation and are not available in all resource settings.[64] Therefore, the joint guidelines from the European Society of Gynaecological Oncology (ESGO), European Society of Pathology (ESP), and European Society for Radiotherapy and Oncology (ESTRO) provide risk stratification criteria with and without molecular findings (table 2).[53]

Molecular classification might evolve as further prognostic and predictive markers are incorporated into routine diagnostic practice; for example, L1CAM, oestrogen receptor (ER), and progesterone receptor (PR) expression in NSMP[65] and HER2 and homologous recombination status in p53-abnormal tumours.[66,67]

Screening

There is no established screening programme for endometrial cancer in either the general population or specific high-risk groups. The aim of screening is to identify atypical hyperplasia or endometrial cancer at the earliest possible stage to improve chance of cure, minimise treatment-related morbidity and reduce deaths from the disease.[68] Demonstrating mortality benefit in a generally good prognosis cancer is challenging and more high-quality research is needed. Transvaginal ultrasound

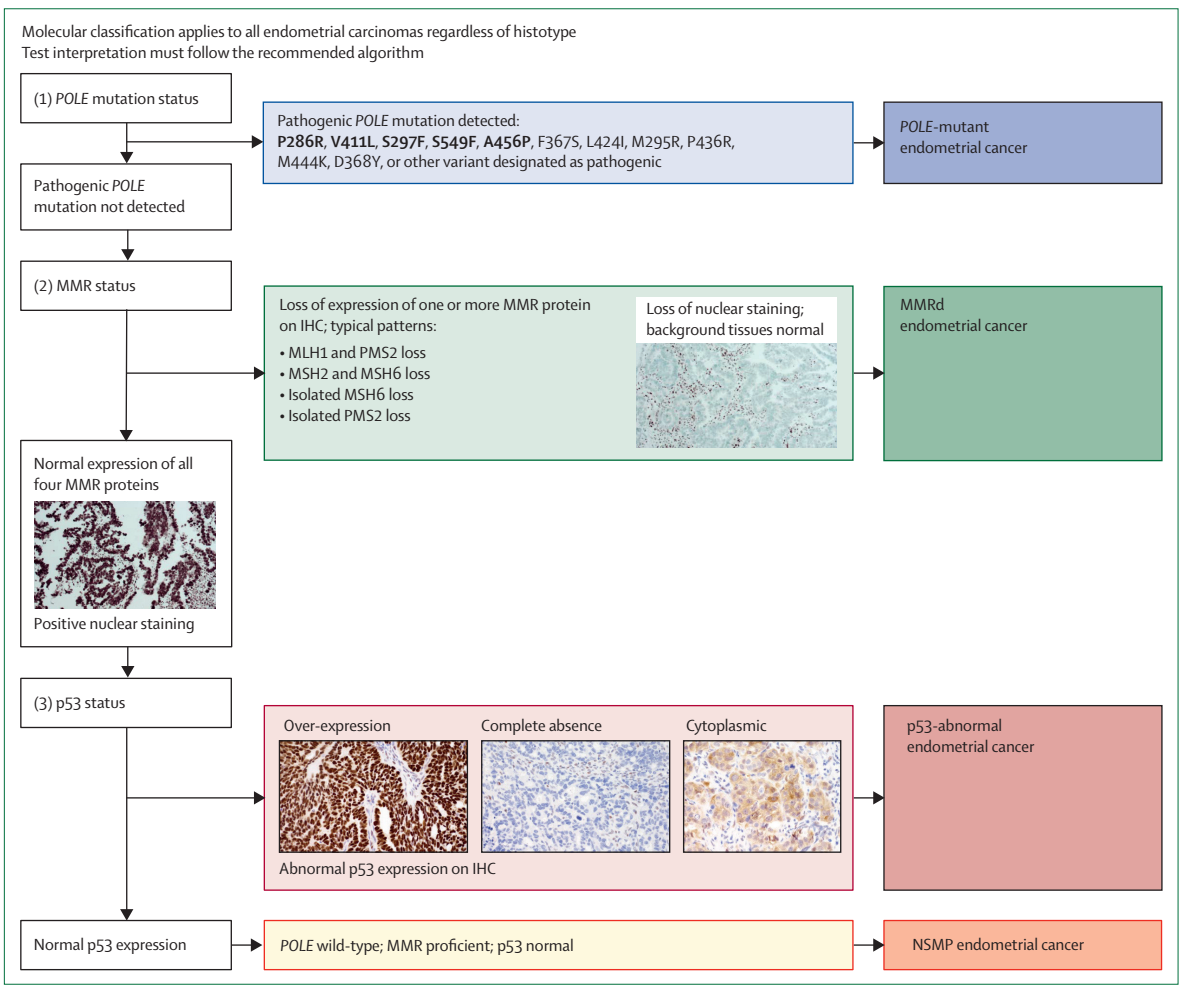


Figure 5: **WHO-endorsed pragmatic approach to molecular classification of endometrial carcinoma in clinical practice**[42,55-59]
The presence of a confirmed *POLE* pathogenic variant classifies a tumour as *POLE*-mutant, regardless of MMR and p53 status. In *POLE*-proficient tumours, loss of MMR expression classifies the cases as MMRd, regardless of the p53 status; in approximately 80% of cases showing MLH1 or PMS2 loss, the underlying cause is *MLH1* promoter hypermethylation and this should be tested for; MLH1 loss with normal *MLH1* methylation status, and all other listed combinations of protein loss are indications for germline Lynch syndrome testing. Once *POLE* pathogenic variants and MMR defects are excluded, abnormal p53 expression identifies p53-abnormal cases. The remainder are currently classified as NSMP. MMR=mismatch repair. MMRd=MMR deficient. IHC=immunohistochemistry.

assessment of endometrial thickness fails to achieve sufficient diagnostic accuracy in asymptomatic post-menopausal women at a cut-off of 5 mm, according to a systematic review of 32 studies and 11 100 participants.[69] Endometrial sampling is effective but invasive, limiting its potential for population-based screening. More acceptable screening tools, including endometrial,[70] cervical[11] and urine cytology[71] show promise and novel genomic and proteomic biomarkers detected in self-collected urogenital biofluid samples may hold the key to home-based screening in high-risk groups.[72] These include women with Lynch syndrome, in whom the high lifetime risk for endometrial cancer justifies annual gynaecological surveillance, in those with an intact uterus,[29] although there is currently no good evidence that screening by ultrasound, hysteroscopy, or endometrial sampling improves outcomes from the disease,[73] and practice varies widely.[74] Educating women about the red flag symptoms of endometrial cancer and the importance of seeking help promptly in the event of abnormal vaginal bleeding may be the most important strategy for early detection.[75] Public awareness is low, with endometrial cancer considered "the most common diagnosis you've never heard of".[76] Campaigns to raise awareness among the public are urgently needed to improve knowledge about risks for endometrial cancer, and ensure rapid presentation following any onset of symptoms women may have.

Prevention

Population-based approaches that focus on achieving and maintaining a healthy body weight will have maximum impact on endometrial cancer rates.[77] Bariatric surgery-induced weight loss reduces endometrial cancer risk,[78,79] but the associated harms, costs, and limited availability in resource poor settings limit its potential for global

endometrial cancer control. The successful treatment of obesity by pharmacological or dietary intervention, coupled with high physical activity levels, significantly reduces endometrial cancer risk,[80,81] but maintenance is a considerable challenge. High lifetime exposure to endogenous progesterone, through regular menstrual cycles, pregnancy and breastfeeding, and exogenous progesterone, through prolonged (>5 years) exposure to the combined oral contraceptive,[82] progestin-containing hormone replacement therapy,[20,83] and the progestin-releasing intrauterine system (IUS; eg, Mirena)[84,85] have been shown to reduce endometrial cancer risk. The IUS provides a strategy for endometrial cancer prevention in high-risk women, although evidence from randomised controlled trials is scarce.[85] The effectiveness of the Mirena IUS in preventing endometrial cancer in women receiving tamoxifen for breast cancer management has not been established.[86] Treating insulin resistance with metformin, an insulin sensitising drug, has theoretical value for endometrial cancer prevention but remains untested. In Lynch syndrome, cancer risk rises sharply from age 35–40 years and risk-reducing prophylactic hysterectomy is offered when childbearing is complete.[87,88] Women might consider concurrent risk-reducing bilateral salpingo-oophorectomy to manage their 10–17% additional lifetime risk for ovarian cancer.[89] Aspirin (600 mg per day) reduces the risk of colorectal cancer (hazard ratio [HR] 0·56; 95% CI 0·34–0·91) in Lynch syndrome and studies are ongoing to establish the optimal dose.[90] Although underpowered to assess sex-specific cancer risks, the CAPP2 trial found there were fewer endometrial cancers in women randomly allocated to receive aspirin compared with placebo (7 *vs* 17 cases, HR 0·50; 95% CI 0·22–1·11).[90] Whether aspirin is effective for the prevention of obesity-associated endometrial cancer is uncertain.[91] Risk prediction models that combine obesity, insulin resistance, and reproductive and genetic risk factors will inform targeted screening and prevention interventions.[38,92]

Surgery

The mainstay of treatment for endometrial cancer is total hysterectomy and bilateral salpingo-oophorectomy. In premenopausal women with apparent early-stage disease, ovarian conservation can be considered to avoid the undesirable consequences of surgical menopause without negatively impacting survival outcomes.[93–95] Randomised controlled trials of minimally invasive hysterectomy show non-inferior oncological outcomes with shorter hospital stay and decreased blood loss, pain, and perioperative morbidity compared with open surgery.[96–99] Minimally invasive surgery is therefore the preferred surgical approach for early-stage disease where the uterus can be safely removed intact. Robotic surgery offers similar oncological outcomes, shorter hospital stays and lower conversion rates but is more expensive than laparoscopy.[100,101] The perils of uterine morcellation are well documented, and intraperitoneal contamination should be avoided.[102] There are discordant data as to whether uterine manipulators increase recurrence risk.[103,104] The use of uterine manipulators is associated with higher positive peritoneal cytology rates, but this is of uncertain clinical significance and washings are no longer incorporated into FIGO staging.[105] Vaginal hysterectomy with or without bilateral salpingo-oophorectomy might be considered for presumed early-stage disease where anaesthetic or surgical fitness prohibit an abdominal approach. In LMICs, endometrial cancer is more commonly diagnosed incidentally—following hysterectomy for presumed benign conditions—and by surgeons not necessarily trained in gynaecological oncology. These circumstances can cause a dilemma regarding the need for further surgical staging; challenges of incomplete staging could lead to overtreatment or undertreatment with adjuvant therapy, with consequences for survival and quality of life.

Surgical staging, lymphadenectomy, and sentinel-lymph-node dissection (SLND)

Whether or not lymph-node dissection is done, and the extent of lymph-node sampling, varies between and within institutions. Pathological parameters (eg, grade and histotype), molecular features, and artificial intelligence models have been used to predict lymph-node metastases and guide surgery.[106] The purported therapeutic role of routine lymphadenectomy in endometrial cancer has been contested by two large randomised controlled trials showing no survival advantage.[107–109] However, lymph-node status is important for surgical staging, guides decisions about adjuvant therapy, and informs prognosis. These benefits must be weighed against the known perioperative morbidity of pelvic and para-aortic lymph-node dissection including the potential for long-term lower extremity lymphoedema.[109]

The emergence of sentinel-lymph-node biopsy (SLNB) has enabled a more unifying approach to nodal assessment in endometrial cancer. Established protocols for SLNB, using a radiotracer (Technetium-99) or FDA-approved contrast dyes have shown safety, high-node-positive detection rates, and high negative predictive values (97–99%) of SLNB, reducing the need for complete lymphadenectomy in endometrial cancer.[110] The first prospective trial to address SLNB in high-risk endometrial cancer evaluated 101 patients and showed SLNB plus side-specific full lymph-node dissection (if a sentinel lymph node was not detected) did as well as complete lymph-node dissection.[111] The FIRES study[112] enrolled a mix of histologies with clinical stage I disease and the SENTOR study[113] enrolled intermediate and high-grade endometrial cancers of all histologies confirming a high accuracy of SLNB potentially superior to complete lymphadenectomy as several patients had nodes detected outside the traditional anatomic dissection boundaries.[112,113] Meta-analyses of nine prospective cohort studies on

SLNB in 429 patients with high-grade tumours confirmed the high accuracy of detecting nodal metastases (92% per patient, 95% CI 84–96, I^2=0%), with a false negative rate (8%, 95% CI 4–16, I^2=0%) comparable to low-grade endometrial cancer and other disease sites where SLNB is routinely employed (eg, vulval or breast cancer).[114] Pathological ultrastaging of sentinel lymph nodes detects more metastases than routine sectioning, including micrometastases and isolated tumour cells.[115] The clinical significance of low-volume nodal disease is unclear, and current consensus is that isolated tumour cells do not warrant adjuvant therapy in the absence of other risk factors and they are not incorporated into FIGO staging.[116,117]

Omental sampling or peritoneal biopsies, or both, are recommended for patients at increased risk of metastatic disease, even in the absence of preoperative imaging or intraoperative evidence of metastases. Pathological parameters associated with microscopic or occult omental disease include high-grade non-endometrioid histology and although omental implants are often seen with concurrent peritoneal implants or ascites, they can be found in isolation.[118,119] A recent series of p53-abnormal endometrial cancer cases identified omental or peritoneal disease, or both, in 44 (24%) of 185 patients, highlighting the importance of this additional staging procedure in this molecular subtype.[120]

Surgery for advanced and recurrent disease

For patients with extrauterine disease on preoperative imaging, recommendations for surgery depend on the location of metastases, the likelihood of complete cytoreduction, and patient suitability. Although most data are from retrospective series, improved outcomes have been observed for patients undergoing primary cytoreduction for advanced stage III–IV disease if debulking to no residual disease can be achieved.[121–123] Neoadjuvant chemotherapy followed by interval cytoreductive surgery is associated with reduced perioperative morbidity and comparable survival rates compared with upfront surgery with suboptimal resection, and improved outcomes compared with chemotherapy alone.[124] For patients with known or suspected cervical involvement (stage II disease) there is no survival benefit from radical rather than simple hysterectomy for staging.[125] Oncological outcomes for stage II endometrial cancer are related to receipt of appropriate adjuvant therapy rather than surgical procedure, suggesting that margin status is less important in endometrial disease than some other cancers. ESGO–ESP–ESTRO and National Comprehensive Cancer Network 2021 guidelines state a preference for up-front surgery in stage II disease and for stage III–IV patients where complete cytoreduction is feasible with acceptable morbidity.[53,126] Engagement of a multidisciplinary team of gynaecological, radiation, and medical oncologists to discuss these challenging cases is essential.

Data in support of surgery for recurrent endometrial cancer, including exenterative procedures, are scarce but suggest patients can experience prolonged post-recurrence survival only if complete cytoreduction is achieved.[127–129] Consideration should be given to time from original diagnosis, location of recurrence (resectability), number of disease sites, and patient performance status. Focused palliative surgical interventions for endome-trial cancer include genitourinary or bowel diversion for fistulas (disease or treatment related) or bowel obstruction.

Surgical staging in molecular classification era

Molecular classification is achievable on diagnostic biopsies, providing an opportunity to direct both where surgery is performed (local hospital *vs* tertiary cancer centre) and what procedures are undertaken. Provocative questions are emerging, including the role of lymph-node dissection where knowledge of occult nodal status might not change management. For example, all poor prognosis p53-abnormal tumours with myometrial invasion are offered adjuvant therapy, and all excellent prognosis *POLE*-mutant endometrial cancers can be considered for observation.[53,130] More research is needed to guide surgical management in this new molecular landscape.

Fertility-sparing treatment

There is a growing need for uterus-sparing treatment options for women with atypical hyperplasia and endometrial cancer who have not completed their families. Experience is largely limited to prospective observational studies but durable complete pathological response rates of approximately 65% for atypical hyperplasia and 50% low-grade early-stage endometrial disease have been reported in those treated with high-dose oral progestin, or intrauterine progestin, or both.[131] Patient selection is crucial to exclude those with adverse clinico-pathological or molecular features, including high-grade histology, myometrial invasion, or synchronous adnexal masses, who are unlikely to respond to progestin. Molecular classification might help guide decision making for these patients as it can be performed on diagnostic biopsies.[132] Response to hormonal therapy takes time (6–12 months or longer), and there are no validated biomarkers that predict response[133] or subsequent fertility outcomes. Careful monitoring with biopsies with or without MRI scans is essential to identify aggressive disease and expedite recourse to hysterectomy. The progestin treatment window offers an ideal opportunity for health optimisation, and weight lost during this period could improve both oncological and fertility outcomes.[134,135] Expedited sleeve gastrectomy or gastric bypass surgery might be indicated in this setting. Oncological recurrence rates of up to 35% have been reported after successful uterus-sparing management[131] and prospects for pregnancy could be short-lived and disappointing

(27% in published series).[136] Hysterectomy is recommended after completion of childbearing.

Adjuvant treatment

Two-thirds of women with endometrial cancer present with stage I disease and most have an excellent prognosis.[51] Within this group there are patients with relatively poor outcomes and the latest ESGO–European Society of Medical Oncology (ESMO) risk stratification model distinguishes those at highest risk who may require treatment intensification, and those at lower risk who might benefit from treatment de-escalation.[53]

Women with stage IA low-grade endometrioid tumours are at low risk of relapse (<5%), requiring no additional treatment (table 2). For patients at intermediate risk of recurrence, studies have shown external beam radiotherapy offers no benefit over vaginal brachytherapy alone.[137,138] Although vaginal brachytherapy does not improve overall survival it is well tolerated and reduces vaginal recurrence from about 14% to less than 2%.[139,140]

The redefined high-intermediate risk group in the ESGO–ESMO guidelines recognises the importance of LVSI as a poor prognostic factor.[53,54] These patients were included in the GOG-249 study,[141] which randomly allocated stage I and II high-risk patients to either pelvic radiotherapy or vaginal brachytherapy followed by three cycles of carboplatin and paclitaxel chemotherapy, and the PORTEC-3 study,[142] which compared pelvic radiotherapy to pelvic radiotherapy with chemotherapy followed by four cycles of carboplatin and paclitaxel. Both studies showed improved loco-regional control with external beam radiotherapy, even where patients had undergone lymph-node dissection, but no survival benefit for either radiotherapy or chemotherapy. Adjuvant treatment options for high-intermediate risk patients include external beam radiotherapy, particularly where there is LVSI or a high-grade tumour, or vaginal brachytherapy, a less toxic treatment after full surgical staging and in the absence of LVSI.[53]

In the GOG-258 study,[143] high-risk patients were randomly allocated to either six cycles of carboplatin and paclitaxel or the same treatment as in PORTEC-3—external beam radiotherapy with cisplatin followed by four cycles of carboplatin plus paclitaxel. GOG-258 showed no relapse-free survival or overall survival benefit for chemotherapy, but as in GOG-249, there were fewer pelvic and para-aortic nodal relapses in those receiving external beam radiotherapy. Updated results from the PORTEC-3 trial, however, with a median follow-up of 72 months, did show improved survival—with a 5% overall survival and 7% relapse-free survival benefit. Benefit was highest in stage III disease and those with serous histotype, regardless of stage.[144]

Molecular classification has now been integrated into the ESGO guidelines and might in the future determine the type of adjuvant treatment to be offered. Regrouping of participants in the PORTEC-3 trial to the four molecular groups has shown that p53-abnormal tumours exhibit a highly significant benefit from the addition of chemotherapy (59% *vs* 36% relapse-free survival). NSMP tumours also show benefit, although to a lesser extent (80% *vs* 68% relapse-free survival). Patients with MMRd tumours did not appear to benefit from chemotherapy (68% *vs* 76% relapse-free survival) whereas those with *POLE*-mutant tumours had excellent outcomes with or without chemotherapy (100% *vs* 97% relapse-free survival). These findings suggest that patients with *POLE*-mutant tumours could be considered for treatment de-escalation; and alternative approaches to carboplatin and paclitaxel, such as immune checkpoint inhibitors, might benefit patients with MMRd tumours.[145]

Advanced and recurrent disease

Management of advanced unresectable disease or multifocal recurrent endometrial cancer is palliative. Standard of care first line treatment is the carboplatin and paclitaxel doublet with a progression-free survival of 13 months.[146] Molecular profiling is increasingly used to select treatment, and although it is considered a recent advance, positive ER and PR status has, for many years, directed treatment in the relapsed and advanced disease setting. Hormone therapy is well tolerated and is often prescribed to patients who are considered too frail for chemotherapy. There are a paucity of randomised data, particularly from recent studies. However, particularly for women with ER-positive or PR-positive tumours, or both, oral progestins give response rates of more than 35%.[147] Sequential tamoxifen and medroxyprogesterone acetate showed similar response rates lasting over 20 months in eight (53%) of the 15 patients.[148] Single agent aromatase inhibitors are sometimes used as an alternative to progestins, perhaps because of familiarity by the oncologist as they are widely prescribed for breast cancer. Although reported clinical benefit is around 40–45% (largely related to improved quality of life), objective response rates are disappointingly low, at approximately 10%, even for patients with ER-positive or PR-positive disease.[149,150] The PI3K–AKT–mTOR pathway, which affects cell growth and survival, is the most commonly disrupted pathway in endometrial cancer. Disappointingly, several clinical trials of mTOR inhibitors either singly or in combination have shown limited activity with response rates of 10%.[151] Because of cross-talk between the PI3K–AKT–mTOR pathway and ER, combining hormones with mTOR inhibitors has been evaluated. The doublet of everolimus and letrozole gave encouraging response rates of 28–32%, which rose to 45% in patients with PR-positive disease; the addition of metformin, however, did not improve outcomes.[152,153] A subsequent randomised phase II study of everolimus and letrozole versus alternating megace and tamoxifen showed similar response rates in both arms of 24% and 22% respectively.[154]

Immune checkpoint inhibitors have been used with some success in the treatment of advanced and

metastatic endometrial cancer. The US Food Drug Administration (FDA) gave approval for pembrolizumab in MMRd advanced or relapsed endometrial cancer based on the Keynote-158 study, where the overall response rate in 49 patients with PD-L1-positive endometrial cancer was 57%.[155] This authorisation has been followed by approval by the FDA and EU for dostarlimab in patients with MMRd tumours, with response rates of 42%.[156] Pembrolizumab and lenvatinib, an oral multikinase inhibitor targeting vascular endothelial growth factor and platelet growth factor receptors, received accelerated approval by the FDA in 2019 for relapsed or advanced endometrial cancer that is not MMRd. This was based on the results of Keynote-146, a phase II study in 108 previously treated women with advanced or metastatic endometrial cancer. Response rates after a median 18 month follow-up for MMR-proficient patients was 36% against 63·6% in MMRd patients with median duration of response similar in both groups at 21 months. Although these results are encouraging, tolerability is of concern as two-thirds of patients had grade 3–4 treatment-related toxicity.[157]

The human epidermal growth factor receptor HER2 is amplified in about a quarter of *TP53*-mutated endometrial cancers.[55] Combining trastuzumab, a monoclonal antibody against HER2, with chemotherapy seems promising in this group of patients with the poorest prognosis. In a phase II randomised study of carboplatin and paclitaxel alone or in combination with trastuzumab followed by maintenance trastuzumab, progression-free survival was 12·9 months and overall survival 29·6 months with additional trastuzumab compared with 8 months and 24·4 months with chemotherapy alone.[158] Another potentially interesting target in *TP53*-mutant cancers is the DNA repair pathway, with 15–53% of p53-abnormal endometrial tumours homologous repair deficient.[159] Homologous repair-deficient ovarian cancer predicts for response to PARP inhibitors and there are preliminary data that p53-abnormal endometrial cancers could also achieve survival benefit.[160,161] Multimodality targeted treatment offers the best opportunity to bring much needed improved outcomes for women with advanced endometrial cancer.

Loco-regional relapse in patients not initially given adjuvant radiotherapy can be treated successfully with radical radiotherapy with local control rates of up to 90%.[162] Stereotactic radiotherapy is an ultra-conformal technique that focuses high radiation doses directly onto tumour and offers lasting control in both local recurrence and oligometastatic disease (defined as 1–5 discreet metastatic deposits).[163]

Survivorship

Follow-up after treatment aims to identify recurrence and address treatment-related morbidity, including lymphoedema and radiotherapy-induced bladder, bowel, and sexual dysfunction, and to provide psychological support to patients and their families. The format and frequency of follow-up varies according to tumour-related factors and treatment history. Traditional hospital-based follow-up might be replaced by nurse-led telephone or patient-initiated follow-up for low-risk patients.[164,165] More intensive follow-up does not improve overall survival or health-related quality of life, even in those at greatest risk of recurrence.[166] All women should be empowered to report bleeding, abdominal pain, change in urinary or bowel habit, and unexplained weight loss, which might indicate recurrent disease. Speculum examination detects the 30% of vaginal vault recurrences that are asymptomatic.[167] There is no role for routine imaging, which has not been shown to improve survival outcomes, but serial blood monitoring for circulating tumour DNA offers hope for detection of recurrence in the future.[168] Women cured of endometrial cancer remain at substantial risk of cardiovascular death due to a preponderance of unrecognised and undertreated risk factors.[169] Optimising survivorship through weight loss and lifestyle interventions could not only reduce deaths from cardiovascular disease[170] but also improve endometrial cancer survival and quality of life.[171] Specialist nurses play a vital role in supporting the social care needs of endometrial cancer survivors, who might have a negative emotional response to their diagnosis, a loss of confidence, change in body image, or relationship difficulties. Providing accurate information and signposting women to peer support networks and charitable organisations can empower endometrial cancer survivors to rebuild their lives, manage living with uncertainty, and forge new friendships.

Outstanding research questions

A gap analysis in 2016 identified the top ten most important research priorities in endometrial cancer according to patients, clinicians, and the general public.[172] These spanned the whole patient pathway, from risk prediction and targeted prevention strategies, through innovations in diagnostics and treatment, to improving survivorship and raising public awareness of the disease. Identifying high-risk individuals for targeted screening and prevention interventions emerged as the most important research priority in this analysis and strong research effort is underway to develop risk prediction models for clinical use.[38,92] Novel non-invasive biomarkers for early detection could enable community or home-based self-sampling for symptomatic women and provide a screening tool for high-risk groups, including those with Lynch syndrome.[173] Subtype-specific clinical trials, stratified by molecular profile, will enable us to define optimal surgery, adjuvant treatment, and survivorship strategies and provide a step towards precision medicine in endometrial cancer. Refining adjuvant treatment in endometrial cancer based on molecular profile (known as RAINBO) is a collaborative international umbrella programme of personalised integrated molecular

profiling to guide adjuvant treatment in women with high-risk endometrial cancer according to molecular subgroup. Through four synchronously running trials, it aims to improve outcomes through individualised adjuvant treatment in those most likely to benefit (p53-abnormal, MMRd, and NSMP tumours) while avoiding the toxicities of unnecessary treatments in those least likely to benefit (*POLE*-mutant).[174] Other trials of targeted treatments, particularly immunotherapy, PARP inhibitors, and antiangiogenic drugs, are underway in the advanced and metastatic disease setting. Improving endometrial cancer survivorship, through weight loss,[171] lifestyle changes, and individualised follow-up schedules, is another area of unmet need. Endometrial cancer is under-researched and prioritisation by major funders is urgently needed if we are to halt accelerating global trends of disease burden and to improve patient care.

Contributors

All authors contributed equally to the writing of this Seminar.

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EJC received fees for participation in a GlaxoSmithKline advisory board in 2020. JNM received grants from the Michael Smith Foundation for Health Research, the Canadian Cancer Society and the Canadian Institute for Health Research, outside the submitted work. She is named as one of the inventors on a US provisional patent application, but this is not being pursued and no payments have been received. AM received royalty payments to her institution for her role in the development of the PARP inhibitor rucaparib, the proceedings of which were donated to women's cancer research in low-income and middle-income countries. NS received honoraria for participation in advisory boards for GlaxoSmithKline and AstraZeneca-Merck-Sharp & Dohme. The other authors declare no competing interests.

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