



Endometrial cancer: A Society of Gynecologic Oncology evidence-based review and recommendations: Part I

Renata Urban^{a,1,*}, Tara Castellano^b, Kemi Doll^{a,1}, Deborah DeLair^c, Jason Wright^d, Ramez Eskander^e, Shannon Westin^f, Matthew Powell^g, Amaranta Craig^h, Whitfield Growdonⁱ, Fernanda Musa^j, Marilyn Huang^k

^a Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Washington School of Medicine, Seattle, WA, USA

^b Department of Gynecologic Oncology, Louisiana State University Health Sciences Center, New Orleans, LA, USA

^c Department of Pathology, New York University Langone Health, New York, NY, USA

^d Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY, USA

^e Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Diego, San Diego, CA, USA

^f Division of Surgery, Department of Gynecologic Oncology and Reproductive Medicine, MD, Anderson, Cancer Center: Houston, TX, USA

^g Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Washington University School of Medicine; Siteman Cancer Center, St. Louis, MO, USA

^h Presbyterian Medical Group, Albuquerque, NM, USA

ⁱ Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, NYU Langone Health, New York, NY, USA

^j Providence Swedish Cancer Institute, Seattle, WA, USA

^k University of Virginia School of Medicine, Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, Charlottesville, VA, USA

¹ Seattle Cancer Care Alliance, Seattle, WA, USA

HIGHLIGHTS

- Incidence and mortality of endometrial cancer are rising.
- In postmenopausal bleeding, endometrial sampling detects endometrial cancer.
- Primary surgical management with minimally invasive staging is recommended.
- 2009 and 2023 WHO staging systems, including molecular assessment, should be used.
- Early-stage disease should be treated after pathologic and molecular assessment.

ARTICLE INFO

Article history:

Received 9 February 2026

Received in revised form 20 March 2026

Accepted 7 April 2026

Available online 27 April 2026

Keywords:

Endometrial cancer

Surgery

Molecular pathology

Surveillance

Chemotherapy

ABSTRACT

Introduction. In the time since the last Clinical Practice Committee review of treatment of women with endometrial cancer in 2021, the field of gynecologic oncology has seen significant changes in endometrial cancer from understanding risk factors, addition of molecular staging, and expanded use of maintenance and targeted therapies. Despite these advances, the incidence of endometrial cancer as well as the deaths attributable to the disease continued to rise. Fortunately, since then, there has been progress in the treatment of patients with endometrial cancer, including increased utilization of molecular pathology, greater understanding of genetic predisposition, enhanced methods for lymph node assessment, a broader understanding of the efficacy of radiation and chemotherapy, and a more efficient approach to survivorship and surveillance. The purpose of this document is to present a comprehensive review of this progress.

Manuscript development process. The authors reviewed the available evidence, contributed to the development of this manuscript, provided critical review of the guidelines, and finalized the manuscript recommendations. The review was also presented to and approved by the Society of Gynecologic Oncology (SGO) Clinical Practice Committee, Document Review Panel, and the Board of Directors prior to submission for publication. The recommendations for this manuscript were developed by a panel of gynecologic oncologists who were members of the SGO Clinical Practice Committee and subject matter experts. Panelists reviewed and considered evidence from current uterine cancer literature. The terminology used in these guidelines was adopted from the ASCCP management guidelines [1] using a two-part rating system to grade the strength of recommendation and quality of evidence (Table 1). The rating for each recommendation is given in parentheses.

© 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

* Corresponding author.

E-mail address: urbanr@uw.edu (R. Urban).

Contents

1.	Clinical considerations and recommendations.	17
1.1.	Risk factors for endometrial cancer (EC)	17
1.1.1.	Clinical question 1	17
1.2.	Hormonal and clinical factors.	17
1.3.	Genetic, population/environmental, and unexplained factors	18
2.	Presentation, diagnostic approach and clinical considerations.	18
2.1.	Clinical question 1.	18
2.1.1.	Recommendation 1.1	18
2.1.2.	Recommendation 1.2	18
2.1.3.	Recommendation 1.3	18
2.1.4.	Literature review	18
2.2.	Clinical question 2.	18
2.2.1.	Recommendation 2.1	19
2.2.2.	Recommendation 2.2	19
2.2.3.	Literature review	19
2.3.	Clinical question 3.	19
2.3.1.	Recommendation 3.1	19
2.3.2.	Literature review	19
2.4.	Clinical question 4.	19
2.4.1.	Recommendation 4.1	19
2.4.2.	Literature review	19
2.5.	Clinical question 5.	19
2.5.1.	Recommendation 5.1	19
2.5.2.	Recommendation 5.2	19
2.5.3.	Literature review	19
3.	Surgical approach	19
3.1.	Clinical question 1.	19
3.1.1.	Recommendation 1.1	19
3.1.2.	Literature review	20
3.2.	Clinical question 2.	20
3.2.1.	Recommendation 2.1	20
3.2.2.	Literature review	20
3.3.	Clinical question 3.	20
3.3.1.	Recommendation 3.1	20
3.3.2.	Recommendation 3.2	20
3.3.3.	Literature review	20
3.4.	Clinical question 4.	20
3.4.1.	Recommendation 4.1	20
3.4.2.	Literature review 4.2	20
3.5.	Clinical question 5.	21
3.5.1.	Recommendation 5.1	21
3.5.2.	Literature review	21
3.6.	Clinical question 6.	21
3.6.1.	Recommendation 6.1	21
3.6.2.	Literature review	21
3.7.	Clinical question 7.	21
3.7.1.	Recommendation 7.1	21
3.7.2.	Literature review	21
4.	Staging, Histology and Molecular Pathology	21
4.1.	Clinical question 1.	21
4.1.1.	Recommendation 1.2	21
4.1.2.	Literature review	21
4.2.	Clinical question 2.	22
4.2.1.	Recommendation 1.3	22
4.2.2.	Literature review	22
4.3.	Clinical question 3.	22
4.3.1.	Recommendation 3.1	22
4.3.2.	Literature review	22
5.	Adjuvant therapy: early stage EC	22
5.1.	Clinical question 1.	22
5.1.1.	Recommendation 1.1	22
5.1.2.	Recommendation 1.2	22
5.1.3.	Recommendation 1.3	22
5.1.4.	Literature review	22
5.2.	Clinical question 2.	22
5.2.1.	Recommendation 2.1	22
5.2.2.	Recommendation 2.2	22
5.2.3.	Recommendation 2.3	22
5.2.4.	Literature review	22

CRedit authorship contribution statement	23
Disclaimer	23
Declaration of competing interest.	23
Acknowledgement	23
References	24

A writing committee consisting of Society of Gynecologic Oncology member volunteers and invited clinical content experts was convened to develop this evidence-based review. The manuscript was organized around select clinical questions addressing the diagnosis and management of endometrial cancer. For each clinical question, a comprehensive review of the medical literature was performed to identify relevant clinical trials, observational studies, and existing guidelines. Evidence pertaining to disease biology, therapeutic targets, clinical efficacy and safety were reviewed by the committee and recommendations formulated through consensus. Each recommendation is followed by a focused literature review summarizing the supporting evidence.

1. Clinical considerations and recommendations

1.1. Risk factors for endometrial cancer (EC)

1.1.1. Clinical question 1

What factors should be considered when discussing increased risk of developing EC and how should these factors affect clinical management?

Table 1
Rating the recommendations.

Strength of recommendation	
A	Good evidence for efficacy and substantial clinical benefit support recommendation for use
B	Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use
C	Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds
D	Moderate evidence for lack of efficacy or adverse outcome supports a recommendation against use
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use
Quality of evidence	
I	Evidence from at least one randomized, controlled trial
II	Evidence from at least one clinical trial without randomization, from cohort or case-controlled observational studies (preferably from more than 1 institution), or from multiple time-series studies, or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
Terminology used for recommendations	
Recommended	Good data to support use when only one option is available
Preferred	Option is the best (or one of the best) when there are multiple options
Acceptable	One of multiple options when there are either data indicating that another approach is superior or when there are no data to favor any single option
Not recommended	Weak evidence against use and marginal risk for adverse consequences
Unacceptable	Good evidence against use

Ratings adopted from the ASCCP Management Guidelines: Massad LS, Einstein MH, Huh WK, et al. 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol* 2013;121 (4):829–46. <https://doi.org/10.1097/AOG.0b013e31828883a4>.

1.1.1.1. Recommendation 1.1. Providers should assess established hormonal (AIII), clinical (AII), genetic (AII), and population/environmental (AII) risk factors for EC and tailor management accordingly.

1.1.1.2. Recommendation 1.2. Routine endometrial biopsy and/or transvaginal ultrasound (TVUS) are not recommended for patients taking menopausal hormone therapy or tamoxifen (AII).

1.1.1.3. Recommendation 1.3. Non-white racial groups are at higher risk of developing non-endometrioid EC and endometrial sampling is recommended (AII).

1.1.1.4. Recommendation 1.4. For individuals with a personal history of definitive pelvic radiation, routine screening outside of transvaginal ultrasound and endometrial sampling is not recommended. However, one should keep a high index of suspicion for metachronous EC and uterine sarcoma (CIII).

1.1.1.5. Recommendation 1.5. Individuals with newly diagnosed EC should have a hereditary cancer risk assessment (AII).

1.1.1.6. Recommendation 1.6. In premenopausal patients with Cowden or Lynch Syndrome, TVUS is not recommended for EC screening but may be considered in select post-menopausal patients. Endometrial sampling every 1–2 years starting at age 30–35 is recommended with the option for risk-reducing hysterectomy upon completion of childbearing or individualized by risk and specific pathologic variants (PVs). For those younger than 30–35 years, education on menstrual regularity is recommended (BII).

1.1.1.7. Recommendation 1.7. Consideration of hysterectomy in a *BRCA1* PV carriers at the time of risk-reducing surgery should be discussed. Hysterectomy can reasonably be offered due to the emerging association of *BRCA* PVs with uterine cancers and the implications of hormone replacement therapy selection (BII).

1.1.1.8. Literature review. The incidence of EC is increasing across all measured racial and ethnic groups in the United States (US). Although declining hysterectomy rates and rising obesity prevalence are likely to contribute, they do not fully account for the increased rates, especially with non-endometrioid EC [1]. Identified EC risk factors across several case-control and longitudinal cohort studies can be organized into hormonal (unopposed estrogen exposure) clinical factors, non-hormonal clinical factors, genetic factors, environmental factors and unexplained factors.

1.2. Hormonal and clinical factors

Unopposed estrogen exposure is a risk factor for endometrial cancer. Endogenous sources include chronic anovulation, excessive peripheral conversion of androgens to estrone in adipose tissue in patients who are overweight or obese and estrogen producing tumors. Increasing obesity is of concern due to the rising impact on the incidence and severity of EC. In the US, from 1999 to 2020, the prevalence of obesity increased from 30% to 41% and, in that same time frame, class 3 obesity nearly doubled from 5% to 10% [2]. Reproductive factors such as nulliparity, infertility, early menarche or late menopause similarly fall

within this construct. Exogenous sources such as hormone therapy and medications, like tamoxifen, increase EC risk [3]. EC risk with increased BMI (>25), nulliparity, estrogen-only hormone therapy for more than 5 years, and tamoxifen use are all secondary to increased estrogen exposure. Tamoxifen, specifically, has been associated with risk ratios of 1.5 to 4 for developing endometrioid and carcinosarcoma EC and even higher for rare uterine sarcomas [4]. Diabetes and hypertension are independent risk factors whose mechanisms are not completely understood [5]. A personal history of definitive pelvic radiation for treatment of non-uterine cancers increases the risk for metachronous EC and uterine sarcoma. If diagnosed, these cancers tend to be of aggressive histology and have been shown to portend a worse outcome [6].

1.3. Genetic, population/environmental, and unexplained factors

Most hereditary EC are due to Lynch Syndrome (LS), an autosomal dominant condition caused by germline PVs in MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, or deletions in *EPCAM*. The lifetime risk of EC in individuals with LS is 40% to 60% varying by specific PV and may equal or exceed the lifetime risk of colon cancer in these individuals [7]. Cowden Syndrome is a rare autosomal dominant condition with majority of cases arising from a germline PV in *PTEN*. These patients carry a 5–10% risk of EC and 25–50% risk of breast cancer [8]. Patients with Lynch or Cowden syndrome electing for risk-reducing hysterectomy, an endometrial biopsy should be considered as part of surgical planning. Individuals with *BRCA 1/2* PVs have an increased but low risk of endometrial cancer, estimated at 3.4% and 1.6% respectively [9,10]. PV carriers are also subject to modifiable factor risks akin to the general population.

One study showed that rurality was not associated with differential histology type but was associated with slightly higher-grade EC [11]. However, individuals who reside in areas of high social vulnerability, determined by the CDC social vulnerability index, which includes socioeconomic, housing, transportation, and demographic factors, are more likely to be diagnosed with non-endometrioid compared to endometrioid histology [12]. Environmental factors such as hair products, specifically heavy and long-term exposure to chemical hair relaxers or straighteners, are associated with EC risk [13].

Analyses from the Surveillance, Epidemiology, and End Results (SEER) (2000–2015) show that EC incidence is rising most rapidly among non-White populations (non-Hispanic Black (NHB), Hispanic, and Asian/Pacific Islander (API)) [14]. NHB individuals have the highest incidence of non-endometrioid EC in the US (26 per 100,000 person-years), compared to non-Hispanic White (NHW) (11.4), Hispanic (10.1), and API (7.5) patients. Among those diagnosed with EC, 43% of NHB, 23% of Hispanic, 20% of API, and 18% of White individuals will have a non-endometrioid histologic type [14]. Compared to NHW patients, APIs were younger at diagnosis (57 vs 62 years old), more often serous or sarcoma histologic subtypes and advanced stage in a National Cancer Database (NCDB) analysis (2004–2017) [15]. In EC patients <50 years old, the largest increases occurred among American Indian/Alaska Native (4.8) followed by NHB (3.3), Hispanic/Latina (3.1), and API (2.4) compared to White (0.9) individuals [1]. These broad racial categories mask important variation, as analyses of disaggregated US Black, Asian, and Native Hawaiian/Pacific Islander populations demonstrate differences in histologic subtype distribution not captured with aggregated racial classifications [1,14]. Established clinical and hormonal risk factors are consistent across groups, indicating unidentified factors driving racial and ethnic risk difference [16,17]. Even when controlling for stage, histology, and socioeconomic factors, NHB EC patients continue to have worse EC outcomes when compared to their NHW counterparts [18]. This suggests that there are yet to be defined hereditary, genetic, and epigenetic factors at odds with complex healthcare and systemic factors. The 2024 changes to US governmental definitions of race and ethnicity, included the new classification of Middle Eastern/North African (MENA) race, and the choice to have a single race or ethnicity question may change EC estimates by race and ethnicity in the future [19].

2. Presentation, diagnostic approach and clinical considerations

2.1. Clinical question 1

How should patients with postmenopausal bleeding (PMB) be evaluated?

2.1.1. Recommendation 1.1

PMB should be promptly evaluated by TVUS and endometrial sampling (All).

2.1.2. Recommendation 1.2

If bleeding persists or recurs after endometrial biopsy, hysteroscopy with dilation and curettage should be performed (All).

2.1.3. Recommendation 1.3

For individuals with poor endometrial visibility (i.e., fibroids) or increased risks of non-endometrioid EC, tissue diagnosis is recommended. Black individuals should be carefully counseled about increased risks of false negative TVUS results (All).

2.1.4. Literature review

More than 90% of individuals diagnosed with EC present with abnormal or PMB, although only 10% of individuals with PMB will have EC [20]. Patients who present with bleeding symptoms may not always identify as 'postmenopausal', as menopausal symptoms can persist for years after cessation of menses. Additionally, recognition of PMB may vary across populations, contributing to delays in evaluation. In patients with PMB who have risk factors for non-endometrioid histology (such as advanced age, prior tamoxifen exposure, or higher-risk racial or ethnic background), or in whom the endometrium cannot be adequately visualized, reliance on ultrasound alone may be insufficient and tissue diagnosis should be strongly considered.

Given the increasing risk of non-endometrioid histology and advanced disease in certain populations, emphasis should be placed on ruling out EC in individuals with bleeding symptoms and additional risk factors. Black and Hispanic individuals are more likely to undergo menopause at younger ages and experience symptoms for twice as long (10 or more years) than White, Chinese and Japanese individuals [21]. In a cross-sectional survey study of people assigned female at birth, 37% did not identify PMB as a symptom of EC and only 59% would notify their provider after one bleeding episode [22]. Among Medicare patients aged >65 years, clinicians were less likely to identify bleeding among Black individuals as post-menopausal despite their older age [23].

Individuals with PMB require further evaluation with imaging and tissue sampling. While prior guidelines have relied on the reported 99% negative predictive value of the 4 mm endometrial thickness (ET) threshold on TVUS [24], more recent work has demonstrated less accuracy of this triage pathway [25,26]. If TVUS does not or cannot clearly visualize the entire endometrium, ET result should not be used to assess EC risk. A prospective clinical cohort study evaluated a risk-based approach to assess diagnostic tests for abnormal uterine bleeding (AUB) and PMB. The authors found the most efficient strategy was to perform a biopsy in all patients age greater than 60 years and in patients less than 60 years with an ET >4 mm [25]. Another study examined TVUS ET 4 mm or greater threshold as a screening tool for PMB. The study found TVUS ET screening missed almost 5 times more EC cases in Black patients compared to White patients [26]. Increasing evidence supports endometrial sampling as the optimal first-line diagnostic test for EC in patients with PMB.

2.2. Clinical question 2

How should AUB in premenopausal individuals be evaluated?

2.2.1. Recommendation 2.1

In the absence of other explanatory features (such as pregnancy, leiomyomas/polyps, ovulatory dysfunction, medication use or bleeding disorders), premenopausal individuals with AUB should undergo biopsy or hysteroscopy with sampling to rule out EC (AII).

2.2.2. Recommendation 2.2

Clinicians should obtain detailed menstrual histories, as the existence of perimenopausal symptoms may mean patients do not identify bleeding as abnormal, regardless of advancing age (BIII).

2.2.3. Literature review

Recent studies have demonstrated significant increase in EC diagnoses, with a disproportionate rise among individuals younger than 50 years old [1]. Given that AUB is common with lower EC risk in premenopausal individuals, young patients are at risk for delayed evaluation and diagnosis. One study found that even with health care access, 36% did not have endometrial sampling for >6 months after AUB presentation [27]. Additionally, individuals with risk factors presenting with AUB often experienced delays in sampling, with some not undergoing biopsy until years after initial TVUS [27]. Risk factors should guide decisions for tissue biopsy or hysteroscopic visualization. TVUS should not be used to triage EC risk in this group, as it has little diagnostic significance. Risk factors for EC among premenopausal individuals presenting with AUB include BMI ≥ 35 kg/m², diabetes, polycystic ovarian syndrome, early menarche and nulliparity [28].

2.3. Clinical question 3

After EC diagnosis is made, who should perform surgery and manage the patient?

2.3.1. Recommendation 3.1

EC patients should be referred to a gynecologic oncologist when possible (BIII).

2.3.2. Literature review

Studies show that patients referred to a gynecologic oncologist were more likely to undergo staging surgery and receive chemotherapy, resulting in improved survival [29]. A 2019 study found that a substantial number of counties across the US lacked access to a gynecologic oncologist. This supports the call for improving access to gynecologic oncology services, especially in rural and underserved geographic areas, to minimize delays in EC care [30]. Prompt referral to gynecologic oncologist remains essential for optimal oncologic outcomes [31].

2.4. Clinical question 4

Are tumor markers and/or imaging necessary in the work-up of EC, and if so, in which patients?

2.4.1. Recommendation 4.1

Imaging after a diagnosis of a grade 1 or 2 endometrioid EC can be individualized based on duration and severity of patient symptoms and patient comorbidities (AIII). CT imaging should be performed for patients with high-risk disease (grade or histology) or clinical concern for metastatic disease, and serum CA-125 may be considered (CIII).

2.4.2. Literature review

Currently, there are no diagnostic or prognostic blood biomarkers in routine clinical use for EC. CA-125 and HE4 are associated with high-grade or advanced EC but may be falsely elevated, such as HE4 in renal dysfunction; results should be interpreted in clinical context [32,33].

Most patients with clinical stage I disease (TVUS imaging without evidence of extrauterine disease, normal pelvic exam) and grade 1–2 endometrioid histology do not require further workup. However, patients with delayed diagnosis or prolonged symptoms prior to evaluation are at risk of extrauterine disease, and imaging should be considered [34]. In patients desiring future fertility, imaging is recommended to rule out myoinvasive disease. Although the data are mixed, patients with BMI > 40 may be at higher risk for failed sentinel lymph node mapping; preoperative imaging may be appropriate to evaluate for lymph node metastases [35,36].

In patients with high-risk histologies (grade 3 endometrioid, serous, clear cell, or carcinosarcoma), imaging and serum tumor markers are indicated prior to surgery. TVUS and pelvic MRI may be used to evaluate the extent of local disease, while CT and PET-CT are typically used to evaluate distant metastases [37,38]. To date, there are no FDA-approved serum or body fluid markers, such as circulating tumor DNA (ctDNA), urine, or cervical vaginal lavage, suitable to detect or screen for early EC. Efforts to utilize urinalysis and vaginal lavage to detect shedding of EC cells are also underway [39]. The field of serum testing for ctDNA and miRNA in solid tumors is rapidly advancing and has shown promising results especially in high-risk, early-stage EC [40].

2.5. Clinical question 5

How should patients considering fertility-sparing options be evaluated?

2.5.1. Recommendation 5.1

Patients desiring fertility sparing treatment should be evaluated by dilation and curettage (D&C with hysteroscopy) (preferred) or endometrial biopsy (AII).

2.5.2. Recommendation 5.2

Pelvic magnetic resonance imaging (MRI) should be performed to assess for myometrial invasion, cervical stromal involvement, lymphadenopathy and any adnexal abnormalities (AII).

2.5.3. Literature review

Fertility-sparing treatment may be considered for select patients with grade 1 endometrioid EC confined to endometrium, following thorough clinical and radiologic evaluation. Histopathologic confirmation, preferably by hysteroscopy with D&C reviewed by gynecologic pathologist, is ideal [17]. Imaging is necessary to verify that disease is limited to the endometrium and to exclude metastatic disease. MRI is the preferred modality for assessing myometrial invasion [41]. Patients should be evaluated for contraindications to medical treatment of EC and pregnancy, with referral to maternal-fetal medicine or reproductive endocrinology if feasible. Tumor assessment should include immunohistochemistry (IHC) for mismatch repair (MMR) proteins and p53. Patients with MMR deficient tumors should undergo *MLH1* hypermethylation testing if indicated, and germline genetic testing should be considered when clinical suspicion for LS remains (i.e. young age, strong family history). Given the poor prognosis associated with p53 abnormalities, and extremely limited data, conservative management should be considered with caution [42].

3. Surgical approach

3.1. Clinical question 1

What is the preferred surgical approach for staging EC?

3.1.1. Recommendation 1.1

Minimally invasive surgical staging is the preferred surgical approach for most EC patients (AI).

3.1.2. Literature review

A randomized controlled trial in the US (GOG LAP2) as well as an international trial (The Laparoscopic Approach to Cancer of the Endometrium, LACE) both demonstrated lower rates of postoperative complications and no difference in survival for minimally invasive surgery (MIS) compared to laparotomy [43–45] in patients with uterine-confined EC. Robotic-assisted surgery offers similar short term perioperative outcomes and survival to conventional laparoscopy [46–48]. A prospective study examining patient-reported outcomes and quality of life for patients who underwent surgery for EC reported that outcomes were similar for laparoscopic and robotic-assisted surgery and that both minimally invasive modalities were associated with less pain and improved quality of life compared to laparotomy [49]. A recent meta-analysis demonstrated the oncologic safety of MIS for high-risk endometrial cancer [50]. Appropriate patient selection remains important, as uterine size, extent of disease, and ability to remove the specimen may influence surgical approach, although evidence regarding the clinical impact of these factors is limited.

3.2. Clinical question 2

What is the optimal strategy for nodal assessment?

3.2.1. Recommendation 2.1

Both sentinel lymph node (SLN) mapping, and an algorithm-based pathologic approach are acceptable alternatives to complete lymphadenectomy (LAD) in EC (All).

3.2.2. Literature review

The benefit of nodal assessment for patients with apparent early-stage EC is to provide prognostic information and to guide adjuvant therapy [51]. Although two randomized controlled trials of LAD failed to show a survival benefit in patients who underwent LAD [52,53], multiple observational studies support nodal assessment in improving staging accuracy and adjuvant therapy management. Surgical staging with lymph node assessment is recommended.

SLN mapping relies on injection of a radiotracer, fluorescent dye or colorimetric substance into the cervix with subsequent identification of the first or sentinel draining nodal basins. Ultra-staging of the sentinel nodal specimen should be performed. Depending on pathology expertise, ultra-staging can be limited to those SLNs in which micro- or metastatic disease is not identified [54]. Compared to LAD, SLN mapping is associated with decreased perioperative morbidity, blood loss and lymphedema [55,56]. If SLN mapping fails to identify a node, a side-specific LAD should be performed [57]. Alternatively, frozen section, utilizing an algorithm-based pathologic assessment may guide need for LAD. All grossly abnormal nodes should be removed. The FIRES trial examined SLN mapping followed by complete pelvic LAD in 385 patients across 10 centers. Mapping was successful in 86% of study participants with a false negative rate of 2.8% [58].

SLN mapping has also been validated in patients with high-risk histologic tumor subtypes including grade 3 endometrioid tumors, serous, clear cell and carcinosarcomas [59,60].

SLN mapping identifies a comparable rate of lymph node metastases with fewer nodes removed and no adverse impact on survival [61,62].

An algorithm-based approach relies on pathologic characteristics to identify patients at higher risk for nodal disease who should undergo intraoperative lymph node assessment. Investigators at the Mayo Clinic found that patients with grade 1–2 endometrioid tumors, <2 cm in size, and ≤50% myometrial invasion on frozen section were at low risk of lymph node metastasis and could safely omit LAD [63]. Patients with tumors with any of these characteristics were deemed high risk and recommended for pelvic and para-aortic LAD. The availability of accurate pathologic risk categorization intraoperatively prevents broader application of this algorithm.

3.3. Clinical question 3

What factors should be evaluated when counseling about ovarian preservation?

3.3.1. Recommendation 3.1

Ovarian preservation may be considered in premenopausal patients with low-grade, early-stage EC and normal adnexa without extrauterine disease (CII).

3.3.2. Recommendation 3.2

Risk-reducing hysterectomy with bilateral salpingectomy (BS) +/- oophorectomy is recommended after appropriate counseling regarding ovarian cancer risk based on specific variant for individuals with Lynch Syndrome (LS) who have completed childbearing, typically between ages 40–45. For those considering hysterectomy with ovarian preservation, complete salpingectomy is recommended (All).

3.3.3. Literature review

Historically, BSO was routinely performed with hysterectomy during surgical staging to detect occult disease; however, given the potential health risks in premenopausal individuals, this practice has been reevaluated. Analyses from the NCDB and SEER showed no increased mortality with ovarian preservation, a finding supported by a recent meta-analysis [29,30,64,65]. Molecular data can inform decisions around ovarian preservation. In a series of patients < 50 years, 4 of 113 experienced isolated ovarian recurrences; two had high-risk molecular features and two had high-risk pathology [66]. Molecular and pathologic factors help guide ovarian preservation decisions. In premenopausal patients with LS and EC, ovarian preservation should be individualized, with consideration of gene-specific risk, age, and patient preferences.

Following completion of childbearing, patients with LS are advised to consider total hysterectomy with BSO to prevent endometrial and ovarian cancer. In a matched case-control study, patients who underwent prophylactic surgery had no cases of endometrial, ovarian, or primary peritoneal cancer, compared to a 33% incidence of EC and 5% incidence of ovarian cancer in those without risk-reducing surgery [67]. Age and gene-specific counseling should guide recommendations for prophylactic surgery in LS. In the setting of ovarian preservation in these patients, a bilateral salpingectomy should be performed [68].

3.4. Clinical question 4

Should surgical staging be completed in all patients with an incidental diagnosis of EC following hysterectomy for another indication?

3.4.1. Recommendation 4.1

Patients with incidental EC after hysterectomy should have an extrauterine risk assessment incorporating clinic-pathologic and molecular subtype. Treatment plans can be individualized based on risk profile and potential morbidity of a second surgery (All).

3.4.2. Literature review 4.2

Following incidental EC diagnosis, the need for re-staging surgery should be individualized based on pathologic factors. A second surgery carries added morbidity, including a 25–50% risk of lymphedema, as sentinel lymph node mapping is no longer feasible [36]. Patients with low-risk features (i.e. grade 1–2, <50% myometrial invasion, tumor size <2 cm) may avoid further surgery, while high-risk cases may warrant staging, especially if surgical findings impact treatment planning [38]. Although age increases extrauterine risk, comorbidities and fitness should guide decisions. Molecular profile may also inform staging needs. Additional diagnostic studies can help assess for extrauterine disease. PET/CT offers greater accuracy than CT alone in detecting lymph node and distant metastases [69].

3.5. Clinical question 5

Is there a role for maximal cytoreductive effort in advanced EC?

3.5.1. Recommendation 5.1

Maximal cytoreduction surgery (CRS) is the preferred approach for patients with advanced stage EC who undergo primary surgery (All).

3.5.2. Literature review

While only 10–15% of EC patients will present with extrauterine disease, they account for the majority of disease-related deaths [70]. A meta-analysis examining primary CRS for advanced stage EC found 75% reached <1 cm residual disease, and no gross residual disease in 52% of patients [71]. Stage IV patients were less likely to achieve either threshold compared to stage III patients and suboptimal cytoreduction (≥ 1 cm versus <1 cm residual tumor) was associated with worse PFS (HR = 2.55; 95% CI, 1.93–3.37) and overall survival (OS) (HR = 2.62; 95% CI, 2.20–3.11). Patients with any residual disease had worse PFS (HR = 2.16; 95% CI, 1.45–3.21) and OS (HR = 2.57; 95% CI, 2.13–3.10) compared to no gross residual disease [71]. These findings highlight the importance of maximal primary CRS for patients with advanced EC.

3.6. Clinical question 6

Is there a role for neoadjuvant chemotherapy (NACT)?

3.6.1. Recommendation 6.1

NACT can be considered in patients with metastatic EC in which optimal cytoreduction is not feasible (BII).

3.6.2. Literature review

NACT followed by interval cytoreductive surgery (ICS) for EC has emerged as an alternative to primary CRS [72–74]. The scarcity of robust comparative data makes comparisons between NACT and primary CRS in advanced EC challenging, as most available studies are retrospective and predate modern systemic therapies. One database study evaluating patients with stage IV EC found 18.2% received NACT, 28.1% no treatment and 53.6% primary CRS. NACT was associated with less perioperative medical complications and similar survival as patients undergoing primary CRS [74]. A systematic review demonstrated similar optimal cytoreduction rates between patients who undergo primary CRS and interval CRS, but pooled data suggest improved rates of optimal CRS for NACT+ICS compared to primary CRS (81.9% vs 51.5%) [72,75]. However, one large retrospective analysis found that patients treated with NACT had superior survival in the first months after surgery, but, with longer follow-up, survival was superior with primary cytoreduction [73]. The decision to utilize NACT versus primary cytoreduction should be individualized. For patients treated with NACT, every effort should be made to perform interval cytoreductive surgery with maximal effort.

3.7. Clinical question 7

What are the treatment options for patients who are not candidates for surgical staging?

3.7.1. Recommendation 7.1

EC patients that are not surgical candidates should be evaluated for radiation. Patients with high-risk or advanced EC may be considered for systemic therapy (All).

3.7.2. Literature review

Patients not able to undergo primary surgical evaluation should have imaging to guide treatment recommendations. Primary radiation, including brachytherapy, is most effective for FIGO 2009 stage I–II disease [76,77]. For extrauterine disease, especially with high-risk histology,

palliative chemotherapy or targeted therapies may be considered. Care should include shared decision-making and palliative support.

4. Staging, Histology and Molecular Pathology

4.1. Clinical question 1

How should the new International Federation of Gynecology and Obstetrics (FIGO) staging system be applied in clinical practice?

4.1.1. Recommendation 1.2

It is acceptable to incorporate elements of both the FIGO 2009 and 2023 staging systems in assessing a newly diagnosed EC. This can include assigning a stage based on the 2023 system or including the molecular classification as complementary information to the FIGO 2009 staging. At a minimum, assessment of MMR and p53 IHC is appropriate (CIII).

4.1.2. Literature review

Historically, EC was classified as Type 1 or 2 in a binary classification system thought to correlate with clinical behavior. Although this system appears straightforward, its clinical application is challenging due to the morphological heterogeneity, particularly in high-grade ECs, which leads to diagnostic ambiguity and poor interobserver reproducibility.

The Cancer Genome Atlas (TCGA) data categorized ECs based on tumor mutational burden (TMB), the level of copy number variations (CNV), and microsatellite instability (MSI). Using these parameters, tumors clustered into 4 molecular subgroups including *POLE*-mutated (ultra-mutated), MSI (corresponding to mismatch repair protein-deficient or dMMR, hypermutated), copy number low (CNL, endometrioid-like), and copy number high (CNH, serous-like) [78]. Approximately 10% of ECs are *POLE*-mutated and carry an excellent prognosis. The MSI/dMMR subgroup comprises 25–30% of cases, while CNH and CNL account for 15% and 50% respectively. The CNH subgroup includes most serous carcinomas and about 25% of grade 3 endometrioid tumors. HER2 amplification occurs almost exclusively in the CNH subgroup and in 15–23% of tumors [78]. Classifying ECs based on molecular profile rather than morphology correlated with progression free survival (PFS). Unfortunately, comprehensive TCGA molecular testing is not feasible for routine clinical use due to its complexity and cost.

Building off the TCGA, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) system was developed using clinically applicable methods. This system classified ECs into 4 molecular subgroups: dMMR, p53 aberrant, *POLE* hypermutated and nonspecific molecular profile (NSMP) [79,80]. In both the development and validation cohorts, hierarchical testing began with IHC for MMR; if MMR was intact, then p53 IHC was performed. *POLE* sequencing was done only in tumors that were MMR intact and normal p53 expression. Tumors with no abnormality in any of the three markers were classified as NSMP. Studies of histologic subtypes not included in TCGA (clear cell carcinoma, carcinosarcoma, and undifferentiated carcinoma) are amenable to classification into these molecular subgroups and show similar associations with prognosis [81–84]. A small proportion of ECs fall into more than one category, designated as multiple classifiers [85]. For example, in the setting of *POLE*-mutated and dMMR cancers, acquired secondary *TP53* mutations can occur due to their hyper- or ultra-mutated state. Studies have shown that, overall, these tumors show outcomes more similar to the *POLE*-mutated or dMMR subgroups, rather than the aggressive behavior seen in the p53 abnormal group [86,87].

Most treatment data are based on FIGO 2009 staging; therefore, both 2009 and 2023 systems may be used in clinical practice. The 2023 FIGO staging incorporates histologic subtype, extent of lympho-vascular space invasion (LVSI), and molecular characteristics into the staging system to better stratify prognosis for EC [88]. The authors of the FIGO 2023 staging acknowledge that full molecular profiling may not be available in all settings but encourages molecular classification when

possible. The system recommends utilization of IHC markers (p53, MSH6, PMS2) and molecular testing (POLE) to categorize tumors into one of the four subgroups. As current EC treatment recommendations are based off FIGO 2009 staging system, elements of both systems may be incorporated in clinical practice.

4.2. Clinical question 2

What are the current challenges to implement FIGO staging?

4.2.1. Recommendation 1.3

Providers should collect the elements relevant to the updated staging as it will have future treatment implications (CIII).

4.2.2. Literature review

The FIGO 2023 staging system is complex, significantly different from prior, and includes variables with evolving definitions and significant inter-observer variation. For example, FIGO 2023 classifies “substantial” as 5 or more LVSI, while the National Comprehensive Cancer Network (NCCN) utilizes a cutoff of 4 or more, and other classification systems have a cutoff of 3 or more [89]. Molecular classification, especially *POLE* evaluation, is not available in all settings. A recent survey of providers associated with NRG Oncology found that fewer than 25% had access to *POLE* testing. Although molecular classification was identified as very important for treatment planning, cost concerns and lack of prospective data were barriers to testing [90]. National consensus guidelines for treatment have not been adjusted to the new staging system. Time and prospective data are necessary to determine if the new system will inform tailored treatment recommendations [90].

4.3. Clinical question 3

When should microcystic, elongated fragmented (MELF) invasion be assessed?

4.3.1. Recommendation 3.1

Routine assessment for MELF invasion has no clinical implications and is not recommended (BII).

4.3.2. Literature review

MELF pattern of myometrial invasion is a distinct histologic feature occasionally seen in low-grade EC and associated with LVSI and lymph node metastasis. A recent retrospective review of MELF pattern found no independent impact on risk of recurrence in early-stage EC [91].

5. Adjuvant therapy: early stage EC

5.1. Clinical question 1

What is the preferred management for disease confined to the uterus?

5.1.1. Recommendation 1.1

Offering observation to individuals who have undergone appropriate surgical staging and have no residual disease in the uterus at the time of hysterectomy is preferred (AII).

5.1.2. Recommendation 1.2

For individuals whose tumors meet high-intermediate risk pathologic criteria, radiation may be considered (AI).

5.1.3. Recommendation 1.3

TCGA classification or the surrogate ProMisE classification should be considered for all patients with EC beyond FIGO 2009 stage IA grade 1 and 2 EC (AII) as it may impact treatment decisions.

5.1.4. Literature review

Historically, “high-intermediate risk” (HIR) EC (based on age, depth of myometrial invasion and presence of LVSI) had a local recurrence rate of 12–25%. Both PORTEC-1 and GOG 99 demonstrated that external beam pelvic radiation (EBRT) reduced locoregional recurrence in this group but did not improve OS, raising concerns for overtreatment [92,93]. Both trials also reported higher rates of treatment-related toxicity in the radiation arms. PORTEC-2 evaluated the efficacy and toxicity of vaginal brachytherapy (VBT) compared to EBRT in patients with HIR EC [94]. Ten-year survival data showed vaginal control rates of >96% in both arms, with similar rates of isolated pelvic recurrence, distant metastasis, and OS. VBT was associated with less toxicity and improved health-related quality of life compared to EBRT. However, as VBT was associated with worse sexual function compared to age-matched controls and did not improve OS, identifying patients within this group who may safely omit adjuvant VBT is warranted. In an analysis of the PORTEC-1 and -2 evaluating molecular classification, patients with p53abn cancers had significantly improved recurrence free survival with EBRT compared with VBT while dMMR EC had improvement with EBRT but not statistically significant [95]. Patients with NSMP tumors derived similar benefits from EBRT and VBT. *POLE*mut EC patients had excellent outcomes, with no recurrences [95]. PORTEC-4a, an international phase III non-inferiority trial in HIR EC patients compared standard adjuvant VBT to a molecular-integrated risk-based strategy, in which radiotherapy is omitted in favorable risk patients, or escalated to VBT or EBRT in unfavorable risk patients [96]. This molecular risk-guided approach resulted in comparable vaginal control while reducing overtreatment. Risk. EN.10 is a Canadian Cancer Trials Group led phase II trial enrolling early-stage EC by molecular subtype that has evolved into a multi-national collaboration including NRG Oncology (NRG-GY032) [97]. Sub-study A (RAINBO BLUE) will assess patients with *POLE*mut tumors and sub-study B (TAPER) will assess patients with p53wt/NSMP tumors. The primary objective is to estimate 3-year pelvic recurrence rates using de-escalated adjuvant therapy based on molecular subtype.

5.2. Clinical question 2

What is the preferred management for surgically staged uterine confined disease with high-risk features?

5.2.1. Recommendation 2.1

Patients with grade 3 endometrioid histology with high-risk pathologic features with uterine-confined disease should be considered for EBRT to reduce recurrence risk (AII).

5.2.2. Recommendation 2.2

Patients with high grade histology (serous, clear cell, grade 3 endometrioid) and/or adverse pathologic or molecular features may be considered for systemic combination chemotherapy. Volume directed radiation may be considered in addition to chemotherapy (AII).

5.2.3. Recommendation 2.3

Patients with high-risk disease should be considered for enrollment in clinical trials (BII).

5.2.4. Literature review

The optimal management for patients with high-risk disease confined to the uterus remains controversial, as these patients carry a high risk for recurrence. Prior studies combined these patients with stage II or III disease, limiting the ability to define treatment effects specific to this subgroup. Pelvic external beam radiation therapy (EBRT) reduces the risk of pelvic recurrence while chemotherapy delays the development of distant metastases; however, neither modality has demonstrated an overall survival benefit. Patients with high-grade endometrioid cancers that are deeply (>50%) invasive into the

myometrium were not included for randomization in PORTEC-2 but were registered through the trial and received postoperative radiation. Compared to the PORTEC-2 cohort, this group experienced significantly higher recurrence rates and reduced survival, with distant metastases occurring in approximately 31% of patients within five years; surgical staging was not performed in the PORTEC trials.

Both the GOG 249 and PORTEC-3 trials investigated the role of radiation and chemotherapy in high-risk EC. Notably, the PORTEC trials did not require surgical staging with lymphadenectomy for enrollment. GOG 249 compared EBRT to three cycles of carboplatin/ paclitaxel followed by VBT in HIR disease (GOG 99 criteria), stage II endometrioid, and stage I-II serous and clear cell histologies. The trial found no significant difference in 5-year OS or distant recurrence between arms. Interestingly, nodal recurrences were higher in the chemo/VBT arm (9% vs 4%), and toxicity was greater [98]. PORTEC-3 randomized patients with stage I grade 3 endometrioid EC with deep myometrial invasion or LVSI, stage II or III endometrioid disease, or stage I-III with serous or clear cell histology to EBRT alone or with concurrent cisplatin followed by four cycles carboplatin/paclitaxel [99]. In patients with stage I-II endometrioid EC, chemoradiotherapy did not improve OS. These two trials support the role of EBRT in patients with early-stage high-risk EC.

Histologic and molecular features may indicate a role for systemic chemotherapy in uterine confined disease. GOG-258 evaluated chemoradiotherapy versus chemotherapy alone in patients with stage I-II serous or clear-cell EC with positive peritoneal washings, and stage III-IVA disease of any histology [100]. There was no difference in recurrence-free survival between arms; however, chemoradiotherapy reduced locoregional recurrences but was associated with higher rates of distant metastases. Notably, stage III disease represented most of the study population, and the findings suggest that chemotherapy alone may be sufficient for these patients.

Post-hoc and exploratory sub-analysis from GOG 249 and PORTEC-3, which were not powered for molecular stratification, have provided insight into potential differences in treatment benefit across molecular subgroups. In PORTEC-3, the greatest benefit of chemoradiotherapy was seen in patients with serous histology, stage III disease and those with p53 abnormal tumors. Molecular classification of PORTEC-3 showed that patients with *POLE*mut EC had excellent outcomes, with 98% 5-year recurrence free survival [101]. In contrast, patients with p53abn tumors derived significant benefit from chemoradiotherapy, with improved recurrence free survival regardless of histologic subtype. These findings support the potential role of molecular classification in guiding adjuvant therapy but should be interpreted cautiously given the retrospective nature of these analyses.

For serous carcinoma confined to a polyp or endometrium, adjuvant treatment remains controversial, though observation is an option [102]. Recent studies suggest benefit from single-modality therapy, but data are conflicting on whether systemic therapy or radiotherapy offers greater benefit [103,104]. In FIGO 2023, high-risk histologies limited to a polyp or endometrium are stage IC; any myometrial invasion upstages IIC [88]. While treatment recommendations remain unchanged, patients should be considered for ongoing clinical trials evaluating adjuvant therapy. Although HER2-directed agents are established in advanced serous EC, their utility in early-stage disease remains unclear.

Carcinosarcomas (CS) of the endometrium are rare, aggressive tumors associated with an extremely poor prognosis. Level I evidence to guide adjuvant therapy in early-stage endometrial CS is lacking; current recommendations are primarily informed by retrospective cohort studies and subgroup analyses from larger trials [105,106]. One recent database study found that patients with stage I disease treated with adjuvant chemotherapy had improved survival compared to no adjuvant therapy [107]. A retrospective multi-institutional series found that patients who received combined modality of radiation with carboplatin and paclitaxel had better PFS and OS compared to observation, chemotherapy alone, or radiation alone [106]. No prospective trials have compared the role of systemic therapy to observation in patients

with CS confined to the inner half of the myometrium. Tumor-directed radiation may be considered to reduce locoregional and retroperitoneal recurrence. Molecular characterization studies of endometrial CS have shown variability in the epithelial component across cohorts, with serous or undifferentiated histology in 81% of TCGA tumors compared with 85% endometrioid histology in a Japanese Foundation for Cancer Research series [83,84].

HER2 IHC expression has also been reported with similar frequency in endometrial CS as serous ECs [108]. Studies are ongoing and underway to stratify early-stage EC by molecular profile to determine optimal adjuvant therapy across histologies. NRG-GY026 is an ongoing trial evaluating paclitaxel and carboplatin alone or combined with either trastuzumab and hyaluronidase-oysk, or pertuzumab, trastuzumab and hyaluronidase-zzxf in patients with HER2 positive stage I-IV EC [109].

Further research elucidating the multifactorial etiologies driving endometrial carcinogenesis including hormonal dysregulation and modifiable behavioral factors are paramount for refining risk stratification and optimizing management paradigms. Management of early-stage EC continues to evolve with the integration of molecular profiling to personalize treatment. Part 2 of this manuscript addresses advanced stage EC medical management strategies.

CRediT authorship contribution statement

Renata Urban: Writing – review & editing, Writing – original draft, Supervision, Project administration, Formal analysis. **Tara Castellano:** Writing – original draft, Data curation. **Kemi Doll:** Writing – original draft, Data curation. **Deborah DeLair:** Writing – original draft, Data curation. **Jason Wright:** Writing – original draft, Data curation. **Ramez Eskander:** Writing – original draft, Data curation. **Shannon Westin:** Writing – original draft, Data curation. **Matthew Powell:** Writing – original draft. **Amaranta Craig:** Writing – original draft, Data curation. **Whitfield Growden:** Writing – original draft, Data curation. **Fernanda Musa:** Writing – original draft, Data curation. **Marilyn Huang:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis.

Disclaimer

SGO Evidence-based Reviews and Recommendations are intended to be educational devices that provide information that may assist in caring for patients. This Evidence-based Review is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring or discouraging any particular treatment. SGO Evidence-based Reviews and Recommendations are not intended to supplant the judgment of the health care provider with respect to particular patients or special clinical situations. Clinical decisions in any particular case involve a complex analysis of a patient's condition and available courses of action with the ultimate determination to be made by the health care provider in light of each individual patient's circumstances. Therefore, clinical considerations may lead a healthcare provider to appropriately take a course of action that varies from this document.

Declaration of competing interest

Dr. Urban reports royalties from UpToDate, Inc. for editorial duties and honoraria from Clinical Care Options. Dr. Castellano reports grant funding from the Bristol Myers Squibb Foundation (Robert A. Winn Diversity in Clinical Trials Scholar award), consulting fees from Nykode, honoraria from the GOG Foundation for speaking/symposium participation and protocol review, travel support from the GOG Foundation (Early Career New Investigator award), and participation on a GSK DEI in endometrial cancer advisory board; she also holds a role on the WAGO Executive Board. Dr. Doll has no disclosures. Dr. DeLair reports

honoraria from ASCO for an advantage course on endometrial cancer. Dr. Wright reports grant funding from Merck, royalties from UpToDate and the American College of Obstetricians and Gynecologists (ACOG), and payment for medicolegal consulting. Dr. Eskander reports consulting fees and advisory board participation with AstraZeneca, Eisai, Repare Therapeutics, MSD, GSK, AbbVie, PMV Pharma, Pfizer, Acrivon, Regeneron, Myriad, Natera, Daiichi Sankyo, LOXO at Lilly, TORL Therapeutics, and Corcept; he also holds leadership role with the GOG Foundation as a GOG Partners associate clinical trial advisory member. Dr. Westin reports grant funding and consulting fees from AstraZeneca, Novartis, Bayer, Bio-Path, Clovis Oncology/Pharma&, Roche/Genentech, AvengeBio, Zentalis, GSK, Jazz Pharmaceuticals, Mereo, and Nuvectis, and consulting fees from ZielBio, EQRX, AstraZeneca, GSK, Clovis Oncology/Pharma&, ImmunoGen, Eisai, Lilly, Merck, Zentalis, Mereo, Roche/Genentech, Mersana, Caris, SeaGen, Vincerx, Nuvectis, NGM Bio, Verastem, Immunocore, Gilead, and LOXO. Dr. Powell reports grant funding from GSK (to institution), consulting fees from GSK, Merck, Eisai, BioNTech, ImmunoGen, AstraZeneca, and Aadi Bioscience (payments to self), advisory board participation with GSK, and leadership roles with SGO, GOG Foundation, and the Foundation for Women's Cancer. Dr. Craig has no disclosures. Dr. Growdon reports consulting fees from GSK (Strategic Council on Endometrial Cancer) and honoraria from ONC Live. Dr. Musa reports institutional grant funding from GSK, AstraZeneca, Duality Bio, Constellation, ImmunoGen, Pfizer, Clovis, Allarity, Aadi, Ideaya, Genmab, and Merck; consulting fees and advisory board participation with Aadi, AbbVie, BioNTech, Duality, GSK, Allarity, AstraZeneca, Genmab, Clovis, Daiichi Sankyo, Lilly, Merck, and Whitehawk (payments to self); honoraria from Merck (speaker bureau) and Cooper Surgical (educational video); travel support from GSK for IGCS 2024; medical writing support from Seagen and GSK; and board of directors roles with the Society of Gynecologic Oncology and the Rivkin Foundation. Dr. Huang reports an institutional grant from Merck (IIT grant, ended February 2023), honoraria for serving as a DOD grant reviewer, an ONC Live educational course, and an ACCC educational podcast, and advisory board participation with ImmunoGen, AstraZeneca, Merck, Pfizer, and AbbVie (payments to self).

Acknowledgement

The authors thank Drs. Jean Siedel and Christopher LaFarge for their comprehensive review and editorial contributions to the manuscript.

References

- [1] V.E. Rodriguez, S.P. Tanjassiri, A. Ro, M.A. Hoyt, R.E. Bristow, A.M.W. LeBren, Trends in endometrial cancer incidence in the United States by race/ethnicity and age of onset from 2000 to 2019, *Am. J. Epidemiol.* 194 (1) (2025 Jan 8) 103–113, <https://doi.org/10.1093/aje/kwae178>. PMID: 38960701; PMCID: PMC12034838.
- [2] CDC, Adult Obesity Facts 2024, Available from: <https://www.cdc.gov/obesity/adult-obesity-facts/> CDC_AAref_Val=<https://www.cdc.gov/obesity/data/adult.html>.
- [3] Practice Bulletin No. 149: Endometrial cancer, *Obstet. Gynecol.* 125 (4) (2015) 1006–1026.
- [4] Committee Opinion No. 601, Tamoxifen and uterine cancer, *Obstet. Gynecol.* 123 (6) (2014) 1394–1397.
- [5] A. Drab, W. Kanadys, M. Malm, K. Wdowiak, J. Dolar-Szczasny, B. Barczyński, Association of endometrial cancer risk with hypertension— an updated meta-analysis of observational studies, *Sci. Rep.* 14 (1) (2024) 24884.
- [6] B. Pothuri, L. Ramondetta, M. Martino, K. Alektiar, P.J. Eifel, M.T. Deavers, et al., Development of endometrial cancer after radiation treatment for cervical carcinoma, *Obstet. Gynecol.* 101 (5 Pt 1) (2003) 941–945.
- [7] K.H. Lu, R.R. Broaddus, Endometrial Cancer, *The New England journal of medicine* 383 (21) (2020) 2053–2064.
- [8] S. Gustafson, K.M. Zbuk, C. Scacheri, C. Eng, Cowden syndrome, *Semin. Oncol.* 34 (5) (2007) 428–434.
- [9] K. Sorouri, F. Lynce, C.M. Feltmate, M.R. Davis, M.G. Muto, P.A. Konstantinopoulos, et al., Endometrial cancer risk among germline BRCA1/2 pathogenic variant carriers: review of our current understanding and next steps, *JCO Precis. Oncol.* 7 (2023), e2300290.
- [10] J. Kotsopoulos, J. Lubinski, B.L. Bychkovsky, P. Moller, R.H. Kim, N. Tung, A. Eisen, W. Foulkes, C.F. Singer, A. Aeilts, S.L. Neuhausen, B. Bordeleau, B. Karlan, R. Fruscio, C. Eng, O. Olopade, D. Zakalik, F. Couch, T.R.Y. Cajal, P. Sun, J. Gronwald, S.A. Narod, Incidence of endometrial cancer in BRCA mutation carriers, *Gynecol. Oncol.* 189 (2024 Oct) 148–155, <https://doi.org/10.1016/j.ygyno.2024.07.687>. Epub 2024 Aug 21. PMID: 39173195.
- [11] B.E. Blackburn, S. Soisson, K. Rowe, J. Snyder, A. Fraser, V. Deshmukh, et al., Prognostic factors for rural endometrial cancer patients in a population-based cohort, *BMC Public Health* 19 (1) (2019) 921.
- [12] A.K. Miller, J.C. Gordon, J.W. Curtis, J. Ajayakumar, F.R. Schumacher, S. Avril, The geographic context of racial disparities in aggressive endometrial cancer subtypes: integrating social and environmental aspects to discern biological outcomes, *Int. J. Environ. Res. Public Health* 19 (14) (2022).
- [13] K.A. Bertrand, L. Delp, P.F. Coogan, Y.C. Cozier, Y.M. Lenzy, L. Rosenberg, et al., Hair relaxer use and risk of uterine cancer in the black women's health study, *Environ. Res.* 239 (Pt 1) (2023), 117228.
- [14] M.A. Clarke, S.S. Devesa, S.V. Harvey, N. Wentzensen, Hysterectomy-corrected uterine corpus cancer incidence trends and differences in relative survival reveal racial disparities and rising rates of nonendometrioid cancers, *J. Clin. Oncol.* 37 (22) (2019) 1895–1908.
- [15] Y. Huang, J.Y. Hou, A. Melamed, C.M. St Clair, F. Khoury-Collado, A. Gockley, et al., Pathologic characteristics, patterns of care, and outcomes of Asian-Americans and pacific islanders with uterine cancer, *Gynecol. Oncol.* 165 (1) (2022) 160–168.
- [16] T.R. Sponholtz, J.R. Palmer, L. Rosenberg, C. Chen, Y. Chen, M.A. Clarke, et al., Risk factors for endometrial cancer in black women, *Cancer Causes Control* 34 (5) (2023) 421–430.
- [17] R. Katagiri, M. Iwasaki, S.K. Abe, M.R. Islam, M.S. Rahman, E. Saito, et al., Reproductive factors and endometrial cancer risk among women, *JAMA Netw. Open* 6 (9) (2023), e2332296.
- [18] D.H. Saris, A.J.B. Smith, C. Brensinger, S.H. Kim, A.F. Haggerty, N. Latif, et al., Disparities in cancer-specific and overall survival in black women with endometrial cancer: a Medicare-SEER study, *Gynecol. Oncol. Rep.* 40 (2022), 100922.
- [19] F. Register, Available from: Revisions to OMB's Statistical Policy Directive No. 15: Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity, 2024.
- [20] M.A. Clarke, B.J. Long, Morillo A. Del Mar, M. Arbyn, J.N. Bakkum-Gomez, N. Wentzensen, Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis, *JAMA Intern. Med.* 178 (9) (2018) 1210–1222.
- [21] P. Paramsothy, S.D. Harlow, B. Nan, G.A. Greenale, N. Santoro, S.L. Crawford, et al., Duration of the menopausal transition is longer in women with young age at onset: the multiethnic study of women's health across the nation, *Menopause* 24 (2) (2017) 142–149.
- [22] M.K. Wise, A.M. Scheffer, J. Brill, K.A. Bharucha, K.M. Tessier, C.A. Terrell, et al., Public awareness and provider counseling regarding postmenopausal bleeding as a symptom of endometrial cancer, *Menopause* 31 (10) (2024) 905–910.
- [23] K.M. Doll, S. Khor, K. Odem-Davis, H. He, E.M. Wolff, D.R. Flum, et al., Role of bleeding recognition and evaluation in Black-White disparities in endometrial cancer, *Am. J. Obstet. Gynecol.* 219 (6) (2018) 593 (e1–e14).
- [24] ACOG Committee Opinion No. 734, The role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding, *Obstet. Gynecol.* 131 (5) (2018) e124–e129.
- [25] M.A. Clarke, B.J. Long, M.E. Sherman, M.A. Lemens, K.C. Podratz, M.R. Hopkins, et al., Risk assessment of endometrial cancer and endometrial intraepithelial neoplasia in women with abnormal bleeding and implications for clinical management algorithms, *Am. J. Obstet. Gynecol.* 223 (4) (2020) 549 (e1–e13).
- [26] K.M. Doll, S.S. Romano, E.E. Marsh, W.R. Robinson, Estimated performance of transvaginal ultrasonography for evaluation of postmenopausal bleeding in a simulated cohort of black and white women in the US, *JAMA Oncol.* 7 (8) (2021) 1158–1165.
- [27] J. Grubman, V. Mora, M. Nguyen, N. Ladwig, L.M. Chen, V. Jacoby, Impact of abnormal uterine bleeding care in premenopausal patients prior to endometrial malignancy diagnosis, *Gynecol. Oncol. Rep.* 50 (2023), 101292.
- [28] N.C. Peeri, K.A. Bertrand, R. Na, I. De Vivo, V.W. Setiawan, V.E. Seshan, et al., Understanding risk factors for endometrial cancer in young women, *J. Natl. Cancer Inst.* 117 (1) (2025) 76–88.
- [29] J.K. Chan, A.E. Sherman, D.S. Kapp, R. Zhang, K.E. Osann, L. Maxwell, et al., Influence of gynecologic oncologists on the survival of patients with endometrial cancer, *J. Clin. Oncol.* 29 (7) (2011) 832–838.
- [30] S.A. Ackroyd, Y.T. Shih, B. Kim, N.K. Lee, M.T. Halpern, A look at the gynecologic oncologist workforce – are we meeting patient demand? *Gynecol. Oncol.* 163 (2) (2021) 229–236.
- [31] M.M. AlHilli, P. Elson, L. Rybicki, A.A. Khorana, P.G. Rose, Time to surgery and its impact on survival in patients with endometrial cancer: a national cancer database study, *Gynecol. Oncol.* 153 (3) (2019) 511–516.
- [32] S.K. Saarelainen, N. Peltonen, T. Lehtimäki, A. Perheentupa, M.H. Vuento, J.U. Maenpää, Predictive value of serum human epididymis protein 4 and cancer antigen 125 concentrations in endometrial carcinoma, *Am. J. Obstet. Gynecol.* 209(2):142 (2013) e1–e6.
- [33] S.L. Antonsen, E. Hogdall, I.J. Christensen, M. Lydolph, A. Tabor, A. Loft Jakobsen, et al., HE4 and CA125 levels in the preoperative assessment of endometrial cancer patients: a prospective multicenter study (ENDOMET), *Acta Obstet. Gynecol. Scand.* 92 (11) (2013) 1313–1322.
- [34] A. Obermair, E. Hanzal, I. Schreiner-Frech, P. Buxbaum, D. Bancher-Todesca, M. Thoma, C. Kurz, N. Vavra, G. Gitsch, P. Sevela, Influence of delayed diagnosis on established prognostic factors in endometrial cancer, *Anticancer Res.* 16 (2) (1996 Mar-Apr) 947–949.
- [35] L. Johnson, M.J. Cunningham, Morbid obesity increases the failure rate of sentinel lymph node mapping for endometrial carcinoma, *J. Robot. Surg.* 17 (5) (2023) 2047–2052.
- [36] A.J. Bodurtha Smith, A.N. Fader, E.J. Tanner, Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis, *Am. J. Obstet. Gynecol.* 216 (5) (2017) 459–76 e10.
- [37] Group SGOCEPCW, W.M. Burke, J. Orr, M. Leitao, E. Salom, P. Gehrig, et al., Endometrial cancer: a review and current management strategies: part I, *Gynecol. Oncol.* 134 (2) (2014) 385–392.
- [38] E. Epstein, L. Blomqvist, Imaging in endometrial cancer, *Best Pract. Res. Clin. Obstet. Gynaecol.* 28 (5) (2014) 721–739.
- [39] E.J. Crosbie, S.J. Kitson, J.N. McAlpine, A. Mukhopadhyay, M.E. Powell, N. Singh, Endometrial cancer, *Lancet* 399 (10333) (2022) 1412–1428.
- [40] A.M. Bolivar, R. Luthra, M. Mehrotra, W. Chen, B.A. Barkoh, P. Hu, et al., Targeted next-generation sequencing of endometrial cancer and matched circulating tumor DNA: identification of plasma-based, tumor-associated mutations in early stage patients, *Mod. Pathol.* 32 (3) (2019) 405–414.
- [41] S.H. McEvoy, S. Nougaret, N.R. Abu-Rustum, H.A. Vargas, E.A. Sadowski, C.O. Menias, et al., Fertility-sparing for young patients with gynecologic cancer: how MRI can guide patient selection prior to conservative management, *Abdom. Radiol. (NY)* 42 (10) (2017) 2488–2512.
- [42] A. Rodolakis, G. Scambia, F. Planchamp, M. Acien, A. Di Spiezio Sardo, M. Farrugia, et al., ESGO/ESHRE/ESGE guidelines for the fertility-sparing treatment of patients with endometrial carcinoma, *Int. J. Gynecol. Cancer* 33 (2) (2023) 208–222.
- [43] M.J. Mourits, C.B. Bijen, H.J. Arts, H.G. ter Brugge, R. van der Sijde, L. Paulsen, et al., Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial, *Lancet Oncol.* 11 (8) (2010) 763–771.
- [44] J.L. Walker, M.R. Piedmonte, N.M. Spirtos, S.M. Eisenkop, J.B. Schlaerth, R.S. Mannel, et al., Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: gynecologic oncology group study LAP2, *J. Clin. Oncol.* 27 (32) (2009) 5331–5336.
- [45] M. Janda, V. Gebiski, L.C. Davies, P. Forder, A. Brand, R. Hogg, et al., Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer: a randomized clinical trial, *JAMA* 317 (12) (2017) 1224–1233.
- [46] K.J. Eoh, T.J. Kim, J.Y. Park, H.S. Kim, J. Paek, Y.T. Kim, Robot-assisted versus conventional laparoscopic surgery for endometrial cancer: long-term comparison of outcomes, *Front. Oncol.* 13 (2023) 1219371.
- [47] H. Fu, J. Zhang, S. Zhao, N. He, Survival outcomes of robotic-assisted laparoscopy versus conventional laparoscopy and laparotomy for endometrial cancer: a systematic review and meta-analysis, *Gynecol. Oncol.* 174 (2023) 55–67.
- [48] J.D. Wright, W.M. Burke, A.J. Tergas, J.Y. Hou, Y. Huang, J.C. Hu, et al., Comparative effectiveness of minimally invasive hysterectomy for endometrial cancer, *J. Clin. Oncol.* 34 (10) (2016) 1087–1096.
- [49] S.E. Ferguson, T. Panzarella, S. Lau, L.T. Gien, V. Samouelian, C. Giede, et al., Prospective cohort study comparing quality of life and sexual health outcomes between women undergoing robotic, laparoscopic and open surgery for endometrial cancer, *Gynecol. Oncol.* 149 (3) (2018) 476–483.

- [50] G. Dinoi, K. Ghoniem, M.H. Murad, B. Segarra-Vidal, V. Zafagnin, P.J. Coronado, et al., Minimally invasive compared with open surgery in high-risk endometrial cancer: a systematic review and meta-analysis, *Obstet. Gynecol.* 141 (1) (2023) 59–68.
- [51] W.T. Creasman, C.P. Morrow, B.N. Bundy, H.D. Homesley, J.E. Graham, P.B. Heller, Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study, *Cancer* 60 (8 Suppl) (1987) 2035–2041.
- [52] P. Benedetti Panici, S. Basile, F. Maneschi, A. Alberto Lissoni, M. Signorelli, G. Scambia, et al., Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial, *J. Natl. Cancer Inst.* 100 (23) (2008) 1707–1716.
- [53] H. Kitchener, A.M. Swart, Q. Qian, C. Amos, M.K. Parmar, Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study, *Lancet* 373 (9658) (2009) 125–136.
- [54] S. Chiang, B. Tessier-Cloutier, E. Klein, O. Ardon, J.J. Mueller, M.M. Leitao Jr., N.R. Abu-Rustum, L.H. Ellenson, Establishing guidelines for sentinel lymph node ultrastaging in endometrial cancer, *Int. J. Gynecol. Cancer* 34 (5) (2024 May 6) 681–688.
- [55] S.C. Dowdy, B.J. Borah, J.N. Bakkum-Gamez, A.L. Weaver, M.E. McGree, L.R. Haas, et al., Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer, *Gynecol. Oncol.* 127 (1) (2012) 5–10.
- [56] R.J.A. Helgers, B. Winkens, B.F.M. Slangen, H.M.J. Werner, Lymphedema and post-operative complications after sentinel lymph node biopsy versus lymphadenectomy in endometrial carcinomas—a systematic review and meta-analysis, *J. Clin. Med.* 10 (1) (2020).
- [57] J.N. Barlin, F. Khoury-Collado, C.H. Kim, M.M. Leitao Jr., D.S. Chi, Y. Sonoda, et al., The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes, *Gynecol. Oncol.* 125 (3) (2012) 531–535.
- [58] E.C. Rossi, L.D. Kowalski, J. Scialici, L. Cantrell, K. Schuler, R.K. Hanna, et al., A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study, *Lancet Oncol.* 18 (3) (2017) 384–392.
- [59] P.T. Soliman, S.N. Westin, S. Dioun, C.C. Sun, E. Euscher, M.F. Munsell, et al., A prospective validation study of sentinel lymph node mapping for high-risk endometrial cancer, *Gynecol. Oncol.* 146 (2) (2017) 234–239.
- [60] Z. Marchocki, M.C. Cusimano, L. Clarfield, S.R. Kim, R. Fazlizada, O. Espin-Garcia, et al., Sentinel lymph node biopsy in high-grade endometrial cancer: a systematic review and meta-analysis of performance characteristics, *Am. J. Obstet. Gynecol.* 225 (4) (2021) 367 (e1–e39).
- [61] J.A. Ducie, A.G.Z. Eriksson, N. Ali, M.E. McGree, A.L. Weaver, G. Bogani, et al., Comparison of a sentinel lymph node mapping algorithm and comprehensive lymphadenectomy in the detection of stage IIIc endometrial carcinoma at higher risk for nodal disease, *Gynecol. Oncol.* 147 (3) (2017) 541–548.
- [62] B.A. Schlappé, A.L. Weaver, J.A. Ducie, A.G.Z. Eriksson, S.C. Dowdy, W.A. Cliby, et al., Multicenter study comparing oncologic outcomes between two nodal assessment methods in patients with deeply invasive endometrioid endometrial carcinoma: a sentinel lymph node algorithm versus a comprehensive pelvic and paraaortic lymphadenectomy, *Gynecol. Oncol.* 151 (2) (2018) 235–242.
- [63] A. Mariani, M.J. Webb, G.L. Keeney, M.G. Haddock, G. Calori, K.C. Podratz, Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? *Am. J. Obstet. Gynecol.* 182 (6) (2000) 1506–1519.
- [64] D. Dolly, A. Mihai, B.J. Rimel, L. Fogg, J. Rotmensky, A. Guirguis, et al., A delay from diagnosis to treatment is associated with a decreased overall survival for patients with endometrial cancer, *Front. Oncol.* 6 (2016), 31.
- [65] E.M. Ko, J.E. Bekelman, K. Hicks-Courant, C.M. Brensinger, G.P. Kanter, Association of gynecologic oncology versus medical oncology specialty with survival, utilization, and spending for treatment of gynecologic cancers, *Gynecol. Oncol.* 164 (2) (2022) 295–303.
- [66] B.L. Manning-Geist, E. Rios-Doria, Y.L. Liu, L.H. Ellenson, Q.C. Zhou, A. Iasonos, et al., Molecular and pathologic data to guide selection of patients with endometrioid endometrial cancer for ovarian preservation, *Int. J. Gynecol. Cancer* 34 (5) (2024) 697–704.
- [67] R. Behrouzi, C.E. Barr, E.J. Crosbie, HE4 as a biomarker for endometrial cancer, *Cancers (Basel)* 13 (19) (2021).
- [68] K.A. Underkofler, K.L. Ring, Updates in gynecologic care for individuals with lynch syndrome, *Front. Oncol.* 13 (2023), 1127683.
- [69] M. Janda, V. Gebiski, A. Brand, R. Hogg, T.W. Jobling, R. Land, et al., Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial, *Lancet Oncol.* 11 (8) (2010) 772–780.
- [70] S.M. Ueda, D.S. Kapp, M.K. Cheung, J.Y. Shin, K. Osann, A. Husain, et al., Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths, *Am. J. Obstet. Gynecol.* 198 (2) (2008) 218 (e1–6).
- [71] B.B. Albright, K.A. Monusko, S.J. Kaplan, B.A. Davidson, H.A. Moss, A.B. Huang, et al., Primary cytoreductive surgery for advanced stage endometrial cancer: a systematic review and meta-analysis, *Am. J. Obstet. Gynecol.* 225 (3) (2021) 237 (e1–e24).
- [72] A.B. Huang, J. Wu, L. Chen, B.B. Albright, A. Previs, H.A. Moss, et al., Neoadjuvant chemotherapy for advanced stage endometrial cancer: a systematic review, *Gynecol. Oncol. Rep.* 38 (2021), 100887.
- [73] C.J. Tobias, L. Chen, A. Melamed, C. St Clair, F. Khoury-Collado, A.L. Tergas, et al., Association of neoadjuvant chemotherapy with overall survival in women with metastatic endometrial cancer, *JAMA Netw. Open* 3 (12) (2020), e2028612.
- [74] J.D. Wright, Y. Huang, A. Melamed, B.B. Albright, G.C. Hillier, R. Previs, et al., Use and outcomes of neoadjuvant chemotherapy for metastatic uterine cancer, *Gynecol. Oncol.* 162 (3) (2021) 599–605.
- [75] I. Wilkinson-Ryan, A.J. Frolova, J. Liu, L. Stewart Massad, P.H. Thaker, M.A. Powell, et al., Neoadjuvant chemotherapy versus primary cytoreductive surgery for stage IV uterine serous carcinoma, *Int. J. Gynecol. Cancer* 25 (1) (2015) 63–68.
- [76] L.B. Reshko, J.T. Gaskins, A. Rattani, A.A. Farley, G.W. McKenzie, S.R. Silva, Patterns of care and outcomes of radiotherapy or hormone therapy in patients with medically inoperable endometrial adenocarcinoma, *Gynecol. Oncol.* 163 (3) (2021 Dec) 517–523, <https://doi.org/10.1016/j.ygyno.2021.09.006>, Epub 2021 Sep 23. PMID: 34563365.
- [77] E. van der Steen-Banasik, M. Christiaens, E. Shash, C. Coens, A. Casado, F.G. Herrera, Ottevanger PB; European Organisation for Research and Treatment of Cancer, Gynaecological Cancer Group (EORTC-CCG). Systemic review: Radiation therapy alone in medical non-operable endometrial carcinoma, *Eur J Cancer* 65 (2016 Sep) 172–181, <https://doi.org/10.1016/j.ejca.2016.07.005>, Epub 2016 Aug 5. PMID: 27501506.
- [78] Cancer Genome Atlas Research N, C. Kandoth, N. Schultz, A.D. Cherniack, R. Akbani, Y. Liu, et al., Integrated genomic characterization of endometrial carcinoma, *Nature* 497 (7447) (2013) 67–73.
- [79] A. Talhouk, M.K. McConechy, S. Leung, H.H. Li-Chang, J.S. Kwon, N. Melnyk, et al., A clinically applicable molecular-based classification for endometrial cancers, *Br. J. Cancer* 113 (2) (2015) 299–310.
- [80] A. Talhouk, M.K. McConechy, S. Leung, W. Yang, A. Lum, J. Senz, et al., Confirmation of ProMIS-E: a simple, genomics-based clinical classifier for endometrial cancer, *Cancer* 123 (5) (2017) 802–813.
- [81] D.F. Delair, K.A. Burke, P. Selenica, R.S. Lim, S.N. Scott, S. Middha, et al., The genetic landscape of endometrial clear cell carcinomas, *J. Pathol.* 243 (2) (2017) 230–241.
- [82] S.R. Kim, B.T. Cloutier, S. Leung, D. Cochrane, H. Britton, A. Pina, et al., Molecular subtypes of clear cell carcinoma of the endometrium: opportunities for prognostic and predictive stratification, *Gynecol. Oncol.* 158 (1) (2020) 3–11.
- [83] O. Gotoh, Y. Sugiyama, Y. Takazawa, K. Kato, N. Tanaka, K. Omatsu, et al., Clinically relevant molecular subtypes and genomic alteration-independent differentiation in gynecologic carcinosarcoma, *Nat. Commun.* 10 (1) (2019) 4965.
- [84] A.D. Cherniack, H. Shen, V. Walter, C. Stewart, B.A. Murray, R. Bowlby, et al., Integrated molecular characterization of uterine carcinosarcoma, *Cancer Cell* 31 (3) (2017) 411–423.
- [85] A. Leon-Castillo, E. Gilvazquez, R. Nout, V.T. Smit, J.N. McAlpine, M. McConechy, et al., Clinicopathological and molecular characterisation of ‘multiple-classifier’ endometrial carcinomas, *J. Pathol.* 250 (3) (2020) 312–322.
- [86] A. Leon-Castillo, H. Britton, M.K. McConechy, J.N. McAlpine, R. Nout, S. Kommoss, et al., Interpretation of somatic POLE mutations in endometrial carcinoma, *J. Pathol.* 250 (3) (2020) 323–335.
- [87] N. Conlon, Paula A. Da Cruz, C.W. Ashley, S. Segura, L. De Brot, E.M. da Silva, et al., Endometrial carcinomas with a ‘serous’ component in young women are enriched for DNA mismatch repair deficiency, Lynch syndrome, and POLE exonuclease domain mutations, *Am. J. Surg. Pathol.* 44 (5) (2020) 641–648.
- [88] J.S. Berek, X. Matias-Guiu, C. Creutzberg, C. Fotopoulou, D. Gaffney, S. Kehoe, et al., FIGO staging of endometrial cancer: 2023, *Int. J. Gynaecol. Obstet.* 162 (2) (2023) 383–394.
- [89] W.G. McCuggage, T. Bosse, C.B. Gilks, B.E. Howitt, J.N. McAlpine, M.R. Nucci, et al., FIGO 2023 endometrial cancer staging: too much, too soon? *Int. J. Gynecol. Cancer* 34 (1) (2024) 138–143.
- [90] E.M. Wilson, R. Huang, K.D. Jones, I.S. Hagemann, S.M. Temkin, J.N. McAlpine, M.A. Powell, M.M. Kepper, A.R. Hagemann, Challenges in implementation of molecular classification in early stage endometrial cancer—An NRG Oncology cooperative group mixed-methods study, *Cancer* 131 (1) (2025 Jan 1), e35596, <https://doi.org/10.1002/cncr.35596>, Epub 2024 Oct 17. PMID: 39420498.
- [91] A. van den Heerik, K.T.S. Aiyer, E. Stelloo, I.M. Jurgensliem-Schulz, L. Lutgens, J.J. Jobsen, et al., Microcystic elongated and fragmented (MELF) pattern of invasion: molecular features and prognostic significance in the PORTEC-1 and -2 trials, *Gynecol. Oncol.* 166 (3) (2022) 530–537.
- [92] H.M. Keys, J.A. Roberts, V.L. Brunetto, R.J. Zaino, N.M. Spiro, J.D. Bloss, et al., A phase III trial of surgery with or without adjuvant external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a gynecologic oncology group study, *Gynecol. Oncol.* 92 (3) (2004) 744–751.
- [93] C.L. Creutzberg, W.L. van Putten, P.C. Koper, M.L. Lybeert, J.J. Jobsen, C.C. Warlam-Rodenhuis, et al., Surgery and postoperative radiotherapy versus surgery alone for patients with stage-I endometrial carcinoma: multicentre randomised trial. PORTEC study group. Post operative radiation therapy in endometrial carcinoma, *Lancet* 355 (9213) (2000) 1404–1411.
- [94] R.A. Nout, V.T. Smit, H. Putter, I.M. Jurgensliem-Schulz, J.J. Jobsen, L.C. Lutgens, et al., Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial, *Lancet* 375 (9717) (2010) 816–823.
- [95] N. Horeweg, R.A. Nout, I.M. Jurgensliem-Schulz, L. Lutgens, J.J. Jobsen, M.A.D. Haverkort, et al., Molecular classification predicts response to radiotherapy in the randomized PORTEC-1 and PORTEC-2 trials for early-stage endometrioid endometrial cancer, *J. Clin. Oncol.* 41 (27) (2023) 4369–4380.
- [96] A.S.V.M. van den Heerik, N. Horeweg, M.A.D. Haverkort, N. Kuijsters, S. Kommoss, F.L.A. Koppe, et al., Molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer (PORTEC-4a): results of a randomised, open-label, phase 3, multicentre, non-inferiority trial, *Lancet Oncol.* 27 (1) (2026 Jan) 23–35.
- [97] J.N. McAlpine, K.C.-Z. Han, M. Kinloch, M. Barkati, S.E. Ferguson, A.W. Fyles, et al., CCTG EN10: A phase II study of tailored adjuvant therapy in POLE-mutated and p53-wildtype/NSMP early-stage endometrial cancer (EC) and RAINBO BLUE and TAPER, *J. Clin. Oncol.* 41 (16-suppl) (2023) TP55632-TPS.
- [98] M.E. Randall, V. Filiaci, D.S. McMeekin, V. von Gruenigen, H. Huang, C.M. Yashar, et al., Phase III trial: adjuvant pelvic radiation therapy versus vaginal brachytherapy plus paclitaxel/carboplatin in high-intermediate and high-risk early stage endometrial cancer, *J. Clin. Oncol.* 37 (21) (2019) 1810–1818.
- [99] S.M. de Boer, M.E. Powell, L. Mileschkin, D. Katsaros, P. Bessette, C. Haie-Meder, et al., Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial, *Lancet Oncol.* 19 (3) (2018) 295–309.
- [100] D. Matei, V. Filiaci, M.E. Randall, D. Mutch, M.M. Steinhoff, P.A. DiSilvestro, et al., Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer, *N. Engl. J. Med.* 380 (24) (2019) 2317–2326.
- [101] A. Leon-Castillo, S.M. de Boer, M.E. Powell, L.R. Mileschkin, H.J. Mackay, A. Leary, et al., Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy, *J. Clin. Oncol.* 38 (29) (2020) 3388–3397.
- [102] L.W. Liang, A.R. Perez, N.A. Cangemi, Q. Zhou, A. Iasonos, N. Abu-Rustum, et al., An assessment of prognostic factors, adjuvant treatment, and outcomes of stage IA polyp-limited versus endometrioid-limited type II endometrial carcinoma, *Int. J. Gynecol. Cancer* 26 (3) (2016) 497–504.
- [103] D. Nasioudis, A.G. Roy, E.M. Ko, L. Cory, R.L. Giuntoli II, A.F. Haggerty, et al., Adjuvant treatment for patients with FIGO stage I uterine serous carcinoma confined to the endometrium, *Int. J. Gynecol. Cancer* 30 (8) (2020) 1089–1094.
- [104] K.C. Kurnit, S.P. Nobre, B.M. Fellman, D.A. Iglesias, K. Lindemann, A. Jhingran, et al., Adjuvant therapy in women with early stage uterine serous carcinoma: a multi-institutional study, *Gynecol. Oncol.* 167 (3) (2022) 452–457.
- [105] A.H. Wolfson, M.F. Brady, T. Rocereto, R.S. Mannel, Y.C. Lee, R.J. Futoran, et al., A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-irradiation and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus, *Gynecol. Oncol.* 107 (2) (2007) 177–185.
- [106] K. Matsuo, K. Omatsu, M.S. Ross, M.S. Johnson, M. Yunokawa, M.M. Klobocista, D.D. Im, S.H. Bush, Y. Ueda, T. Takano, E.A. Blake, K. Hasegawa, T. Baba, M. Shida, S. Satoh, T. Yokoyama, H. Machida, S. Adachi, Y. Ikeda, K. Iwasaki, T.M. Miyake, S. Yanai, M. Nishimura, T. Nagano, M. Takekuma, S. Takeuchi, T. Pejovic, M.M. Shahzad, F.R. Ueland, J.L. Kelley, L.D. Roman, Impact of adjuvant therapy on recurrence patterns in stage I uterine carcinosarcoma, *Gynecol. Oncol.* 145 (1) (2017 Apr) 78–87, <https://doi.org/10.1016/j.ygyno.2017.02.001>, Epub 2017 Feb 16. PMID: 28215838; PMCID: PMC7529360.
- [107] L. Cory, C. Brensinger, R.A. Burger, R.L. Giuntoli 2nd, M.A. Morgan, N. Latif, et al., Patterns of adjuvant treatment and survival outcomes in stage I uterine carcinosarcoma, *Gynecol. Oncol. Rep.* 39 (2022), 100930.
- [108] D. Rottmann, O.L. Snir, X. Wu, S. Wong, P. Hui, A.D. Santin, et al., HER2 testing of gynecologic carcinosarcomas: tumor stratification for potential targeted therapy, *Mod. Pathol.* 33 (1) (2020) 118–127.
- [109] ClinicalTrials.gov, Testing the Addition of Trastuzumab or Trastuzumab/Pertuzumab to the Usual Chemotherapy for HER2 Positive Endometrial Cancer, Available from: <https://clinicaltrials.gov/study/NCT0526225>; 2024.