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Endometrial Cancer

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Abstract

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While endometrial cancer management remains challenging, a deeper understanding of the genetic diversity as well as the drivers of the various pathogenic states of this disease has led to development of divergent management approaches in an effort to improve therapeutic precision in this complex malignancy. This comprehensive review will provide an update on the epidemiology, pathophysiology, diagnosis and molecular classification, recent advancements in disease management, as well important patient quality of life considerations and emerging developments in the rapidly evolving therapeutic landscape of endometrial cancers.

Introduction

Endometrial cancer (EC) is a malignancy of the inner epithelial lining of the uterus (Fig. 1), with an increasing incidence and disease-associated mortality, worldwide.¹ EC comprises distinct histological subtypes and molecular phenotypes. Historically, EC was categorized as Type I (association with unopposed estrogen stimulation, comprising low-grade cells that are more common and have a favorable prognosis) or Type II (not estrogen driven, comprising high-grade cells that are less common and have an unfavorable prognosis). Type I ECs are primarily composed of grade I or grade II endometrioid adenocarcinomas, whereas Type II ECs include grade III endometrioid adenocarcinomas, serous clear cell, undifferentiated and carcinosarcomas.

The incidence of EC in 2020 was 417,336, worldwide, and EC is the sixth most commonly occurring female cancer.² Most cases occur between 65 and 75 years of age.³ Racial disparity and socioeconomic and geographical differences are important determinants of EC incidence and mortality. Although 67% of patients present with early-stage disease, which is associated with an 81% 5-year overall survival (OS), the 5-year OS for stage IVA and IVB EC are only 17% and 15%, respectively.⁴

As outlined in this Primer, although The Cancer Genome Atlas (TCGA) endeavor has substantially advanced our understanding of the biological heterogeneity of EC, optimal use of molecular classification relating to surgical staging, adjuvant therapy and surveillance scheduling has not been clearly defined. To comprehensively manage EC, dedicated efforts to more precisely delineate host factors, such as microbiome composition and the effect of body mass index (BMI), are imperative, as is a deeper understanding of the molecular and immunological drivers of response and resistance to emerging therapies, which is critically important for the optimal design of next-generation studies. Additionally, studies must consider not only efficacy and survival endpoints, but also quality of life (QOL) and economic implications of therapeutics.

Epidemiology

Incidence and mortality

EC was diagnosed in 417,367 women in 2020, worldwide, with the highest disease burden in North America and Western Europe (Fig. 2). The incidence of EC is rapidly increasing.² The high incidence rate in North America and Western Europe could be attributed to a high

prevalence of lifestyle risk factors for EC, such as obesity, which is associated with ~50% of EC cases.⁵

Based on a 2016 pooled analysis of epidemiological studies from 1971-2014, EC-associated mortality has increased by an average of 1.9% per year.⁶ In the United States, the number of women diagnosed with EC by 2030 will double to 122,000 cases per year if current trends continue.⁷ As of 2020, uterine cancer is the fourth most common female neoplasm in Europe, with an incidence of 12.9-20.2 per 100,000 women and a mortality of 2.0-3.7 per 100,000 women.^{8,9}

Socioeconomic and racial disparities—Geographic, socioeconomic and racial disparities also affect EC incidence and mortality. EC is more prevalent in high-income countries compared with low-income and middle-income countries.^{2,10} Factors that contribute to geographical disparities in incidence and mortality may include access to high-quality healthcare, and oncologist density.¹¹ In a Swedish study, variations in EC outcome were also influenced by socioeconomic status (SES), as assessed by, for example, income, social class, and educational attainment. Women of higher SES were less likely to present with advanced, type II EC and typically had more favorable outcomes due to enhanced access to healthcare compared with women of lower SES.¹² Diagnosis at late cancer stages and reduced survival were more common in individuals of lower SES.¹² Moreover, Black women from lower SES are twice as likely to receive delayed treatment and 2.5 times more likely to die from EC due to a lack of healthcare insurance, compared with white women from higher SES.¹³

Studies in the USA have shown that Black women are diagnosed with poorer prognostic histological subtypes and higher stage and grade of EC compared with white women, and Black women also have worse outcomes at every stage, grade and histological type of EC.¹⁴ Indeed, one study found worse OS in non-Hispanic black women with EC compared with non-Hispanic white women with EC, with survival disparities persisting despite adjustment for factors including age, tumor histology, grade, stage, and adjuvant treatment, suggesting that additional factors, such as molecular phenotypic differences, may contribute to differences in these outcomes.¹⁵ Black women are also less likely to receive chemotherapy and radiation therapy¹³ or undergo hysterectomy compared with white women.^{16,17} Socioeconomic factors such as lower median household income and access to healthcare coverage, and differences in medical comorbidities and genetic susceptibility to malignancy, are also believed to play a role.

Furthermore, compared with White women, Black women have experienced an increase in incidence of aggressive, high-grade, type II tumors compared with white.^{18,19} Tumor genomic differences are also important factors, and it is postulated that *TP53* and *PIK3R1* mutations in type II EC in Black women, along with higher HER2 expression, may be associated with a more unfavorable prognosis.^{16,20}

Of note, a SEER data analysis from 1992-2001 found that Asian women presented with EC at a younger age (mean 58.4 years) compared with white women (mean age 65.1) and with more advanced-stage disease (21.5% for Asian women versus 15.4% for white women).

Moreover, the 5-year OS for Asian women was 79.4% compared with 75.2% for white women, and 5-year OS for both early-stage (stage I or II) and late-stage (III or IV) EC were significantly higher in Asian women compared with white women (stages I/II 89.3% in Asian women versus 82.3% in white women, and for stages III or IV, 41.2% in Asian women and 34% in white women.²¹ US-born Asian women compared with immigrant Asian woman have type I EC at a significantly higher rate (65% vs. 56%, respectively; $P < .01$).²²

Risk factors

Increased risk of EC is associated with increased age, certain ethnicities, higher BMI, endogenous or exogenous estrogen exposure, tamoxifen use, early menarche, late menopause, lower parity, metabolic syndrome, family history and genetic predisposition. By contrast, a lower risk of EC is associated with normal BMI, higher parity and oral contraception use.²³

Health and lifestyle factors.—Prolonged unopposed estrogen exposure (such as with estrogen replacement therapy, chronic anovulation and tamoxifen treatment), and age 55 years are very well-known risk factors for EC.^{3,24} In developed countries, an increasing rate of obesity has been paralleled by an increasing incidence of EC.^{2,5,6} The association between obesity and EC is well established and is particularly pronounced for endometrioid EC, with approximate relative risks of 1.5 for those with overweight, 2.5 for those with class 1 obesity (BMI 30.0-34.9 kg/m²), 4.5 for those with class 2 obesity (BMI 35.0-39.9 kg/m²) and 7.1 for class 3 obesity (those with BMI 40.0 kg/m²).^{6,25} The main mechanism by which obesity promotes endometrial carcinogenesis is through increased estrogen production by conversion of androgens to estrogen by adipocytes, which in turn stimulates endometrial proliferation and, potentially, the development of hyperplasia and cancer.²⁶ Moreover, obesity-associated hyperglycemia and insulin resistance can lead to abnormalities in IGF-1 signaling and activation of the Mammalian target of rapamycin (mTOR) pathway, resulting in increased cell proliferation. Associated inflammation and oxidative stress, as well as alterations in cytokines, steroid hormones and adipokine pathophysiology, and cellular and vascular perturbations, can also promote endometrial oncogenesis in women with obesity.²⁷ Remedial actions such as intentional weight loss have provided encouraging data for this as an effective preventive measure. Indeed, after adjustment for baseline BMI, post-menopausal women who lost 5% of body weight had an ~30% reduction in EC risk, which rose to a 66% reduction for women with obesity.²⁸

Meta-analyses have demonstrated an independent association between diabetes mellitus and increased risk of EC.²⁹⁻³¹ Insulin resistance, hyperinsulinemias, hyperglycemia, inflammation and disturbances in the IGF-1 pathway may contribute to carcinogenesis in individuals with diabetes.³² In addition, a positive association between metabolic syndrome (that is, obesity, hypertension, insulin resistance and dyslipidemia) and risk of EC has been established³³⁻³⁵ and has been confirmed by the findings of a Women's Health Initiative cohort study. Patients with metabolic syndrome have approximately a 2-fold increased risk of EC development.³⁶ Of note, after excluding obesity from the definition of metabolic syndrome, the association remained positive although it no longer reached statistical significance, suggesting that the association between metabolic syndrome and EC risk is

not solely explained by level of adiposity.³⁶ Studies have yielded inconsistent results on the association of bisphosphonates and EC risk.³⁷⁻³⁹ Data from one meta-analysis of seven studies found that the risk of EC in postmenopausal women was decreased by 27% after bisphosphonate administration with a duration of use of up to 1 year or more.⁴⁰ The anti-tumor effects of bisphosphonates are not fully understood and may involve complex underlying mechanisms including decreased cancer cell proliferation, disturbed mitosis, decreased angiogenesis, and an effect on immune cells/immune cell interactions.⁴¹⁻⁴³

Genetic factors.—Some germline mutations increase the risk of EC, of which Lynch syndrome has the strongest association. This autosomal dominant syndrome is characterized by a germline mutation in one of the *MMR* genes: *MLH1* (encoding MutL homologue 1), *MSH2* (encoding MutS homologue 2), *MSH6* (encoding MutS homologue 6), or *PMS2* (encoding postmeiotic segregation increased 2). Approximately 3% of ECs are due to Lynch syndrome,⁴⁴ and the estimated lifetime risk of EC by age 70 years is approximately 46-54% for women with *MLH1* mutations, 21-51% for women with *MSH2* mutations, 16-49% for women with *MSH6* mutations and 13-24% for women with *PMS2* mutations.⁴⁵⁻⁴⁷

Somatic mutations in *PTEN* are common in sporadic EC, whereas germline *PTEN* mutations are rare and associated with Cowden syndrome.⁴⁸ Cowden syndrome is characterized by an increased risk of breast cancer, thyroid cancer and EC, along with other diseases. The lifetime risk of EC in women with Cowden syndrome has been reported to be as high as 28%.⁴⁹

The association between *BRCA* germline mutations and the risk of EC remains controversial, especially for serous carcinomas. A link between *BRCA1* mutations and uterine serous cancer has been suggested in small, retrospective studies, whereas other studies have established no such risk.^{50,51} In addition, as many studies include only Ashkenazi Jewish populations or are confounded by tamoxifen exposure, results are challenging to interpret. One large study found an increased risk of serous and serous-like in *BRCA1*-positive patients undergoing risk-reducing salpingo-oophorectomy (RRSO) without hysterectomy⁵² in which 4 of 627 patients with *BRCA1*-mutations developed serous/serous-like EC (a 2.6-4.7% risk of developing these carcinomas by age 70). However, as these data are based on only 4 cases, making firm recommendations regarding the use of risk-reducing hysterectomy in *BRCA* mutation carriers is not feasible. In a study of 1,170 women with EC in which germline panel testing was performed, 4 women had *BRCA1* mutations (including one serous carcinoma and one carcinosarcoma) and 3 had *BRCA2* mutations (all endometrioid histology). These findings indicate a low incidence of germline *BRCA* mutations in this cohort of unselected patients with EC, and provides insufficient data to justify prophylactic hysterectomies in patients with *BRCA* mutations.⁵³

Mechanisms/pathophysiology

Precursor lesions

EC is often a hormone-sensitive disease thought to commonly arise in the context of excessive estrogenic stimulation of the endometrial lining of the uterus. This estrogenic stimulation leads to mitogenic stimulation, and ultimately, malignant transformation of

the endometrial glandular epithelium, and accounts for the development of the more common and lower grade endometrioid ECs. Risk factors for hyperestrogenism include obesity, hormone therapy (such as tamoxifen), ovarian cortical hyperplasia (hyperthecosis), polycystic ovarian syndrome, and hormone-producing tumors. Other histological subtypes of EC, including serous, clear cell, undifferentiated carcinoma and carcinosarcoma, are not as commonly associated with hyperestrogenism.

Endometrioid ECs develop through malignant transformation of the precursor lesions atypical endometrial hyperplasia (AEH) also known as endometrial intraepithelial neoplasia^{54,55}. AEH often contains somatic *PTEN* mutations; loss of *PTEN* is necessary for the development of AEH but is insufficient for progression to invasive carcinoma.⁵⁶ *ARID1A* has a critical role in the transition of precursor AEH lesions to invasive endometrioid carcinomas,⁵⁷ and inactivation of *TGF β* also contributes to the progression of AEH to invasive carcinoma.⁵⁸

The less common and more aggressive uterine serous carcinomas and the rarer uterine clear cell carcinomas are likely manifestations of increased genotoxic stress that is directly mediated through mutational and epigenetic activation of endometrial precursor cells. These EC subtypes often arise from precursor lesions such as serous endometrial intraepithelial carcinoma (SEIC). SEIC precursor lesions are thought to contain initiating *TP53* mutations, as evidenced by abnormal immunohistochemistry staining of p53 and some reports of identifiable somatic *TP53* mutations in SEIC precursor lesions and invasive disease.⁵⁹

Uterine carcinosarcomas – characterized by carcinomatous and sarcomatous elements - are high-grade biphasic carcinomas with a rising incidence, and account for ~5% of ECs.⁶⁰ Uterine carcinosarcomas are considered high-grade epithelial endometrial carcinomas with mutational profiles that overlap those of endometrioid and serous endometrial carcinomas.⁶¹⁻⁶⁴

Molecular subgroups

Four molecular subgroup of EC defined by mutation burden and copy number alterations have been categorized in a study of 373 cases of EC by the TCGA⁶¹ (Fig. 3). Most ECs have near diploid tumors or focal copy number alterations. Moreover, the mutational burden of most ECs reflects that of most solid tumors, with ~2-3 somatic mutations per megabase sequenced.⁶¹

In this study, one subgroup was defined by widespread genomic alterations and extensive amplifications and deletions and was termed the copy number high (CNH) group. The CNH group contained most high-grade, aggressive cancers, and included all uterine serous carcinomas and ~25% of the high-grade endometrioid tumors. The clinical outcome of this subgroup was poor. Most of these tumors had pathogenetic mutations in *TP53*. These tumors also have frequent somatic mutations in *PIK3CA*, and mutations in *FBXW7* and *PPP2R1A*, which are unique to CNH tumors. Moreover, these tumors have frequent amplification of *CCNE1*, which can lead to increased replication stress and likely chemoresistance.⁶⁵ Some tumors also have amplification of *ERBB2*, which is a therapeutic target being evaluated in prospective clinical trials.⁶⁶ *L1CAM* (a cell adhesion molecule that can affect cell motility)

is commonly expressed in uterine serous carcinomas and has been associated with poor outcomes.^{67,68}

Another subgroup of EC was tumors with microsatellite instability (MSI) (Fig. 3). These tumors have mismatch repair defects and a tumor mutational burden that is ~10-fold greater than that of a general mutational background. These tumors have mutations in many genes owing to their generally high mutation burden, therefore, it can be difficult to differentiate passenger from driver mutations. *PTEN*, *ARID1A*, *PIK3CA*, *PIK3R1* and *RPL22* are all commonly mutated in the MSI subgroup of EC. Moreover, mutations or epigenetic silencing of *MLH1*, *MSH2*, *MSH6*, *PMS2*, and less commonly *EPCAM*, are often responsible for MSI. These tumors often have unusual histological morphology that can make classification challenging, but they are uniformly endometrioid tumors often with cancer involvement of the lower part of the uterine body and with extensive tumor-infiltrating lymphocytes (TILs).

The third subgroup was identified owing to the discovery of recurrent mutations in *POLE* (encoding the exonuclease domain of polymerase-ε), which is present in ~7% of tumors. These tumors have a mutational burden ~100-fold greater than that of a general mutational background, and therefore, have somatic mutations in many frequently mutated cancer genes with difficult attribution to either passenger or driver mutations. These tumors also have a brisk lymphocytic infiltration, which may account for the better prognosis of this subgroup. Initially, tumors in this group were not thought to recur; however, there are some reports of recurrence, but at a lower rate than seen in any of the other molecular subgroups.⁶⁹ Whether the favorable outcomes in this subgroup are due to tumor inherent biology or the interaction of adjuvant therapy with the tumor microenvironment is unclear. Mutations in ECs with *POLE* mutations are likely the consequence of both replication errors and increased polymerase activity, leading to amplification of these errors reflected in the genomic mutation rate.⁷⁰

The fourth molecular subgroup consists of tumors with low amount of copy number alterations and no increased mutation burden, termed the copy number low (CNL) group (also known as the no specific molecular profile (NSMP) group by the TRANSPORTEC consortium).⁷¹ This group uniformly contains endometrioid tumors that are generally low grade. Unique to this subgroup are common *CTNNB1* mutations that are associated with a worse outcome that would otherwise be expected from these tumors with favorable histopathologic features, presumably through activation of the canonical WNT pathway.⁷² This group also contains a subgroup of tumors with amplification of chromosome arm 1q, which seem to have a much worse outcome than would be expected.⁷³ These two molecular features, *CTNNB1* mutations and 1q amplifications, make this a fascinating group for future study and for stratified clinical trials.

The identification of the molecular subgroups has rapidly changed the way ECs are stratified and treated. Several groups have taken these initial findings from TCGA and extrapolated them for better application to clinical practice. One approach - known as ProMisE (proactive molecular risk classifier for EC) - uses IHC to identify mismatch repair proteins and p53, and sequences the *POLE* exonuclease domain.⁷⁴ ProMisE has identified four molecular subtypes of EC that are analogous but not identical to the four genomic subtypes described

in TCGA study: MMRd, DNA POLE (corresponding to the ultramutated (*POLE* mutated) subtype), p53abn (which demonstrates aberrant p53 immunohistochemical staining and corresponds to the CNH subtype) and p53wt (which corresponds to the CNL subtype). Cases lacking enough information to classify are designated NSMP.^{75,76}

The National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC) has completed an integrated proteogenomic analysis of EC specimens.⁷⁷ This approach further defined a critical role linking Wnt signaling and histone acetylation for a subset of low-grade endometrial tumors and identified new regulatory pathways linking circRNAs to the epithelial-mesenchymal transition (EMT). Other important molecular features that may help to explain the response to immuno-oncology agents were also reported, and all data are in the public domain.

Uterine Carcinosarcomas

Endometrioid-like mutations in uterine carcinosarcoma include *ARID1A* (occurring in 10-25% of tumours), *KRAS* (10-15%) and *PTEN* (10-50%); and serous-like mutations include *TP53* (60-90%), *FBXW* (10-40%), and *PPP2R1A* (15-30%),^{62,64,78-80} with *TP53* and *FBXW7* mutations occurring more frequently in uterine carcinosarcoma than in other EC subtypes.⁷⁸ Additional work has found that the four TCGA molecular subgroups, previously described, can be reproduced in carcinosarcoma tumor samples.⁸¹ Further molecular analyses confirm that uterine carcinosarcoma differentiation develops through EMT. Evaluation of the immune microenvironment of uterine carcinosarcoma found a higher immune infiltration in tumors with increased mutation burden,⁸² with increased plasma cells and M2 macrophages in the sarcomatous component. The immune profile of uterine carcinosarcoma was associated with clinical outcome.⁸²

Immune landscape and tumor microenvironment (TME)

In normal endometrium, the immune system protects against pathogens and safeguards fetomaternal tolerance, whereas in carcinomatous endometrium, it exerts both pro-tumorigenic and anti-tumorigenic functions.⁸³ The tumor microenvironment includes supporting cells of stromal cells, mainly composed of ER- α -positive fibroblasts and myofibroblasts, considered cancer-associated fibroblasts (CAFs), inflammatory cells and endothelial cells, which facilitate EMT induction and drive metastatic progression through interaction with cancer cells (Fig. 4).⁸⁴ Leukocytes, especially tumor-associated macrophages (TAMs), as well as fibroblasts and myofibroblasts, have a crucial role malignant progression of hyperplasia to EC.⁸⁵

Stromal and immune cells.—The carcinogenic process involves fibroblast migration and proliferation at the neoplastic site, leading to increased collagen production and alpha-smooth muscle actin expression by fibroblasts - termed the desmoplastic response - which in the presence of the growth factor PDGF, is a hallmark of CAFs.⁸⁶ And the reduced ER- α expression in this setting of CAFs, associated with a more myofibroblastic phenotype, is sufficient to promote endometrial hyperplasia and carcinogenesis.⁸⁷ CAFs, through modulation of the PI3K/Akt and MAPK/ERK pathways and promote immune cell recruitment, can also stimulate EC proliferation.⁸⁸ Moreover, APC controls Wnt/ β -

catenin signaling, which is involved in uterine cancer development. Preclinical studies in mice suggest *APC* decreases ER α and PR expression and induces a lack of response to estradiol-17 β (E2) treatment in uterine stromal cells, in addition to decreasing stromal levels of TGF β and BMP activity, and increasing levels of VEGF and stromal derived factor signaling components that can lead to the development of EC.

The initial step in EC formation is the recruitment of leukocytes from blood, which is regulated by several chemokines, including SDF-1 α (also known as CXCL12) and its receptor, CXCR4.^{14,88} Monocytes attracted to tumors via CCL2, differentiate into TAMs,⁸⁹ with higher tumor microenvironment macrophage density correlated with poor prognosis.⁹⁰ Compared with benign endometrium, ECs have a higher CD68+ macrophage density in epithelial and stromal compartments,⁹¹ which is associated with higher risk of myometrial invasion, lymph-vascular space invasion (LVSI), lymph node metastasis, higher International Federation of Gynecology and Obstetrics (FIGO) stage, histological grade, as well as angiogenesis, higher micro-vessel density, and expression of Ki-67 and p53.⁹²

TAMs have several functions, including stimulation of tumor-associated blood vessel growth via secretion of VEGF and creation of an immunosuppressive microenvironment through expression of PD-L1 and PD-L2 immune checkpoint ligands and secretion of immunosuppressive factors like prostaglandins. Additionally, matrix metalloproteases (MMPs) induce remodeling of the extracellular matrix via TAMs and metabolic starvation of T cells through arginase activity and production of immunosuppressive metabolites by IDO1/2. TAMs also promote the activity of regulatory T cells (Tregs) via secretion of IL-10 and TGF β , creating an immune-suppressive milieu that is conducive for EMT and subsequent metastasis.⁹³ TAM density is also inversely correlated with the expression of PR and enhanced estradiol sensitivity and the addition of EC cells to estrogen and progesterone hormones via ER expression⁹⁴ (Fig. 4).

In comparison to early well-differentiated EC, CD8+ and CD4+ T cells, Tregs, and Tregs/CD8+ or Tregs/CD4+ ratios are significantly higher in advanced poorly differentiated EC with LVSI.⁹⁵ Additionally, high Treg counts and high Tregs/CD8+ ratios are associated with a worse prognosis.⁹⁵ Although *POLE*-ultramutated and mismatch repair deficient (MMRd) subtypes are enriched for TIL-high tumors, 22% of these tumors have been shown to be TIL-low, and TIL-low tumors are also enriched for p53abn (abnormal) and p53wt (wild-type).^{96,97}

In contrast to other subtypes of EC, *POLE* ultramutants have a robust cytotoxic T-cell response, denoted by increased CD8+ TILs and CD8A expression, augmented tumor-infiltrating T-cell gene signature, upregulation of T-cell cytotoxic differentiation, and overexpression of T-bet, Eomesodermin, IFN- γ , perforin and granzyme B effector markers.^{98,99} Additionally, T-cell exhaustion markers (including LAG3 TIM-3 and TIGIT) and T-cell inhibitors (PD-1 and CTLA-4) are expressed, suggesting prolonged antigenic exposure.¹⁰⁰ Inhibition of dendritic cell function also seems to be involved in the development of EC. In support of a role, one study reported dendritic cell invasion in 49% of patients with endometrioid carcinoma, which was significantly higher than that for control normal endometrium.¹⁰¹

PD-1/PD-L1 axis.—One study found a high level of PD-L1 expression in 92% of EC samples.¹⁰² By contrast, PD-L2 expression was very low, as also reported in ovarian and cervical cancers.⁸³ *POLE* tumors, followed by MMRd tumors, have the highest epithelial PD-1+CD8⁻ (putative CD4⁺) and PD-1+CD8⁺ TILs densities, whereas p53abn and p53wt tumors are associated with significantly lower levels of these cells.⁹⁶ In the stromal compartment, a similar trend is noted, with the exception of the p53abn subtype, which ranks second for PD-1+CD8⁻ TILs. Among *POLE*, MMRd, and p53abn tumors, the proportion of PD-1+CD8⁺ cells is similar (75-79%), with the percentage declining sharply to 33% in p53wt tumors.⁹⁷ One study reported infrequent PD-L1 expression in tumor cells, which was common in intraepithelial immune cells.⁹⁶ Greater PD-L1 expression in Lynch syndrome-associated ECs compared with MLH1 promoter hypermethylated EC was shown by another study.¹⁰³ Similar to PD-L1, IDO-1 expression was significantly higher in TIL-high tumors across the four molecular subtypes. However, IDO-1 was expressed in only 21% of the examined EC samples.⁸³ A higher prevalence of IDO-1 expression in MMRd tumors, particularly Lynch syndrome-associated EC, has previously been suggested.¹⁰⁴

Endothelial cells, angiogenesis & EMT.—In response to cytokine and growth factor synthesis and hypoxia due to perfusion or diffusion dysregulation or anemia in the setting of malignancy, soluble proangiogenic factors are secreted by endothelial cells.¹⁰⁵ These factors include VEGF, bFGF, TNF α , and IL-1 β .¹⁴

Angiogenesis, marked by VEGF and MMP production, is essential to the normal functioning of the endometrium both during and after the menstrual cycle. However, MMP and VEGF overexpression in EC are associated with tumorigenesis and metastasis.¹⁰⁶ In addition, hypoxia and EMT are key occurrences in tumor invasion and metastasis. HIF1 stabilization controls the expression of EMT regulators SNAIL, SIP and ZEB, and the HIF1A/TWIST/E-cadherin system appears to have a key role in the acquisition and progression of metastatic phenotype in endometrioid EC.¹⁰⁷

Moreover, E-cadherin loss and upregulation of β -catenin promotes EMT in numerous malignancies, including EC.¹⁰⁸ *CTNNB1* mutations, which are frequently associated with endometrial hyperplasia and endometrioid EC, result in abnormal expression of β -catenin.¹⁰⁹ This mesenchymal microenvironment homeostatic imbalance leads to a compromise of epithelial cell-to-cell adhesion and subsequent apoptotic escape, as well as the ability of malignant cells, in response to ER activation, to migrate and invade⁸⁵ (Fig. 4).

Role of hormones in microenvironment

Development of endometrioid adenocarcinomas has been linked to increased circulating levels of E2.¹¹⁰ Both E2 and stromal cell-derived pathways activate ER. These pathways include SDF-1 α /CXCR4 and HGF/c-Met activated downstream kinases, including MAPK and PI3K/AKT, which phosphorylate ER.¹¹¹ Surrounding stromal cells also contribute directly to estrogen biosynthesis in which peritumoral stromal cells are primarily comprised of ER α + fibroblasts and myofibroblasts that are activated by the binding of E2 and the ER α stromal receptor, leading to upregulation of cell-cycle-related proteins

(CDKN1A) and certain growth factors (IGF-1, TGF and MAD2L1) that mediate E2 proliferative stimulation of adjacent endometrium, promoting the paracrine secretion of mesenchymal cells.¹¹² Additionally, uterine epithelial differentiation and proliferation, as well as interactions between β -catenin and paracrine hormonal stimuli, are mediated by stromal cells. The higher β -catenin/E-cadherin expression in the post-menopausal state also suggests that this pathway is under the influence of the endometrial hormonal milieu¹⁰⁸ (Fig. 4).

Involvement of the uterine microbiome

The microbiome is suspected to have an effect on carcinogenesis by stimulating proinflammatory cytokine or growth factor secretion,¹¹³ in addition to affecting the hormonal status of the host or serum levels of sex hormones. Numerous mechanisms, including preventing apoptosis, stimulating proliferation and driving genomic instability, which are hallmarks of cancer, can be driven by microbioma. Higher proportions of Firmicutes at the phylum level and *Lactobacillus*, *Gardnerella*, *Bifidobacterium*, *Streptococcus*, and *Alteromonas* were reported in samples of patients with chronic endometriosis, a known risk factor for EC development, compared with healthy individuals. High vaginal pH (an indicator of vaginal dysbiosis) was also significantly associated with EC in one study.¹¹⁴ Of note, evidence supporting a resident population of bacteria in the uterus is lacking. Accordingly, the uterine microbiota is likely comprised by non-resident bacteria.¹¹⁵

Diagnosis, screening, and prevention

Clinical presentation and diagnostic assessment

Among perimenopausal and postmenopausal women, postmenopausal bleeding (PMB) accounts for approximately two-thirds of all gynecological visits and is a common symptom of EC. Indeed, one meta-analysis found that PMB occurred in ~90% of patients with EC; however, it led to a diagnosis of EC in only 9% of cases.¹¹⁶ Although abnormal uterine bleeding is the most common symptom of EC, bleeding can be accompanied by vaginal discharge and pyometra (uterine infection) in some women. Patients diagnosed with advanced EC might also present with symptoms similar to those of advanced ovarian cancer, such as pain and abdominal distension along with either constipation or diarrhoea.

Diagnostic work-up is recommended to rule out EC in all women presenting with PMB. The standard work-up to investigate and determine the cause of PMB may comprise pelvic ultrasonography, endometrial biopsy or dilatation and curettage (D&C; involves cervical dilation with scraping of the endometrial lining) with or without hysteroscopy.^{117,118} Measurement of the endometrial thickness using transvaginal ultrasonography should be performed in the sagittal plane at the thickest point; the majority of authors consider 5 mm as the normal upper limit for endometrial thickness in postmenopausal women, and this cut-off value has a sensitivity of 96% and a specificity of 61% for EC in post-menopausal women with abnormal uterine bleeding.^{119,120} Pelvic ultrasonography can be omitted in patients who already have an endometrial sampling showing an invasive cancer. When histopathological findings from endometrial biopsy are insufficient to confirm diagnosis, a

D&C should be carried out; of note, biopsy under hysteroscopy has a higher accuracy than 'blind' D&C and remains the gold standard for the diagnosis of EC when possible.¹²¹

Of note, biomarkers of EC, namely, CA-125 nor HE4, can be incorporated into routine diagnostic and follow-up practice for EC management owing to lack of evidence in support of their clinical impact.¹²²⁻¹²⁵

Pre-operative staging: imaging

Although EC is a surgically staged disease, preoperative staging using imaging may help establish those at risk of recurrence and inform surgical management, as imaging can identify myometrial or cervical invasion and lymph node metastasis (Fig. 5). Staging using imaging is indicated for patients who present with symptoms suggestive of extrapelvic disease and those with a poor performance status who are unable to independently perform activities of daily life for whom metastatic disease must be ruled out and in consequence surgery would not be an option.

MRI is the most accurate imaging technique for preoperative staging of EC due to its excellent soft tissue contrast resolution. Depth of myometrial invasion and cervical stromal invasion are both important aspects of EC staging and can be determined using dynamic contrast-enhanced MRI (DCE-MRI) and T2-weighted imaging (T2WI).¹²⁶ Diffusion-weighted imaging (DWI) can be carried out in patients who cannot receive intravenous gadolinium, which is typically used for DCE-MRI. In support of the use of DWI, one meta-analysis did not identify differences in the diagnostic performance of DWI compared with DCE-MRI, and combining T2WI and DWI was superior to DWI or DCE-MRI alone.¹²⁷

CT has low sensitivity (83%) and specificity (42%) for myometrial and cervical stromal invasion and is generally not used for the initial diagnosis of EC.¹²⁷ However, CT is useful in evaluating the extent of disease in women with more advanced disease with extra-uterine spread. For detection of lymph node metastases, both CT and MRI have a sensitivity of 27-66% and a specificity of 73-99%.¹²⁷ Integrated PET and CT (PET-CT) is not an appropriate screening tool for detection of primary EC due to its limited spatial resolution and is only indicated for initial staging if extra-uterine involvement is suspected or is observed on a preoperative MRI. Moreover, when PET-CT is performed as initial staging, primary intratumoral heterogeneity of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake seems to be a negative prognostic sign, correlating with a greater likelihood of tumor recurrence¹²⁸; these patients may benefit from more aggressive monitoring. In advanced disease, PET-CT may be particularly useful in detecting pelvic and paraaortic lymph node metastasis, with a sensitivity and specificity ranging from 51-69% and 90-100%, respectively. In addition, PET-CT and either CT or MRI has a higher sensitivity and specificity for detecting recurrence compared to CT and/or MRI alone.¹²⁷ Nevertheless, no correlation was found between early detection of recurrence and overall prognosis. Therefore, integration of PET-CT in the diagnosis and follow-up of EC is not routinely indicated.¹²⁹

Histological and molecular classification

Historically, EC is broadly classified into two subtypes — type I and type II — based on histological characteristics, grade and hormone receptor (ER and PR) expression.¹³⁰ Type I EC is the most common subtype, and comprises low-grade, endometrioid, diploid, hormone-receptor-positive EC that have a good prognosis (5-year OS rate of 85%).² Type II EC is non-endometrioid, high-grade, aneuploid, *TP53*-mutated, hormone-receptor-negative EC, and is associated with a higher risk of metastasis and a poorer prognosis (5-year OS rate of ~55%).¹³¹ These two types of EC have mutational profiles that differ substantially. Of note, it is increasingly clear that this traditional dualist classification of EC is suboptimal as a guide to risk classification, and consequently, as a tool to tailor therapy.

The histopathological classification for EC is a challenging task even among expert gynecopathologists, resulting in a frequent lack of consensus.¹³² As a result of this, EC risk assessment has been inaccurate and has possibly led to over- or undertreatment.¹³³ In this context, the molecular classification of EC provides a reproducible and prognostically relevant classification system; therefore, its integration into EC diagnostic procedures should be requisite.

As previously described, the TCGA identified four molecular subtypes of EC based on genomic abnormalities (Figs. 3 and 6). Although the TCGA study is a milestone in EC classification, these methods require fresh-frozen material and costly and complex methodologies. To try and decrease costs and technical challenges associated with these methods, a simplified, pragmatic molecular classifier—ProMisE—has been developed using methods that can be easily adopted at most centers.^{74,134,135} As previously mentioned, this classification system identifies four molecular subtypes of EC: MMRd, DNA POLE, p53abn and p53wt. Cases lacking enough information to classify are designated NSMP.^{75,76} Molecular classification drives the treatment of EC in the adjuvant and recurrent metastatic setting.

Although determining MMR and p53 status using IHC is widely available, sequencing *POLE* cannot be widely carried out. IHC analyses as part of an EC diagnosis should be universally implemented to guide and personalize the treatment of patients with EC.

Prognosis by molecular subtype

The survival differences between the molecular subtypes of EC have been replicated in several studies incorporating the surrogate marker approach (Fig. 7).^{74,134-136} In these studies, the p53abn group consistently had the poorest prognosis, with a risk of death or progressive/recurrent disease 3–5-fold higher than that of the p53wt group, and 2-fold higher when adjusted for clinicopathological features. The MSI group was associated with a 1.5–2-fold increased risk of death compared with the p53wt group, which was non-significant upon adjusting for clinicopathological features. However, heterogeneity of the latter group might account for the prognostic overlap with the p53wt group, underscoring the need for further stratification of the p53wt group. The *POLE*-mutant group was least affected by clinicopathological features and was associated with the most favorable prognosis.

The integration of biomarkers into prospective clinical trials is vitally important to more optimally delineate the relationships between molecular phenotypes and outcomes.

Screening

The strongest risk association for the development of EC is with Lynch Syndrome. Although some clinicopathologic features, such as <50 years of age at diagnosis, a personal or family history of Lynch syndrome-associated cancers and the presence of lymphocytic infiltration in the tumor specimen, which may indicate the need for germline testing for Lynch Syndrome, none are sensitive enough.¹³⁷ A more sensitive strategy is universal molecular tumor testing for all ECs diagnosed in women <60 years of age. The most cost-effective screening strategy is IHC for MLH1, MSH2, MSH6, and PMS2 expression in tumor samples, which can be performed in most pathology laboratories. However, most cases of MLH1 loss are due to MLH1 hypermethylation, with only 2-6% associated with germline mutations in *MMR* genes^{138,139}; therefore, tumor samples with loss of MLH1 should subsequently be analyzed for MLH1 hypermethylation, followed by germline testing in those without MLH1 hypermethylation. Although universal screening in patients with EC who are <70 years of age is cost-effective owing to prevention of colorectal cancer in both patients with EC and their relatives,¹⁴⁰ there are logistical barriers to such screening, for example, insufficient tissue for testing and patients declining tissue or germline testing.¹³⁸

Management

Estimating the risk of disease recurrence has historically been challenging for EC given variability in surgical practice and the lack of reproducible pathological classification.¹⁴¹ Consequently, treatment of newly diagnosed EC is variable between regions and across treatment centres. For early-stage disease, the main treatment is surgery. Depending on stage of disease and other risk factors, adjuvant radiotherapy and/or chemotherapy can be used to reduce risk of recurrence.¹⁴² Studies investigating adjuvant endocrine therapy have been small and negative; therefore, endocrine therapy is not recommended in the adjuvant setting.¹⁴³ Options for metastatic disease are limited, with both chemotherapy and endocrine therapy considered standard of care.¹⁴⁴ More recently, immunotherapy alone or in combinations has become standard of care, although these therapies are not universally available across all jurisdictions.¹⁴⁵

Surgery

Surgery is the primary treatment for women with localized EC. Surgical staging is used for prognostication and identification of women who might benefit from adjuvant treatment. Total hysterectomy with bilateral salpingo-oophorectomy (BSO) is standard of care and can be performed by an open or a minimally invasive approach. Minimally invasive techniques have similar oncological outcomes, shorter hospital stay and fewer complications compared with open laparotomy in early-stage EC.¹⁴⁶⁻¹⁴⁹ Intraoperative complications, such as bleeding and bowel-associated complications, occurred in ~8% of women who underwent laparotomy compared with 10% who underwent laparoscopy. Moreover, postoperative adverse events such as infection, thrombosis and fistula formation occur less often in those who undergo laparoscopy compared with laparotomy.¹⁴⁹ The benefit of minimally invasive surgery is arguably greatest for women with morbid obesity and the frail elderly, in whom

perioperative morbidity from laparotomy is highest.¹⁵⁰ However, minimally invasive surgery should only be performed by a surgeon with appropriate training, and the uterus should be removed intact, not morcellated. Neoadjuvant chemotherapy can sometimes be considered but has not been universally adopted.¹⁵¹ Surgery for advanced or recurrent EC is more controversial. Most benefit has been described for those who undergo optimal (microscopic) cytoreduction.¹⁵²

Lymphadenectomy is a controversial topic in the management of EC. GOG 33 found a role for lymphadenectomy in staging EC,¹⁵³ and retrospective analysis found a survival benefit for pelvic and paraaortic lymphadenectomy in patients with higher risk histologies and for those with intermediate-risk or high-risk disease.^{154,155} The necessity of paraaortic lymphadenectomy (to detect metastatic deposits) is also controversial and can be particularly challenging in patients with obesity. The risk of paraaortic metastases if no metastatic deposits are identified in the pelvic lymph nodes is dependent on other factors, such as LVSI, tumor histology, and grade.¹⁵⁶ Two randomized studies did not find a survival benefit with lymphadenectomy in early-stage EC, however, lymphadenectomy is important in staging.^{157,158} In addition, a Cochrane review did not find evidence that lymphadenectomy was associated with a decreased risk of death or EC recurrence compared with no lymphadenectomy.¹⁵⁹

Practice differs across jurisdictions, ranging from no lymph node assessment, sentinel lymph node mapping, and complete pelvic and paraaortic lymphadenectomy as standard of care.^{157,160} At a minimum, lymph node assessment with removal of suspicious-appearing lymph nodes is recommended. Sentinel lymph node evaluation can be considered as a strategy for nodal assessment for low-risk or intermediate-risk EC and it can be omitted in patients without myometrial invasion (MMI). Lymphadenectomy should be considered for tumors exhibiting MMI >50% or grade 3 or non-endometrioid histology.¹⁴² Moreover, the National Comprehensive Cancer Network (NCCN) guidelines suggest evaluation of the pelvic nodes, with or without paraaortic nodal dissection (based on higher risk features such as deeply invasive lesions and high-grade histology), and suggests sentinel lymph node mapping may be considered.¹⁶¹ ESMO-ESGO-ESTRO guidelines do not recommend lymphadenectomy for low-grade, low-risk disease but suggest reserving it for patients with medium- or high-risk disease. Lymphadenectomy can be considered (with sentinel lymph node dissection as an option) for >50% MMI and is recommended for all stages of non-endometrioid histology and grade 3 tumors with >50% MMI. Gross extra-uterine disease should be biopsied and removed where possible.²³ Removal of the omentum is considered in those with higher risk histology (such as serous and carcinosarcoma)¹⁶² owing to the high incidence of involvement even when EC is apparently confined to the uterus. The British Gynecological Cancer Society (BGCS) does not advise lymphadenectomy for grade 1 and 2 presumed FIGO stage I-II EC. Surgical staging, including pelvic and paraaortic lymphadenectomy and omental biopsy, may be appropriate for high-grade disease and non-endometrioid EC.¹⁶³ Moving forward, the incorporation of molecular subgroups, in addition to traditional histopathologic parameters, may offer better predictive models to guide surgical decision making.¹⁴¹

Conservative management of EC

Fourteen percent of ECs are diagnosed in premenopausal women, and 5% occur in women aged <40 years,¹⁶⁴ usually in those who are nulliparous, and often at an early stage. Women with low-grade endometrioid EC and no evidence of MMI on imaging (including MRI) who wish to preserve their fertility can be considered for a non-surgical approach. High-dose oral progestins and/or levonorgestrel-release intrauterine devices (LNG-IUDs) can be used with careful monitoring to ensure disease progression is not occurring.^{165,166} According to NCCN and ESGO guidelines,^{161,164} monitoring should encompass endometrial evaluation with a D&C or endometrial biopsy every 3-6 months. Surgery is recommended if EC is identified at 6-12 months, whereas conception with continued surveillance followed by completion surgery when childbearing is complete or progression occurs is advised in women with a complete response.

The rationale for progestin therapy is the role of unopposed estrogen in the development of precursor and low-grade EC development. Although the mechanisms of action of progestin therapy and resistance to this therapy are not fully known, progestin exposure downregulates ER and PR and reduces mitotic indices.¹⁶⁷

Oral progestins can be used for EC treatment but are associated with some challenges, including weight gain and compliance. LNG-IUDs have been explored for early-stage cancers, as they result in constant low-dose progestin exposure within the uterus. In one meta-analysis of oral medroxyprogesterone acetate, a pooled regression rate of 76.2% (95% CI: 68-85.3%) and a live birth rate of 28% was reported, which were similar to response rates with LNG-IUDs.¹⁶⁵ However, although response rates are high with these treatments, relapse rates are also high, therefore, these fertility-sparing options are temporizing measures.¹⁶⁵

Treatment with LNG-IUD may also be appropriate in patients, in addition to those wishing to preserve fertility, such as those with significant comorbidities. Indeed, one study demonstrated a response rate of 75% in patients with complex atypical hyperplasia and early-grade endometrioid EC (grade 1, 67%; grade 2, 75%).¹⁶⁸ Clinical trials to improve the efficacy of progesterone therapy in this population are warranted. Combining endocrine therapy with lifestyle interventions, particularly those that target obesity, is also an attractive approach.

Ovarian preservation can be considered in younger women with low-grade, early-stage EC to mitigate the menopausal symptoms associated with more extensive surgery. One study using SEER population data suggested that overall survival might be improved for women <50 with low-grade, early-stage disease, as risk of cardiovascular death is reduced.¹⁶⁹ However, defining which low-risk women are candidates for this type of surgical approach is challenging, and careful expert discussion and counselling is required.

Adjuvant treatment

Low-risk EC.—Adjuvant treatment is not required for women with EC at low risk of recurrence, defined as low-grade (1 or 2) endometrioid histology, disease limited to the

endometrium, or disease exhibiting <50% MMI. Local control rates are >95% with surgery alone.^{170,171}

Intermediate-risk EC.—Intermediate-risk EC includes tumors of higher grade endometrioid histology that exhibit MMI (up to occult stage II disease). In addition, the GOG and PORTEC groups have defined a group of women at high-intermediate risk (HIR) based on age, tumor grade, MMI (outer one-third [GOG] and 50% [PORTEC]), and the presence of LVSI (GOG).¹⁷²⁻¹⁷⁴

Postoperative radiotherapy can significantly reduce the risk of local recurrence for women with intermediate-risk EC.¹⁷²⁻¹⁷⁴ However, the lack of an OS benefit coupled with variability in lymph node staging practices has resulted in a failure to establish a uniform adjuvant approach globally.¹⁷⁵ Guidelines and treatment algorithms differ across jurisdictions, leading to variability in clinical practice.¹⁴⁸ Whole pelvis external-beam radiation therapy (EBRT) and intracavity vaginal brachytherapy (VBT) can be used to deliver postoperative radiotherapy in patients with EC. Although no OS benefit was observed in GOG-99 and PORTEC-1 with adjuvant EBRT compared with observation in women with intermediate-risk EC, adjuvant EBRT decreased the recurrence rate by ~9%. For women with high-intermediate risk (HIR) features, the benefit was 13-20%, although for those at lower risk, the benefit was only 3-4%.¹⁷²⁻¹⁷⁴ Based on these studies, women with HIR disease should be offered radiotherapy with either EBRT or VBT. The presence of LVSI (focal vs diffuse) should guide decisions for other patients with intermediate-risk EC who do not fully meet HIR criteria.

For intermediate-risk EC in the absence of LVSI, VBT can be considered, but decisions need to be balanced against the risk of toxicity and the potential effect on QOL as part of the patient-physician decision-making process.¹⁷⁵ The ESMO-ESGO-ESTRO guidelines suggest that in intermediate-risk patients no adjuvant therapy may be considered, especially for patients older than 60 years of age. The BGCS guidelines are also less in favor of radiotherapy. Guidelines differ across jurisdictions in women with intermediate-risk cancers. Consideration of tumor characteristics and discussion with the individual patient is essential.

The most common site of recurrence in the GOG-99 and PORTEC-1 studies was vaginal vault. In the PORTEC-2 trial, >96% of women remained free of vaginal vault recurrence with either VBT and EBRT.¹⁷⁶ Moreover, 10-year survival data confirmed excellent similar rates of isolated pelvic recurrence, distant metastasis and OS. Accordingly, VBT alone is an option for some women with HIR EC based on careful evaluation of clinicopathologic risk factors.¹⁷⁶ Combining EBRT and VBT can be considered on a case-by-case basis for women thought to be at high risk for both pelvic and vaginal recurrence. Factors such as deeply invasive grade 3 tumors, LVSI, or those with limited or no lymph node staging may be taken into account when considering EBRT and VBT. Although no randomized data are available, data from retrospective series support this practice.¹⁷⁵

Of note, the addition of chemotherapy to VBT for patients with HIR or high-risk EC did not result in a superior outcome for those with early-stage disease in GOG-249 (Supplementary Table 1). The addition of 3 cycles of chemotherapy did not improve OS or recurrence

endpoints compared to pelvic EBRT alone.¹⁷⁷ However, chemotherapy was associated with increased toxicity. These results suggest pelvic radiation therapy as the standard treatment for HIR disease.

High-risk EC.—High-risk EC includes stage III-IVA optimally debulked disease and any stage of disease with high-risk histology (serous or clear cell). For these patients, chemotherapy or a combination of radiotherapy and chemotherapy should be considered. Two randomized trials have addressed the relative roles of chemotherapy and radiotherapy in this high-risk patient population (Supplementary Table 1).

In PORTEC-3, patients were randomized to receive CTRT or EBRT alone. Although there was no improvement in OS, an improvement in failure-free survival (FFS) was observed in the CTRT arm. The greatest benefit was observed in women with stage III disease and in women whose tumor exhibited serous histology.¹⁷⁸ Interestingly, molecular subgroup analysis demonstrated an improvement in FFS with CTRT over EBRT in women with p53abn EC.⁷¹ Other molecular subgroups did not appear to derive benefit from the addition of chemotherapy, although there was a trend toward benefit in the NSMP subgroup. With long-term follow-up, no significant differences in grade 3 adverse events between women who received CTRT or those who received EBRT were reported. However, 25% of patients reported the persistence of sensory neurological symptoms.¹⁷⁹

GOG-258 found no difference in recurrence-free survival or OS between women with stage III/IVA EC who received chemotherapy or CTRT. However, rates of vaginal recurrence and pelvic/para-aortic recurrence were higher in the chemotherapy arm compared with the CTRT arm. This was balanced by a higher rate of distant recurrence in the CTRT arm compared to chemotherapy arm.¹⁸⁰ This has resulted in many centers in the US omitting radiotherapy for stage III disease.

Taking these studies and other smaller trials^{178,181-183} into consideration, the optimal approach for treating women with high-risk disease has yet to be defined. Planned or ongoing studies are looking at whether adjuvant strategies for higher stage EC should be informed by molecular subgroup. These include trials considering de-escalation of treatment for women with *POLE* cancers and the inclusion of immunotherapy for women with MMRd tumors. Furthermore, the optimal sequencing of chemotherapy and radiation therapy has yet to be determined and remains controversial, with various smaller studies providing evidence for sequential, sandwich, and concurrent CTRT.^{178,181-183}

Recurrent and metastatic disease

Although EC generally carries a good prognosis, molecular subgroup data suggest that women with p53abn (serous or serous like) EC have the highest risk of metastatic spread. When considering high-risk cancers, 5-year relapse-free survival rates were 46.6% for p53abn ECs compared with 98% for *POLE*, and 77.1% and 74.4% for MMRd and NSMP ECs, respectively.⁷¹ Recurrence can occur locally within the vagina or in the pelvic lymph nodes or within paraaortic lymph nodes or peritoneum. Distant metastases most commonly occur in the lung and lymph nodes. Less common sites of metastasis include the bones,

brain, and intra-abdominal organs.¹⁸⁴ Treatment for local disease includes the consideration of surgery or radiotherapy, whereas systemic therapy is considered for more distant disease.

Chemotherapy.—Most women with metastatic EC, except those with low-grade, low-volume metastatic EC (confined to the pelvis, managed by radiation therapy), will receive chemotherapy. Frontline chemotherapy for metastatic EC is platinum-based; GOG-209 confirmed the non-inferiority of carboplatin/paclitaxel compared with the more toxic TAP regimen (cisplatin/doxorubicin/paclitaxel), with an OS of ~15 months.¹⁸⁵ The benefit of second-line chemotherapy is debatable, with response rates <20% and PFS around 4 months.¹⁸⁶ Retreatment with platinum-based chemotherapy is an option for women who demonstrate prior benefit, with retrospective data suggesting response rates of ~40% with a platinum-free interval <12 months and ~60% with a platinum-free interval >12 months.^{187,188}

HER2 overexpression occurs in 25% of serous or serous-like ECs.⁶¹ Based on a small, randomized phase II study, the combination of trastuzumab and carboplatin/paclitaxel improved PFS (12.9 versus 8 months) and OS (24.4 versus 29.6 months) compared with chemotherapy alone in HER2 overexpressing advanced or serous EC.^{66,189} This treatment regimen has become a standard of care for this subgroup of women in the United States.

Modest benefits for single-agent anti-angiogenics and the rapalog class of mTOR inhibitors, with PFS of around 3 months (some women experiencing durable response) resulted in their inclusion, post chemotherapy, as a treatment option. However, these agents are not universally available, have no identified predictive biomarkers (with the possible exception detailed below), and their use needs to be balanced against their toxicity in the context of modest gain.¹⁴⁴ The combination of carboplatin/paclitaxel with either bevacizumab or temsirolimus did not demonstrate a benefit compared with chemotherapy alone.¹⁹⁰ However, a subgroup analysis suggested that the presence of a *TP53* mutation in the tumor may predict greater benefit to bevacizumab but not temsirolimus.¹⁹¹ This finding warrants further investigation.

Endocrine therapy.—A range of endocrine therapy agents are used in the clinic, including progestins, aromatase inhibitors, and tamoxifen.¹⁶¹ Despite the strong rationale for its use owing to ER and/or PR expression, one Cochrane review in 2010 could not conclude that endocrine therapy improved survival for women diagnosed with advanced EC. This result was due to a lack of randomized trials and too many small studies conducted across more than 6 decades.¹⁹² In a meta-analysis, endocrine therapy in an unselected EC population had a response rate of 21.6%, with an associated PFS of 2.8 months¹⁹³ and a higher response in those with ER/PR EC (35.5%) and a response of 0% in ER/PR-negative tumors.¹⁹³ There is no accepted standard for measuring or defining ER/PR positivity in EC. In addition, given the modest benefit, it is likely better if predictive signatures are required to optimize the use of this approach in the future. Planned studies incorporating endocrine therapy require high-quality correlative studies to answer fundamental questions and to incorporate patient-reported outcomes to better inform patients and clinicians of any potential benefit. Current indications for the use of endocrine therapy are based on clinicopathologic features; endocrine/hormonal agents can be considered for low-grade

endometrioid histology with low-volume/indolent disease. Randomized comparative data on single-agent efficacy sequencing of endocrine therapy to inform subsequent use is lacking.¹⁹⁴

Given that endocrine therapy is generally well tolerated they are attractive options for EC treatment. Furthermore, downstream interactions of the ER/PR pathways lend themselves to potential combinations with some of the newer targeted agents (Supplementary Table 2).¹⁸⁷⁻¹⁹² The combination of everolimus (an oral mTOR inhibitor) and letrozole appears as a standard of care option within NCCN Guidelines.

Immunotherapy.—Approximately 30% of ECs belong to the MSI-H/MMRd subgroups.¹⁸⁶ These tumors have higher mutational burden and are susceptible to immune checkpoint blockade.

The Keynote-158 study reported an objective response rate (ORR) of 57.1% with pembrolizumab treatment in 49 EC patients whose tumors were MSI-H/MMRd, with a complete response in 16% and partial response in 40%.²⁰¹ In this study, median PFS was 25.7 months. Activity was also observed in women with tumor mutation burden-high (TMB-H) solid tumors, defined as ≥ 10 mut/Megabases, with an ORR of 29%.²⁰² Accordingly, pembrolizumab is FDA approved for the treatment of previously treated MMRd/MSI-H and TMB-H EC.

The GARNET trial is a phase Ib study of the anti-PD1 agent dostarlimab, and has found ORRs of 44.7% for patients with MMRd EC and 13.4% for those with MMRp with dostarlimab treatment.²⁰² Based on these results, dostarlimab has been granted approval by the FDA and conditional marketing authorization by the European Commission for women with MMRd or MSI-H EC that has progressed after prior therapy.

Several other studies have evaluated the activity of checkpoints inhibitors in EC. For example, the Phaedra Study²⁰³ evaluating durvalumab (anti-PD-L1 agent) reported an overall tumor response rate (OTRR) according to iRECIST of 43% for women with MMRd EC.²⁰³ In addition, a non-randomized, two-cohort, phase II study of avelumab (anti-PD-L1 agent) in women with advanced or recurrent EC after at least one previous therapy found an overall response rate of 26.7% in the MMRd cohort and 6.25% in the MMRp/non-*POLE* cohort. In the MMRd cohort, 40% of patients were progression free at 6 months.²⁰⁴

The KEYNOTE-146/Study 111 and the randomized phase III study KEYNOTE-775/Study309 evaluated the combination of pembrolizumab with lenvatinib, an oral multikinase inhibitor in women with previously treated EC. In KEYNOTE-146, with a primary endpoint of ORR at 24 weeks (ORR_{Wk24}) as evaluated by investigators per iRECIST, 87% of patients had MMRp/MSS tumours. The ORR_{Wk24} was 38.0%, and response occurred regardless of MSI and PD-L1 status or histology. Median PFS was 7.4 months and median OS was 16.7 months, with long-term responders observed. As a result of these data, pembrolizumab with lenvatinib have been granted accelerated approval by the FDA, Australian Therapeutic Good Administration, and Health Canada for treatment of advanced non-MSI-H/ non-MMRd EC that has progressed following prior therapy.²⁰⁵ Adverse events were manageable but

significant; 69% experienced grade 3/4 toxicities, of which hypertension was the most frequent (32.4%). Other adverse events of any grade were hypertension, diarrhea, decreased appetite, fatigue, and hypothyroidism. Dose interruption occurred in 72%, and lenvatinib dose reduction occurred in 65% of patients.

The KEYNOTE-775/Study 309 included patients with advanced or recurrent EC who had received at least one prior platinum-based regimen, and found a significant improvements in OS, PFS, and ORR with lenvatinib and pembrolizumab compared with treatment of physician's choice, regardless of MMR status.²⁰⁶ For the entire population, the median OS was 18.3 vs. 11.4 months, the median PFS was 7.2 vs. 3.8 months, and the ORRs were 31.9% vs. 14.7% favoring lenvatinib and pembrolizumab. Based on these data, lenvatinib and pembrolizumab combination therapy was FDA approved for patients with advanced EC that is not MSI-H or MMRd, who have disease progression following prior systemic therapy in any setting, and by the European Medicines Agency for all EC following prior platinum-based therapy in any setting. Furthermore, large, randomized trials exploring this and a number of other novel treatment combinations are ongoing.

Quality of life

In general, several adverse effects are associated with EC treatment, including lymphedema, neurotoxicity, fatigue and bowel-bladder issues, and result in a decline of QOL. However, few studies focused exclusively on QOL in patients with EC have been carried out. Measurement of QOL has been generally conducted by patient-reported outcome (PRO) questionnaires, including the EORTC QLQ-C30, SF-36, FACT-G and FSFI, among others. These questionnaires are widely used to assess the QOL of patients with cancer, although not specifically for EC. Based on a systematic review of PROs in women who survived EC,²⁰⁷ obesity was associated with lower QOL and physical functioning. Moreover, surgical procedures, specifically laparoscopy over laparotomy was associated with better QOL outcomes, and vaginal brachytherapy was associated with better outcomes over external-beam radiation.

As most cases of EC are estrogen-linked, BSO is recommended in addition to total hysterectomy, in many patients (see Management, above even in young patients. In premenopausal patients, reduction of QOL associated with hypoestrogenism due to BSO needs to be managed. In general, climacteric and emotional symptoms caused by surgical menopause are more severe than those associated with spontaneous menopause.²⁰⁸ Performing BSO in those <50 years of age is associated with increased risk of all-cause mortality, coronary heart disease and stroke.^{209,210} Moreover, patients undergoing BSO for EC have a higher frequency of hypertriglyceridemia compared with those undergoing BSO for non-EC reasons, and serum low-density lipoprotein cholesterol levels are higher in those with a history of premenopausal BSO for EC.²¹¹ Cardiovascular disease is the most common cause of death in survivors of EC.²¹² Treatment of EC by BSO, radiation therapy and chemotherapy may increase the risk of reduction of bone mass and osteoporosis; however, some reports have shown that total adipose mass is correlated with a high bone mass,²¹³ and that osteoporosis is less frequent in patients with EC with hypertriglyceridemia.²¹⁴

Hormone replacement therapy is an effective treatment for symptoms caused by BSO, and was not associated with increased risk of EC recurrence in a meta-analysis and randomized controlled trial.^{211,215} However, an increased risk of recurrence was observed in Black patients who received estrogen replacement therapy in the randomized controlled trial.²¹⁶ These findings suggest that conjugated estrogens or E2 can be used to alleviate hypoestrogenism-associated symptoms after EC surgery. Selective estrogen-receptor modulators (SERMs) may be another option, but no comparisons of long-term treatment with estrogen and SERMs have been carried out.²¹⁷ As previously mentioned, no significant increase in risk of EC recurrence was observed in a meta-analysis of EC survivors using hormonal replacement therapy; however, in subgroup analysis, a protective effect on EC recurrence was seen with combined estrogen-progesterone hormone replacement therapy compared with estrogen-only therapy. Of note, these data must be interpreted with caution, as there was significant heterogeneity across estrogen-alone studies. Progesterone can increase the risk of breast cancer; therefore, it is important to provide accurate information about these hormones to patients. Patients who are considered poor candidates for hormone replacement therapy (such as smokers, those with a history of breast cancer or multiple strokes) may be considered for non-hormonal therapies, such as selective serotonin reuptake inhibitors (SSRIs), serotonin, norepinephrine uptake inhibitors (SNRIs), and anticonvulsants.^{218,219}

Outlook

As previously discussed, EC is associated with many molecular aberrations that present myriad opportunities for targeted therapy and precision medicine.^{61,220,222} Although four major molecular subgroups have been identified, the majority of patients are treated in the same way, regardless of molecular differences in their tumors. However, recent publications and novel clinical trials are beginning to change this. Over the past year two new therapies have been approved by the FDA for advanced or recurrent EC: pembrolizumab for MSI-H/MMRd tumors²²² and pembrolizumab plus lenvatinib for non-MMRd/non-MSI-H tumors.²⁰⁵

Based on TCGA findings, two groups of investigators developed pared down programmatic molecular classifiers that could be incorporated into clinical decision-making and counseling of patients with EC. The TransPORTEC initiative established a stratification model based on *TP53* mutation, MSI, *POLE* mutation or NSMP status.²²³ These features were associated with the rate of distant metastases and recurrence-free survival.²²³ The TransPORTEC model has been further refined through the integration of clinical factors (LVSI) and other important molecular features (*CTNNB1* mutation status and L1-CAM expression).²²⁴ The PORTEC-4a trial is prospectively testing this model to assign treatment to patients with HIR EC (Fig. 8).²²⁵ This exciting trial focuses on the use of radiation as a treatment strategy; thus, there still remains opportunity to incorporate targeted agents and immunotherapy into adjuvant therapy based on TransPORTEC classification.

ProMisE uses surrogate markers to create a stepwise path to stratify patients with EC analogous to TCGA molecular subtypes.¹³⁴ Tumors are classified based on MMRd, presence of *POLE* mutation, presence of p53 loss or overexpression on

immunohistochemistry, or no abnormality. Similar to the TransPORTEC model, these four subtypes were associated with disease-free survival and OS.¹³⁴ More recently, another group⁷¹ confirmed the association of MMRd, P53 IHC, and *POLE* mutational status with prognosis, using samples collected as part of the PORTEC-3 clinical trial. Furthermore, the molecular subgroups may have predictive value. Women whose tumors belonged to the P53-aberrant group appeared to benefit from the addition of chemotherapy to radiation, whereas those with MMRd tumors did not appear to derive a benefit. In addition, women within the *POLE*-mutant group had an excellent prognosis regardless of treatment arm.⁷¹ These findings require further exploration and have important implications for the future design of adjuvant therapy trials.

Immune checkpoint inhibitors as monotherapy,^{201,222,226} as well as in combination with lenvatinib, have led to an increase in clinical trials designed to identify the ideal timeframe to employ immunotherapy in the treatment of EC. Response rates of checkpoint inhibition in MMRd/MSI-H EC ranges from 27-57% based on the agent assessed. These responses are durable and deep, but there are still many unanswered questions. For example, whether these treatments should be used for adjuvant treatment. The NRG Oncology group is looking to answer this question by randomizing patients with MMRd HIR EC to adjuvant radiotherapy with or without pembrolizumab (NCT04214067). In addition to survival outcomes, this study will explore important QOL endpoints to determine whether the addition of pembrolizumab to radiation, compared with radiation alone, is associated with decreased QOL at 6 and 24 weeks, as measured by the Functional Assessment of Cancer Therapy (FACT)-Endometrial (En) Trial Outcome Index (TOI); with increased gastrointestinal symptoms, as measured by the gastrointestinal subscale; and with increased fatigue as measured by the PROMIS-Fatigue scale.

Another key question relates to the maximization of the treatment of patients with advanced and recurrent EC. Preclinical evidence indicates that combining chemotherapy and immune checkpoint inhibition has the potential for synergy in solid tumors, including EC.²²⁷ Based on these data and the exciting single-agent activity of checkpoint inhibitors, there are a number of large randomized phase III trials exploring the addition of checkpoint inhibition to chemotherapy in women with advanced or recurrent EC (Supplementary Table 3). Importantly, these trials also incorporate assessment of the checkpoint inhibitor as a maintenance strategy. Moreover, there is interest in replacing chemotherapy entirely in the frontline setting. The LEAP-001 study is a randomized phase III trial comparing standard of care platinum-based chemotherapy to the lenvatinib and pembrolizumab combination in stage III, stage IV, and treatment-naïve EC (NCT 03884101). Beyond single-agent checkpoint inhibition, there are a number of interesting novel immunotherapy techniques that may warrant exploration in EC, including dual checkpoint inhibition and adoptive cell therapies. Furthermore, to better determine the relevance of the microbiome, future research incorporating studies of host-microbiota and host-metabolome interactions within the endometrial environment are needed.

Outside of immunotherapy, there are a number of novel targeted agents demonstrating promise in EC. One study found an OS benefit with the addition of trastuzumab to standard chemotherapy in women with HER2-overexpressing uterine serous cancers.⁶⁶ This success

led to a compendium listing and several planned trials assessing dual HER2 combinations in this population. Moreover, although p53 has long been considered an ‘undruggable’ target, the development of Wee1 inhibition to create a synthetic lethal situation in the setting of *TP53* mutation has improved the prospects of action on this aberration. A phase II study of the Wee1 inhibitor adavosertib in uterine serous tumors led to durable and deep responses in ~30% of patients.²²⁸ Larger studies are moving forward to determine the ideal setting for this class of drugs. As noted above, *TP53* mutations has also been explored as a potential predictor of benefit from the combination of chemotherapy and bevacizumab in the advanced/recurrent setting.¹⁹¹² Additional studies will be necessary to confirm TP53 as a marker that can be used for decision-making. Finally, due to presence of homologous recombination deficiency in EC,²²⁹ PARP inhibitors are also under development, alone and in combination with other targeted therapies. Ultimately, the success of precision medicine in EC will depend on careful validation of biomarker candidates and thorough vetting of agents with innovative trial designs. Window of opportunity studies hold promise for rapid assessment of novel therapies with pre-therapy and post-therapy tissue assessments that can guide biomarker development and treatment selection.^{230,231}

A key point is that none of these advances will yield maximum impact if health disparities persist in EC. Outcomes for women with EC are drastically different based on ethnicity. As previously discussed, Black women have significantly higher mortality rates compared with white women, even when controlling for known high-risk factors such as stage and non-endometrioid histology.²³² The reasons for this disparity are not entirely clear but may include quality of care given to women of color, implicit racial bias and systemic racism.²³³ Further, the lack of inclusion of underrepresented minorities in clinical trials and molecular studies, such as TCGA, is a missed opportunity to improve outcomes for all women with EC.^{234,235} Therefore, there is a critical need for systematic investigation and research funding so these disparities can be scrutinized, addressed, and successfully overcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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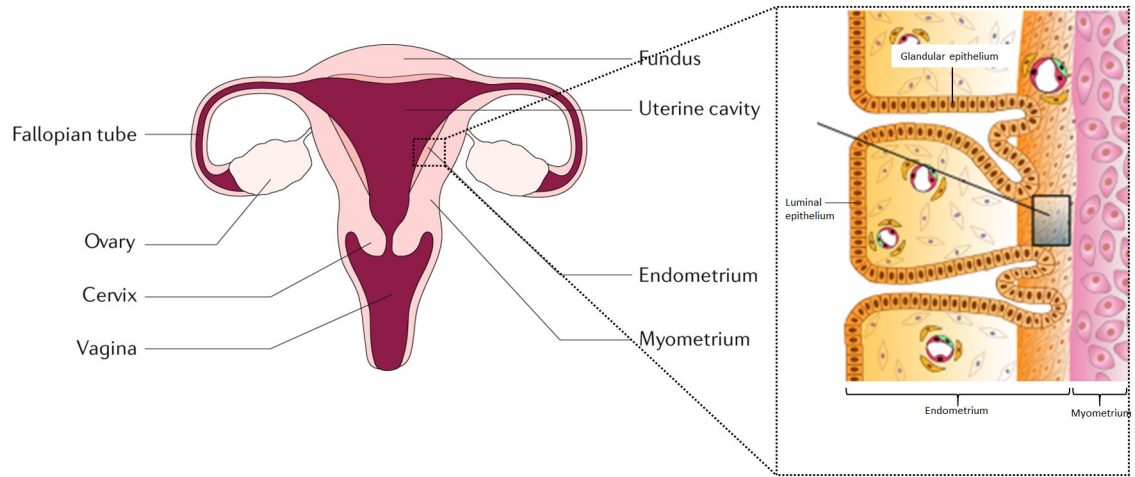


Figure 1. Uterine anatomy.

The endometrium is the inner lining of the uterus. Endometrial cancer arises from the endometrial glandular epithelium.

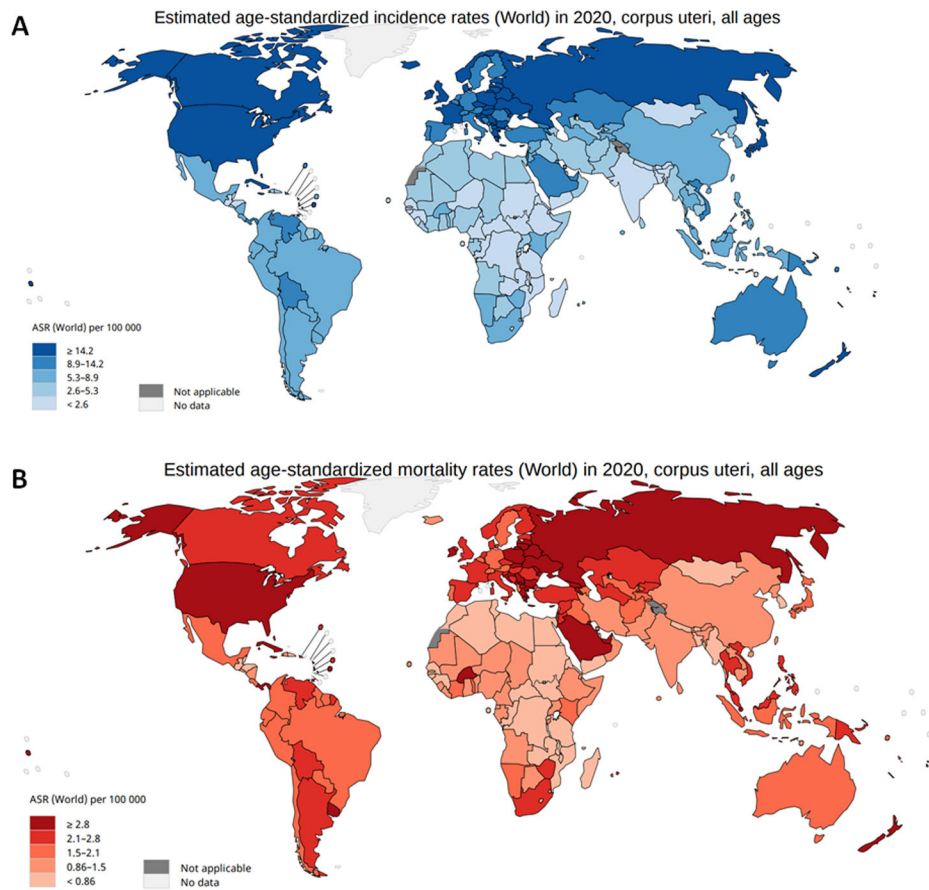
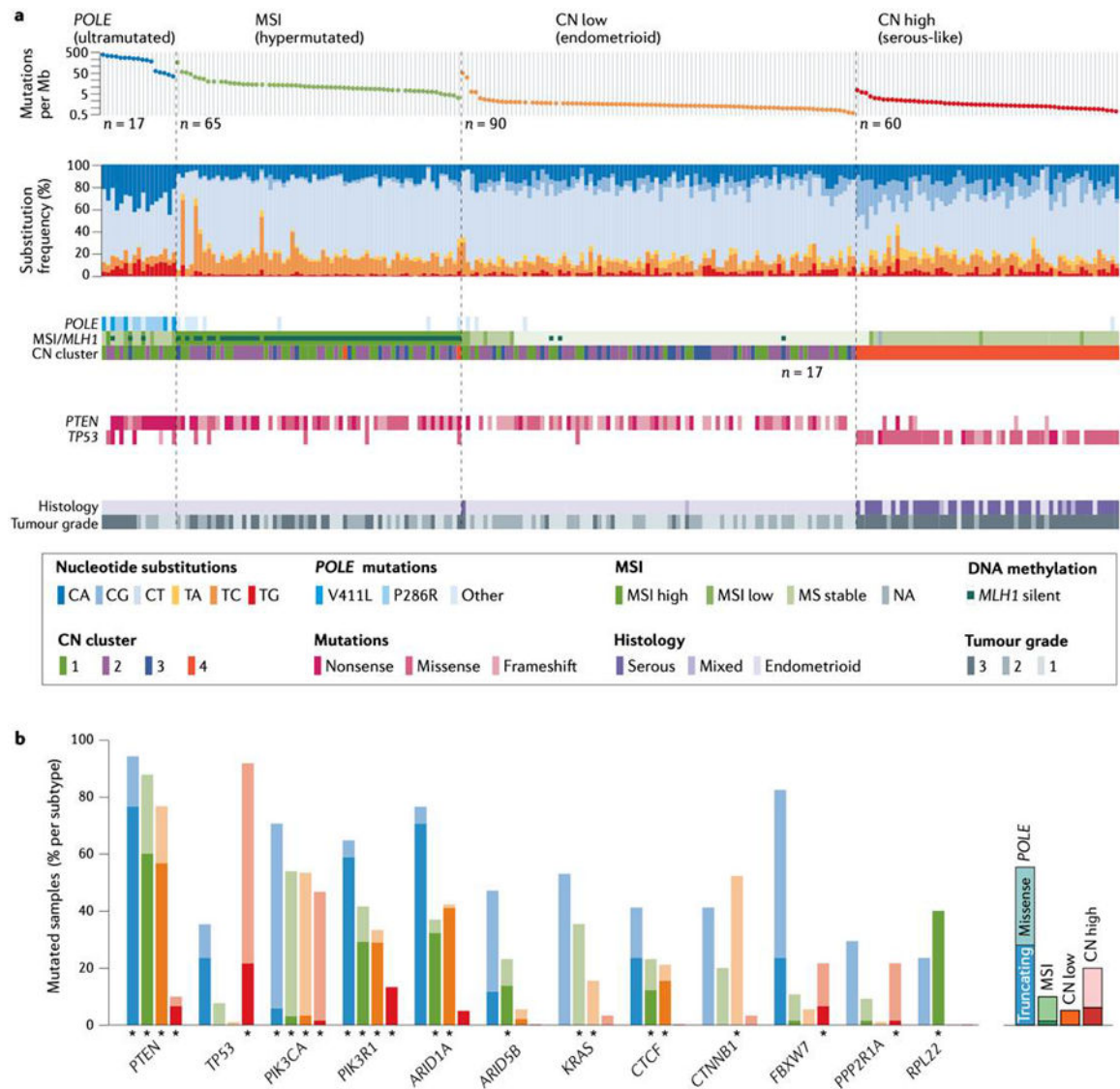


Figure 2. Incidence and mortality of cancers of the corpus uteri.

A| Worldwide incidence of cancers of the corpus uteri. B| Worldwide mortality of cancers of the corpus uteri. Data from the Globocan Registry.

**Figure 3.**

Molecular subgroup of EC. A. Genomic features of the four molecular subgroups of endometrial cancer (EC) identified by The Cancer Genome Atlas project. B. The frequency of mutations in specific EC-associated genes varies between molecular subgroups. MSI, microsatellite instability; Mb, megabase; CN, copy number. From The Cancer Genome Atlas Research Network; Nature 2013;497(7447):67-73. Springer Nature.

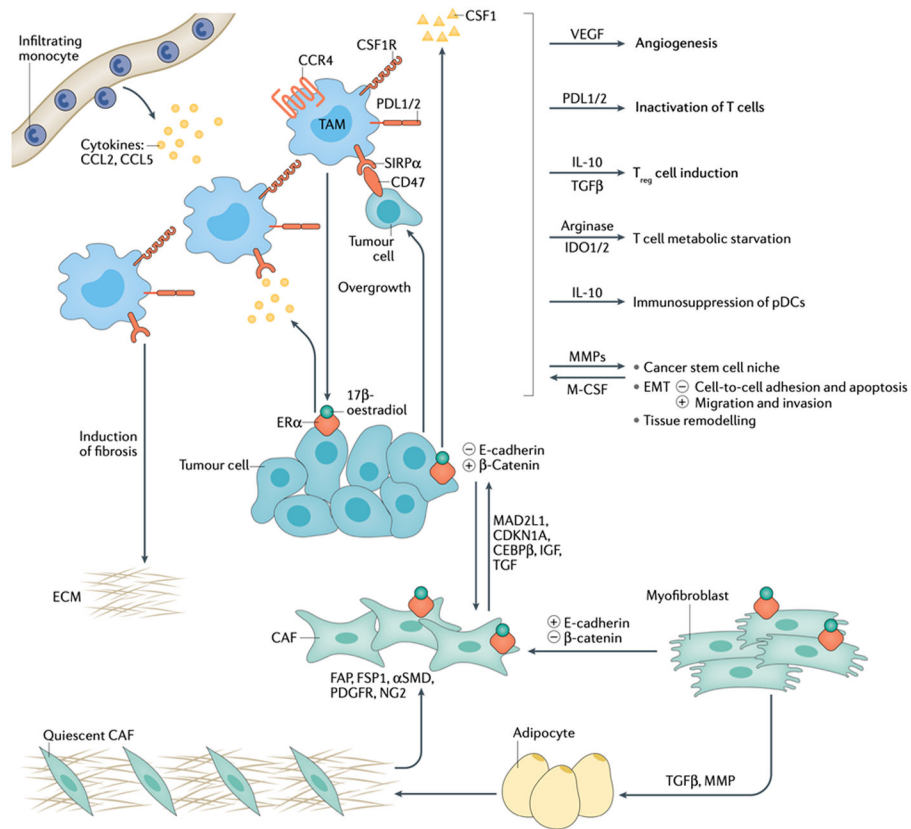


Figure 4. Crosstalk endometrial cancer's cell, TAMs and microenvironment.

Infiltrating monocytes are recruited to tumor foci via chemokines such as CCL2 and CCL5 which induced accumulation of tumour-associated macrophages (TAMs). Tumors produce CSF-1, which acts as both a chemoattractant and a mitogen for circulating monocytes which differentiate into TAMs. TAMs produce angiogenic factors such as VEGF to stimulate tumor-associated blood vessel growth. Through the expression of the immune checkpoint ligands PD-L1/2 and secretion of immunosuppressive factors like prostaglandins, TAMs create an immunosuppressive environment by acting on T cells. Reciprocally, TAMs remodel the extracellular matrix via matrix metalloproteases (MMPs) to create an environment that is a niche for cancer stem cells and conducive for the epithelial-mesenchymal transition (EMT), which leads to metastasis. Amino acid metabolism in TAMs causes metabolic starvation of T cells via IDO1/2 pathway. IL-10 and TGFβ secreted by TAMs promote regulatory T cells (Treg) activity, leading to immunosuppression. Fibroblasts and myofibroblasts, activated by the binding 17-β-estradiol and its receptor ERα, secrete cell-cycle-related proteins (MAD2L1, CDKN1A and CEBPβ) and growth factors (IGF and TGF), leading to EMT, which reduces cell-cell adhesion and triggers the ability of cells to escape from apoptosis, migrate and invade. The contemporary loss of E-cadherin and the up-regulation of β-catenin drive the EMT process leading to the alteration of the endometrial architecture and the subsequent multistep process towards endometrial cancer (EC). Fibroblasts and myofibroblasts act as sentinel and amplifier of estrogens on the neighboring endometrium. They are characterized by an opposite expression of E-cadherin/β-catenin compared to the epithelium.

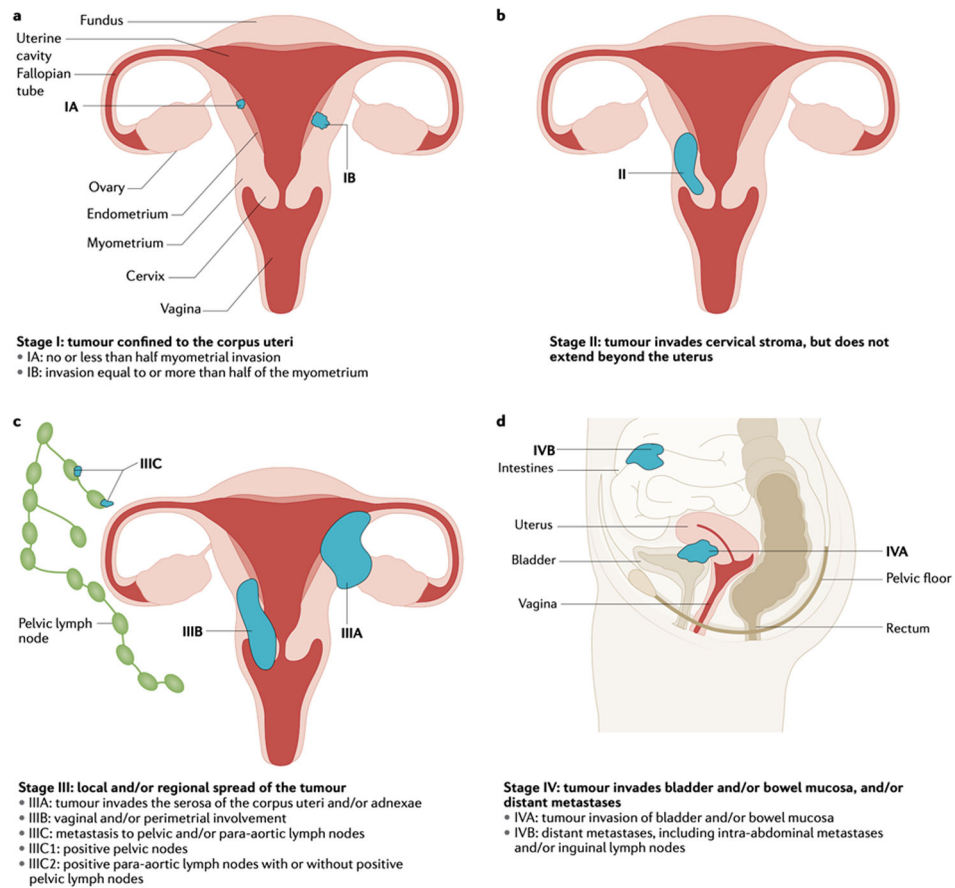


Figure 5. Staging of endometrial cancer.

Endometrial cancer is staged according to 2009 International Federation of Gynecology and Obstetrics (FIGO) criteria. This staging system comprises four stages (I-IV): tumour limited to the corpus uteri (Stage I; panel a), tumor invasion of cervical stroma but confined to the uterus (stage II; panel b), local and/or regions tumor spread (stage III; panel c) and tumour invasion of bladder and/or bowel mucosa and/or distant metastases (stage IV; panel d).

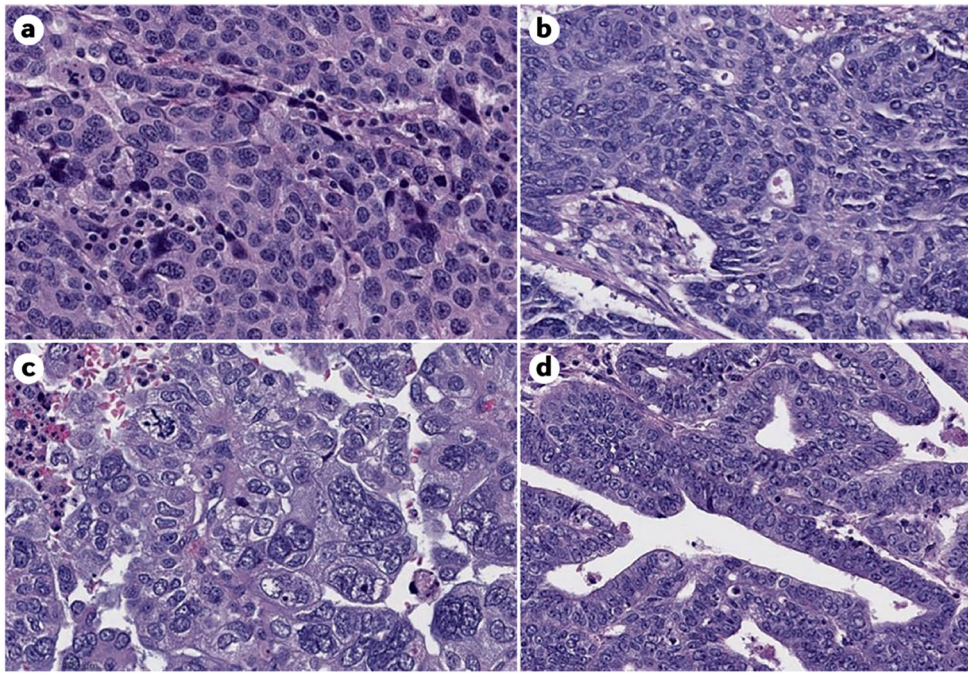


Figure 6. Histological features of endometrial cancer.

A. POLE ultramutated. B. Microsatellite Instability High. C. Copy number high. D. Copy number low. Image credit to Dr. Lora H. Ellenson, Chief Attending, GYN pathology.

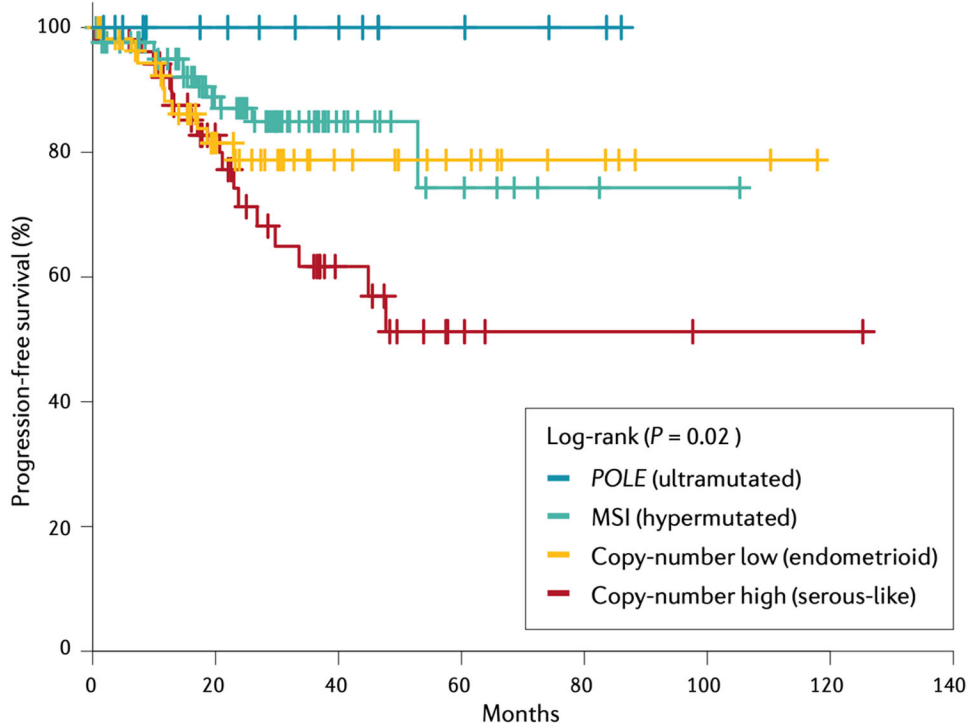


Figure 7. Progression-free survival of EC.

Survival varies according to the molecular subtype of endometrial cancer (EC). Copy-number high EC is associated with the poorest prognosis out of all subtypes, whereas the ultramutated subtype is associated with high survival. Adapted from From The Cancer Genome Atlas Research Network; Nature 2013;497(7447):67-73. Springer Nature.

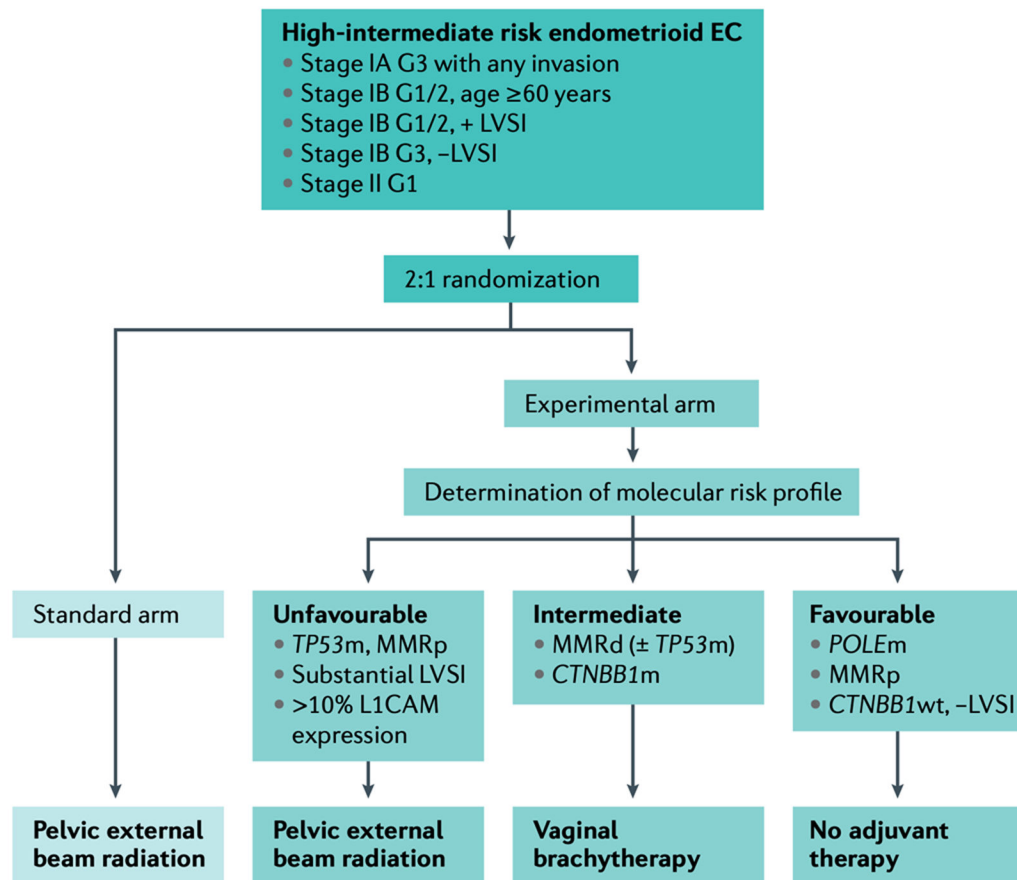


Figure 8. PORTEC-4a Trial Schema.

This was a multicenter randomized phase III trial in high-intermediate risk endometrial cancer investigating the role of an integrated clinicopathological and molecular risk profile to determine adjuvant management with options of no adjuvant therapy, vaginal brachytherapy, or external-beam radiotherapy-based profile compared to standard adjuvant vaginal brachytherapy. G1: Grade 1; G2: Grade 2; G3: Grade 3; LVSI: lymphovascular space invasion; POLEm: POLE mutant; MMRp: mismatch repair proficient; wt: wildtype; MMRd: mismatch repair deficient; CTNBB1m: *CTNBB1* mutant; TP53m: *TP53* mutant