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Review Article

Endometrial cancer: A society of gynecologic oncology evidence-based review and recommendations

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HIGHLIGHTS

- Advances in molecular pathology complement clinical management of endometrial cancer.
- Increased estrogen exposure and genetic predisposition remain important risk factors
- Judicious evaluation of abnormal bleeding and cancer referrals to gynecologic oncologists optimize management
- Most patients benefit from minimally invasive surgery and tailored lymph node evaluation.
- Risk stratification based on recent trials should influence adjuvant therapy decisions.

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ABSTRACT

Introduction. In 2014, the Society of Gynecologic Oncology's Clinical Practice Committee published a clinical update reviewing the treatment of women with endometrial cancer. At that time, there had been significant advances in the diagnosis, work-up, surgical management, and available treatment options allowing for more optimal care of affected women. Despite these advances, the incidence of endometrial cancer as well as the deaths attributable to the disease have continued to rise; from 1987 to 2014 there has been a 75% increase in cases and almost 300% increase in endometrial cancer deaths. Fortunately, since then, there has been progress in the treatment of patients with endometrial cancer with 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, SGO Publications Committee, and the SGO board members 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 and Education Committees. 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.

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Contents

Clinical Considerations and Recommendations

1. Histopathology and molecular pathology

1.1. Clinical question 1

How should newly diagnosed endometrial cancer be classified to help guide clinical management?

1.1.1. Recommendation 1.1. Currently histology, grade, stage, age of the patient and presence or absence of LVSI are the clinicopathologic prognostic parameters that should guide initial clinical management for all endometrial cancer (AI).

1.1.2. Recommendation 1.2. Estrogen receptor status can be considered in stage III/IV patients (BII).

1.1.3. Recommendation 1.3. For patients with stage III/IV serous uterine cancer, HER2Neu testing by immunohistochemistry with reflex to FISH on formalin fixed tissue is recommended to determine eligibility of adding trastuzumab to their adjuvant chemotherapy (AI).

1.1.4. Recommendation 1.4. Mismatch repair status and/or microsatellite instability testing should be performed on all endometrial tumors to screen for Lynch syndrome (AII). This can also help determine future eligibility for immune checkpoint monotherapy or combination therapy with Pembrolizumab and Lenvatanib [2].

1.1.5. Recommendation 1.5. Next generation sequencing and further molecular classification, including identification of TP53 mutations in the near term, may help guide future treatment decisions, especially for advanced stage disease (BIII).

1.1.6. Recommendation 1.6. Biomarker testing should be reported to the greatest extent possible in accordance with College of American Pathologists (CAP) guidance (BIII) [3].

1.1.7. Literature review. For over three decades, endometrial cancer has been classified into two types [4]. Type I tumors are primarily International Federation of Gynecology and Obstetrics (FIGO) grade 1 and 2 endometrioid, stimulated by estrogen and typically preceded by endometrial intraepithelial neoplasia (EIN) or hyperplasia. PTEN loss is

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 is 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. Doi: https://doi.org/10.1097/AOG/0b013e31828883a34.

found in about 83% of these tumors. The majority are diagnosed at an early stage and have a good overall prognosis. Type II tumors include carcinosarcoma, serous, clear cell, mixed, undifferentiated, and high grade endometrioid carcinomas. These tumors are typically estrogen insensitive and less likely associated with endometrial intraepithelial neoplasia. Serous cancers are likely to be associated with endometrial intraepithelial carcinoma (EIC) [5]. *TP53* mutations are found in 90% of Type II tumors and, despite representing less than a third of endometrial cancers, these tumors result in nearly 75% of endometrial cancer deaths [6,7]. Though this dichotomized system remains a clinically useful construct, it is subject to significant interobserver variability, particularly in high grade cancers [8,9].

Advances in molecular and genomic classification may enhance both consistency of classification and prognostic information upon which to base clinical decisions. The Cancer Genome Atlas (TCGA) defined four distinct categories: 1) DNA polymerase epsilon (*POLE*) ultra-mutated (very high mutation rates); 2) microsatellite instability (MSI) hypermutated, and frequently associated with *MLH1* promoter methylation (MSI-H) 3) copy-number low, endometrioid tumors characterized by high frequency of *CTNNB1* mutations and a range of other modest to highly recurrent gene defects; and 4) copy-number high, characterized by *TP53* mutation and high frequency of *FBXW7* and *PPP2R1A* mutations. Cancer specific survival correlated with these groups even among patients with high grade endometrioid adenocarcinoma. *POLE*-mutant tumors have the best prognosis, followed by MSI-H, then copy-number low, and then copy-number high tumors with the poorest outcomes [10,11]. Researchers subsequently developed and validated a simplified, pragmatic molecular classification tool, ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) that identifies four molecular subtypes (mismatch repair deficient, *POLE* mutated, *p53* abnormal, and *p53* wild-type) that are analogous but not identical to the four distinct TCGA prognostic molecular subtypes [12]. Investigators from NRG Oncology have similarly developed a molecular classification for risk prediction in endometrioid endometrial cancer. This classification assigned four molecular groups paralleling the TCGA classifier [13].

PORTEC investigators demonstrated the potential of molecular classification to guide treatment. They applied a TCGA-like molecular classifier post-hoc to high-risk endometrial cancer patients in the PORTEC-3 trial in which patients were randomized to combined adjuvant chemotherapy and radiotherapy versus radiotherapy alone. Patients with TP53 aberrant tumors regardless of histology had significantly improved recurrence free survival in the combined modality treatment group versus radiation alone. Patients with POLE ultra-mutated cancers had excellent recurrence free survival regardless of treatment modality. These findings highlight the promise of molecular classifiers [14].

Likely, the best method for stratifying patients into prognostically distinct groups for tailored treatment is one that integrates genomic and traditional clinicopathologic prognostic parameters [15]. However, to date, large prospective studies have not been completed to validate this hypothesis.

2. Risk factors

2.1. Clinical question 1

What factors should be considered when discussing increased risk of developing endometrial cancer?

2.1.1. Recommendation 1.1. Any source of increased (exogenous or endogenous) estrogen (AI).

Any germline mutation including: PTEN (Cowden Syndrome), MLH1, MSH2, MSH6, PMS2, and EPCAM (Lynch Syndrome) (AI).

2.2. Clinical question 2

How should these risk factors effect clinical management?

2.2.1. Recommendation 2.1. For women receiving menopausal hormone therapy or on tamoxifen, routine endometrial biopsy and/or uterine ultrasound is not recommended, but those with postmenopausal bleeding or irregular bleeding in a premenopausal woman should undergo an endometrial biopsy or dilation and curettage (D&C) with or without hysteroscopy (AII).

2.2.2. Recommendation 2.2. In women with Cowden or Lynch syndrome, the option of hysterectomy upon completion of childbearing should be discussed and screening with an endometrial biopsy every 1–2 years can be considered (BII).

2.2.3. Literature review. The majority of risk factors for endometrial cancer are associated with estrogen (often unopposed) exposure. A helpful construct is to consider endogenous versus exogenous sources of estrogen exposure. 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. Reproductive factors such as nulliparity, infertility, early menarche or late menopause similarly fall within this construct. Exogenous sources of estrogen that increase endometrial cancer risk include menopausal estrogen therapy and tamoxifen, while combination oral contraceptive pills and other progestin containing contraceptives can lower risk [16,17]. Tamoxifen specifically has been associated with an increased risk of endometrioid endometrial cancer and uterine sarcoma [18].

Women with Lynch and Cowden Syndrome are at increased risk of developing endometrial cancer, though only 2% - 5% of all endometrial cancer are hereditary. Most hereditary endometrial cancers are due to Lynch Syndrome, an autosomal dominant syndrome caused by germline mutations in mismatch repair genes *MLH1, MSH2, MSH6, PMS2, and EPCAM*. The lifetime risk of endometrial cancer in women with Lynch Syndrome is 40% - 60% varying by specific mutation and may equal or exceed the lifetime risk of colon cancer in these women. Cowden syndrome, a rare autosomal dominant syndrome, resulting from a germline mutation in *PTEN* is associated with an increased risk of breast, thyroid, and endometrial cancer [19–21]. Some data suggests that patients with a *BRCA1* mutation may have an increased risk of serous uterine cancer, but the degree to which this is increased compared to the general population is not known.

3. Presentation and diagnostic approach

3.1. Clinical question 1

What clinical evaluation and diagnostic tests should be performed for patients with postmenopausal bleeding?

3.1.1. Recommendation 1.1. Postmenopausal bleeding should be evaluated by endometrial sampling and/or transvaginal ultrasound (AI).

If on transvaginal ultrasound, endometrial thickness is greater than 4 mm, or if bleeding persists or recurs after ultrasound or outpatient biopsy, hysteroscopy with dilation and curettage should be performed (level of evidence: AI).

3.1.2. Literature review. Women with postmenopausal bleeding require further evaluation. The American College of Obstetricians and Gynecologists (ACOG) May 2018 Committee Opinion provides a guideline-based approach to the evaluation of postmenopausal bleeding. In short, either transvaginal ultrasound or endometrial sampling (by office biopsy or dilation and curettage) are reasonable first approaches. If transvaginal ultrasound demonstrates a thin endometrial echo less than or equal to 4 mm, the negative predictive value for endometrial cancer is 99%. If the lining is greater than 4 mm, then sonohysterography, office hysteroscopy, or endometrial sampling should be pursued. If bleeding persists or recurs after reassuring transvaginal ultrasound and/or endometrial biopsy, hysteroscopy with dilation and curettage should be performed [22]. Highlighting the

importance of further assessment of persistent symptoms, one institutional series found that 25% of women diagnosed with type II endometrial cancer had a thin/indistinct endometrial stripe on transvaginal ultrasound [23].

3.2. Clinical question 2

How should abnormal bleeding in a premenopausal woman be evaluated?

3.2.1. Recommendation 2.1. Evaluation of abnormal bleeding in premenopausal women should be based on symptoms and presentation and is similar to postmenopausal women except that ultrasound measurement of endometrial thickness has no diagnostic value [22]. An endometrial biopsy should be performed if the patient has additional risk factors and/or the workup of the bleeding has been negative (i.e. absence of polyp/fibroid, etc.) (AII).

3.2.2. Literature review. More than 90% of women diagnosed with endometrial cancer present with abnormal or postmenopausal bleeding. In most cases this warning sign leads to early diagnosis but educating women and providers alike remains a challenge and priority. Data indicates that gaps remain in prompt reporting of these symptoms and guideline-based evaluation. These gaps may be more pronounced in black women, leading to a later stage of diagnosis and poorer prognosis [24]. Symptoms at presentation with late stage disease may include abdominal or pelvic pain, bloating, early satiety, or change in bowel or bladder habits [16,17].

3.3. Clinical question 3

Once a diagnosis of endometrial cancer is made: who should perform the surgery and manage the patient?

3.3.1. Recommendation 3. A diagnosis of endometrial cancer should prompt a referral to a gynecologic oncologist when possible. (BIII).

3.4. Clinical question 4

Are tumor markers and/or imaging necessary and if so, in which patients?

3.4.1. Recommendation 4.1. Imaging after a diagnosis of a grade 1 or 2 endometrioid endometrial cancer to evaluate for metastasis is not necessary (AIII). Serum CA125 and/or CT scans can be considered for high-risk disease (high grade or high-risk histology) or concern for metastatic disease (CIII).

3.4.2. Literature review. Once a diagnosis of endometrial cancer is made, the provider should refer the patient to a gynecologic oncologist. In most cases, the patient should be medically optimized for surgical management unless the patient desires and is a candidate for fertility preservation or if the medical risk of surgery is too great (see special situations below) where alternative therapies should be considered. Most patients require no further imaging to detect metastatic disease; although CT imaging or CA 125 levels are reasonable in the context of high-risk disease (grade 3 or type II) or if there is concern for metastatic disease at the time of presentation [16].

4. Surgical approach

4.1. Clinical question 1

What is the preferred surgical approach for staging early endometrial cancer?

4.1.1. Recommendation 2.1. Minimally invasive surgical staging should be the preferred surgical approach for most endometrial cancer patients (AI).

4.1.2. Literature review. Staging of endometrial cancer requires removal of the uterus, cervix, adnexa, and lymph node assessment. In high risk subtypes, addition of peritoneal biopsies and omentectomy is reasonable. Minimally invasive surgery is the standard of care surgical approach for women with newly diagnosed endometrial cancer. Randomized controlled trials comparing laparoscopy to laparotomy demonstrate the benefits of minimally invasive approaches [25–27]. The Gynecologic Oncology Group (GOG) LAP2 trial enrolled over 2600 women and was the first reported randomized trial comparing laparoscopy to then standard of care laparotomy. While the conversion rates were high at 25.8%, laparoscopy was associated with fewer postoperative adverse events and shorter length of hospital stay [25]. The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial conducted in Australia, New Zealand and Hong Kong, similarly reported that laparoscopy was associated lower rates of postoperative complications and serious adverse events. Both studies reported improved short-term quality of life after laparoscopy [26].

While perioperative outcomes are important, in oncologic surgery, we must confirm that the long-term outcomes are not compromised. In 2012, the follow up data on GOG LAP2 reported a small difference in recurrence rate between the two groups (11.4% after laparoscopy and 10.2% after laparotomy) with an estimated hazard ratio for laparoscopy of 1.14 (95% CI 0.92–1.46). The study was designed as a non-inferiority trial, for which the 95% CI for the hazard ratio did not meet its pre-specified criteria for non-inferiority. The outcome differences were statistically insignificant, and the 5-year overall survival was almost identical in both arms at 89.8% and the study supported the safety of laparoscopic hysterectomy in endometrial cancer. The authors concluded that any difference in recurrence-free survival was likely to be very small. More recently, the long-term outcomes of the LACE trial were reported. In this study, the disease-free and overall survival were equivalent between laparoscopy and abdominal hysterectomy confirming that minimally invasive surgery should be considered for all patients with clinical stage I endometrial cancer [28]. A post-hoc analysis of the LAP2 trial evaluated high grade uterine cancers including grade 3 endometrioid carcinoma, serous, clear cell, and uterine carcinosarcoma and found that surgical approach did not impact patterns of recurrence and survival [29].

During the time it took to critically assess the role of laparoscopy in the treatment of endometrial cancer, there was a significant increase in the number of endometrial cancer cases done robotically. The benefits of robotic surgery were similar to standard laparoscopy in terms of less blood loss and shorter length of stay when compared to open surgery [30–32]. These concepts, as well as the advantage the robotic platform provides in the morbidly obese patient, support the benefits of robotic surgery as alternative approach to conventional laparoscopic hysterectomy [33]. A recent prospective study comparing quality of life and patient reported outcomes between open and minimally invasive approaches showed benefit in women who underwent minimally invasive surgery for endometrial cancer [34]. Among 468 women surveyed for both short term (1 and 3 weeks) and long-term (12 and 24 week) outcomes, there was no difference between robotic and laparoscopic approaches. Patients who underwent minimally invasive surgery, however, had significantly higher quality of life scores, with less pain and decreased impact of pain on relevant aspects of life compared to women undergoing laparotomy. These benefits were sustained during long-term follow up. Surgical approach had no impact on sexual health. For women in whom the risks of an open, laparoscopic, or robotic approach to surgery may outweigh the benefits, vaginal hysterectomy is an acceptable alternative [35].

4.2. Clinical questions 2

Who needs a lymphadenectomy and what is the best strategy for nodal assessment?

4.2.1. Recommendation 3.1. Both sentinel lymph node mapping or an algorithm-based approach to staging are acceptable alternatives to complete nodal staging in all grades and types of endometrial cancer (AII).

4.2.2. Recommendation 3.2. If sentinel lymph node mapping is utilized, when a sentinel lymph node is not identified, a side-specific lymphadenectomy should be performed. Alternatively, a frozen section to assess the need for a side-specific lymphadenectomy, as used in the algorithm-based approaches, can be completed. All grossly abnormal lymph nodes should be removed (AII) [36].

4.2.3. Literature review. This question has fueled debate for over two decades and a full discussion of the history of this controversy is beyond the scope of this review. Surgical management of endometrial cancer historically included exploratory laparotomy, pelvic washings, hysterectomy, bilateral salpingo-oophorectomy, selective biopsies of suspicious areas, and lymph node sampling in patients at risk for extra-uterine disease. Complete surgical staging is not only prognostic but also facilitates adjuvant therapy. This, in theory, maximizes survival and minimizes morbidity by reducing both under- and over-treatment. Unfortunately, patients with endometrial cancer are often poor surgical candidates due to obesity, diabetes, other significant co-morbidities. As a result, complete lymph node staging can potentially cause significant morbidity nullifying the benefit gained from staging. Different strategies have been used to determine which patients need more extensive nodal evaluation based on their risk for distant spread.

According to GOG 33, the overall risk of lymph node metastasis in women with clinical stage I or occult stage II disease was 11% [37]. The Mayo Clinic identified a subset of women with endometrial cancer who are at "low risk" for lymph node spread. They found that women with a grade 1 or 2 endometrioid adenocarcinoma with less than 50% myometrial invasion and a tumor less than 2 cm in size on intra-operative frozen section had no risk of lymph node involvement [38]. In their patient population, 27% of all women with endometrial cancer (all histologies) met these criteria and did not require surgical staging. Of those with endometrioid tumors, 33% of patients met these criteria. The conclusion from these studies was that "low risk" patients could safely be treated with total hysterectomy and bilateral salpingo-oophorectomy alone [38]. Based on these findings, the Mayo Clinic developed guidelines for intra-operative assessment that many adopted to identify patients with low risk disease who did not need lymphadenectomy. The Mayo Clinic algorithm applied to endometrioid adenocarcinoma and allowed omission of lymphadenectomy in patients with any grade or tumor size if there was no myometrial invasion, and in patients with grade 1 or 2 with less than 50% myometrial invasion and tumor diameter less than or equal to 2 cm.

The algorithm-based approach is imperfect. In larger, multi-institutional studies, including GOG 33, the risk of lymph node involvement was based on final tumor histology and depth of myometrial invasion. While many algorithms, including the algorithm used at the Mayo Clinic, base the decision for complete surgical staging on intra-operative frozen section, this is not universally available and is not always reliable [39]. In addition, the reproducibility of the diagnosis of endometrial cancer and endometrial hyperplasia among pathologists is poor [40].

Two randomized studies evaluating the role of lymphadenectomy in endometrial cancer showed no benefit in disease-free or overall survival [41,42]. Despite these findings, many agree that the identification of metastatic disease in the lymph nodes is critical in the diagnosis and treatment of women with endometrial cancer and lymph node metastases are an important prognostic factor in overall survival [43,44].

The use of sentinel lymph node (SLN) mapping plus ultra-staging could potentially maximize the identification of positive nodes, while minimizing the known risks of lymphadenectomy including longer surgical times, intraoperative injury, blood loss, and lymphedema [45,46]. Published studies describe SLN detection rates as high as 85% to 100% with bilateral detection rates of 60% to 97% [47–52]. An initial retrospective report of implementation of a SLN algorithm that included performing a side-specific pelvic lymphadenectomy when a SLN is not detected resulted in a significant decrease in the false negative rate from 15% to 2% in women with low-risk endometrial cancer [53]. Based on this and other studies, SLN mapping was recognized as an option for nodal assessment in the 2014 and reaffirmed in the 2019 National Comprehensive Cancer Network (NCCN) guidelines for endometrial cancer.

Since that time, prospective trials have shown that sentinel lymph node mapping can accurately identify women with positive nodes in both the low risk and high-risk populations. The FIRES trial, a prospective, multi-center study, evaluated the efficacy of SLN mapping in patients with all histologic subtypes with required completion pelvic +/− paraaortic lymphadenectomy to validate the SLN algorithm [54]. They enrolled 385 patients who underwent surgery by 18 surgeons at 10 different centers. SLN mapping was successful in 86% of patients with a false negative rate of 2.8%. Soliman et al. also performed a prospective study evaluating the accuracy of SLN in high-risk endometrial cancer [55]. Women with grade 3 endometrioid, serous, clear cell and carcinosarcoma were included. Patients with grade 1 to 2 tumors could also be included if they had suspected deep myometrial invasion or cervical involvement. One hundred and one patients underwent SLN mapping followed by pelvic and para-aortic lymphadenectomy up to the renal vessels. Eighty-nine percent were mapped successfully with a false negative rate of 4.3%. These studies further validated the sentinel lymph node algorithm in both low risk and high-risk women, leading to its adoption in a majority of clinical practices.

A series of publications compared strategies for lymph node assessment based on institutional databases. For patients with endometrioid adenocarcinoma of any grade with less than 50% myometrial invasion, the SLN algorithm resulted in significantly more patients having pelvic nodes excised, a lower number of lymph nodes per patient, and a higher detection rate of stage IIIC1 disease compared to the Mayo algorithm [56]. Within this cohort, a study of patients with endometrioid adenocarcinoma with greater than or equal to 50% myometrial invasion, or serous or clear cell carcinoma revealed that stage IIIC disease was detected with similar frequency between the SLN group and the systematic lymphadenectomy even though the SLN group had fewer total lymph nodes removed [57]. A follow-up study on the oncologic outcomes of the deeply invasive endometrioid endometrial carcinoma found no association between nodal assessment strategy and progression free or overall survival [58] after controlling for age and adjuvant therapy. Both algorithms had similar metastatic nodal detection rates and oncologic outcomes at these institutions.

4.3. Clinical question 3

Is there a role for maximal cytoreductive effort in advanced endometrial cancer?

4.3.1. Recommendation 4.1. Aggressive surgical cytoreduction improves progression-free and overall survival in patients with advanced or recurrent endometrial cancer (BII).

4.3.2. Literature review. Extra-uterine disease is found in approximately 10% to 15% of new endometrial cancer cases. These cases account for more than 50% of all uterine cancer-related deaths, with survival rates as low as 5% to 15% [59]. No randomized prospective surgical trials currently provide insight on the best treatment. Therefore, treatment often consists of radical surgery followed by any combination of radiation, chemotherapy, and novel therapeutic agents. Support for initial maximal cytoreductive effort is provided by data showing that the extent of residual disease among advanced-stage endometrial cancer appears to have a direct influence on survival. In a recent retrospective comparative study of women with advanced endometrial cancer, patients with optimal cytoreduction had improved median overall survival compared to those with residual disease (29 versus 17 months, $p=0.02$) [60]. In

older reports, patients in whom the tumor was determined to be unresectable had median survivals of two to eight months, regardless of adjuvant treatment with radiation and/or chemotherapy [61,62]. In contrast, when patients underwent optimal cytoreductive surgery, survival was twice that of those who underwent a suboptimal cytoreduction. In a study by Bristow and colleagues, the median survival for patients who had less than 1 cm residual disease was 15 months, compared with 40 months among those who had microscopic disease [63]. A similar study by Shih et al. reported median survival for patients with no residual disease of 40 months compared with 19 months for those who had any residual disease [61]. While the data are retrospective and come from small studies and/or single institution reviews, the findings are consistent that patients may benefit from a maximal surgical effort when feasible.

4.4. Clinical question 4

Does surgical management improve outcome in recurrent endometrial cancer?

4.4.1. Recommendation 5.1. Surgical resection may be reasonable for patients with localized pelvic recurrence who have not previously undergone radiation. (CIII).

4.4.2. Recommendation 5.2. Total pelvic exenteration offers the only curative option in patients with recurrent endometrial cancer who have received previous irradiation (CIII).

4.4.3. Literature review. Multiple studies have addressed the potential benefit of secondary cytoreductive surgery on overall survival in patients with recurrent endometrial cancer. Whether recurrent endometrial cancer is localized to the pelvis or disseminated throughout the abdomen, secondary cytoreduction has been shown to improve both progression-free and overall survival. More specifically, survival seems to be dependent on the type of recurrence (solitary recurrence vs. carcinomatosis), the ability to achieve optimal cytoreduction, and the time from original treatment to recurrence [64]. Median overall survival after secondary cytoreductive surgery for recurrent endometrial cancer ranges from 39 to 57 months after surgery [65,66]. For patients with isolated vaginal recurrence or recurrence localized to the pelvis, radiation treatment may be considered in those who have not received prior radiation therapy [67]. Local surgical resection may be a reasonable alternative, particularly in patients who are not candidates for or decline radiation. In previously irradiated patients with localized recurrence who have been previously treated with, or who are not candidates for immunotherapy or approved targeted therapies, pelvic exenteration remains the only curative option, although it is associated with significant postoperative morbidity (60% to 80%) and even mortality (10% to 15%). Despite such high postoperative morbidity, the reported 20% to 40% 5-year survival rates makes pelvic exenteration the only curative option and may justify the radicality of the approach [68].

5. Adjuvant therapy

5.1. Clinical question 1

How should we define postoperative endometrial cancer risk categories and can women with intermediate risk disease be separated into low-intermediate risk and high-intermediate risk?

5.1.1. Recommendation 1.1. Postoperative endometrial cancer risk can be categorized as low, intermediate, or high. The Gynecologic Oncology Group further defined a high intermediate risk group which included patients with (1) moderate to poorly differentiated tumor, presence of lymphovascular invasion, and outer third myometrial invasion; (2) age 50 or greater with any two risk factors listed above; or (3) age of at least 70 with any risk factor listed above. All others were deemed low intermediate risk. Patients with clear cell or serous histology were considered high risk [69].

Similarly, the Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC-1) trial defined a high-intermediate risk group in mostly unstaged patients, as having two of three clinicopathologic factors: outer half myometrial invasion, poorly differentiated histology, and age greater than 60 years. Serous and clear cell histologies were included in the trial but grade 3 tumors that had >50% invasion were excluded (AI) [14,70].

5.1.2. Literature review. Selecting adjuvant therapy for patients with endometrial cancer is based on the risk of recurrent disease and the ability to modify this risk with either radiation therapy or chemotherapy. The definitions of low, intermediate, high-intermediate, and high risk are guided by data from prospective randomized trials, though most trials included overlapping risk cohorts. Also, inconsistent clinical trial staging requirements complicate our ability to draw conclusions and make decisions. Some trials required comprehensive surgical staging [69], while others have left staging to surgeon discretion [71–76]. There is broad consensus that women with grade 1 endometrioid tumors confined to the endometrium are at low risk of recurrence and do not require postoperative adjuvant therapy.

5.2. Clinical question 2

What is the preferred treatment of high-intermediate risk endometrial cancer?

5.2.1. Recommendation 2.1. Observation is appropriate for endometrial cancer patients without high-risk features. Adjuvant vaginal brachytherapy can be utilized for high-intermediate risk endometrial cancer patients. However, in the absence of an overall survival advantage with adjuvant radiation, observation is an alternative and reasonable approach for high-intermediate risk patients (AI).

5.2.2. Literature review. Both PORTEC-1 and GOG 99 demonstrated that pelvic radiotherapy (RT) significantly reduced locoregional recurrence and the largest absolute reductions were in the designated high-intermediate risk groups. In PORTEC-1, locoregional recurrence at five years was reduced from 23% to 5% with pelvic RT and in GOG 99, cumulative incidence of recurrence at four years was reduced from 27% to 13%. It is important to note that adjuvant radiation increased toxicity in both trials and did not provide an overall survival advantage [69,70]. If overall survival is considered the most clinically relevant endpoint, to date, no level one data supports adjuvant therapy and, in its absence, 73% of patients will remain recurrence free at 48 months.

As the majority of recurrences for PORTEC 1 and GOG 99 were in the vaginal vault, PORTEC 2 evaluated the efficacy and toxicity of vaginal brachytherapy (VBT) compared to external beam RT in the PORTEC 1 defined high-intermediate group. Ten-year survival data confirmed excellent vaginal control rates (>96%) in both arms with similar rates of isolated pelvic recurrence, distant metastasis, and overall survival [77]. Importantly, VBT was associated with significantly less toxicity and improved health-related quality of life (HRQL) [73]. Specifically, in the long-term analysis of HRQL, external beam RT had a persistent negative impact, largely due to bowel toxicity (diarrhea, fecal leakage, urgency) with moderate to severe limitation of daily activity reported by 10% of patients. Urinary urgency also became significantly different at seven years showing the combined impact of aging and EBRT [78]. Based on this data, VBT is likely the treatment of choice in most high-intermediate risk patients who opt for treatment to decrease risk of local recurrence.

5.3. Clinical question 3

How do we define high-risk endometrial cancer?

5.3.1. Recommendation 3.1. High-risk endometrial cancers include serous and clear cell histologies, carcinosarcomas, grade 3 deeply invasive endometrioid cancers, and pathologic stage II, III and IV disease. It becomes apparent in reviewing these definitions that the trials guiding treatment included patients across risk strata. Indeed, these designations have been quite fluid, have evolved over the past several decades, and continue to evolve. (AI).

5.4. Clinical question 4

What is the preferred treatment of high-risk endometrial cancer?

5.4.1. Recommendation 4.1. With myoinvasive, high-risk, early stage disease, pelvic RT with vaginal brachytherapy (VBT) alone appears appropriate, though systemic chemotherapy plus vaginal brachytherapy may be considered for highest risk (serous, clear cell, carcinosarcoma) histology (AI).

5.4.2. Recommendation 4.2. For noninvasive, high risk histology, observation, VBT alone or chemotherapy with VBT could be offered (CII). Shared decision making between the patient and provider is paramount as there is retrospective evidence to support several treatment recommendations.

5.4.3. Recommendation 4.3. For stage III and IV disease chemotherapy should be utilized [79]. For Stage III disease, chemoradiotherapy appears to have a role based on PORTEC 3 and there was a survival advantage for women with serous carcinoma in subgroup analysis (BI) [74,80]. In GOG 258, chemotherapy plus radiation was not associated with longer relapse-free survival than chemotherapy alone in patients with stage III and IVA endometrial cancer after surgery with residual less than 2 cm (AI) [77].

5.4.4. Literature review. Defining optimal therapy for high risk disease (and even defining what high risk disease is) has been challenged by lack of uniformity in defining this group, treatment paradigms, and a corresponding lack of level 1 data. The high-risk group typically includes, but may not be limited to, serous, clear cell, and carcinosarcomas as well as stage II and advanced stage disease (stage III-IV). Two trials, each published over a decade ago, evaluated adjuvant platinum-based chemotherapy versus radiotherapy in patients with high-risk early stage or advanced disease and found no overall survival advantage [81,82]. The trial by the Japanese Gynecologic Oncology Group did identify, in a post hoc subgroup analysis, a benefit in favor of chemotherapy in the high-intermediate risk group [81].

GOG 249 was a phase III trial evaluating the impact on recurrence free survival of substituting VBT followed by three cycles of paclitaxel and carboplatin for pelvic RT in patients with high-intermediate and high-risk early stage endometrial cancer. The trial enrolled women meeting GOG 99 high-intermediate risk criteria (outer half rather than outer third myoinvasion substituted as risk factor), stage II, or stage I-II serous or clear cell carcinoma. The chemoradiotherapy arm was not superior to RT and though 5-year recurrence free and overall survival were very similar, chemotherapy with vaginal brachytherapy was associated with more pelvic and para-aortic nodal failure and more frequent and severe acute toxicity. Subgroup analyses evaluating treatment effect by histology found no statistically significant evidence of heterogeneity with respect to recurrence free or overall survival. The authors concluded that pelvic RT remained the appropriate, standard treatment for high-risk early stage disease without prospective evidence to support a benefit of adjuvant chemotherapy [72].

Based on the benefit of chemotherapy for advanced disease reported in GOG 122 [79], three prospective cooperative group trials evaluated the addition of adjuvant chemotherapy to radiation in high-risk patients. The Nordic Society of Gynecologic Oncology (NSGO)/Mario Negri Gynecologic Oncology Group (MaNGO) study was a combined analysis of two independently designed trials comparing RT with chemotherapy and RT. The NSGO/EORTC study initially included only patients with high-risk stage I endometrial cancer, but later allowed the inclusion of patients with stage II-III disease. The MaNGO trial included patients with stage IIB-IIIC disease. Women with serous and clear cell cancer were included in the NSGO/EORTC study but excluded in the MaNGO trial. In the pooled analysis, progression free survival was improved with combined therapy (78% vs 69%, $p=0.01$) but the overall survival trend did not reach statistical significance (82% vs 75%, $P=0.07$). In women with serous or clear cell cancer from the EORTC trial (MaNGO trial excluded the atypical histologies), PFS was not significant (HR 0.83; CI 0.42–1.64, $p=0.59$) [76].

Recent trials provide data to better define reasonable treatment approaches. PORTEC 3 evaluated the role of adjuvant chemotherapy during and after radiotherapy versus pelvic RT in women with high risk endometrial cancer, inclusive of patients that would have been at highest risk in PORTEC 1 and 2. The trial enrolled women with stage IA, grade 3 endometrioid cancer with LVSI; stage IB grade 3 endometrioid cancer; stage II endometrioid cancer of any grade; stage III endometrioid of any grade, stage IA-III uterine serous or clear cell carcinoma. Fifty-five percent of patients had high risk early stage disease. Both treatment arms received pelvic RT. The chemoradiotherapy arm received two cycles of cisplatin 50 mg/m2 on week 1 and 4 of RT followed by 4 cycles of paclitaxel and carboplatin. The trial's coprimary endpoints were overall survival and failure free survival (defined as any relapse or death related to endometrial cancer or treatment). The addition of chemotherapy did not improve overall survival but did improve 5-year failure-free survival by 7% (69% to 76%; $p=0.02$). Patients with stage III disease had a clinically relevant 11% absolute improvement in failure-free survival exceeding the 10% improvement used when designing the study [74]. The recently published update of PORTEC 3 did show a significant improvement in overall survival (absolute improvement 19%; HR0.48 [95% CI 0.24–0.96]) in women with serous carcinoma who were randomized to the chemoradiotherapy arm as compared to radiotherapy alone. However, the addition of chemotherapy resulted in significantly higher treatment related toxicity (60% vs 12% grade 3 or higher) but these differences resolved from 12 months onward. Both the authors and commentaries agreed that in stage III patients, particularly those with a serous histology, that the benefits of chemotherapy may justify the additional toxicity [80].

GOG 258 was a prospective study of cisplatin and tumor directed RT followed by carboplatin and paclitaxel (as in PORTEC 3) versus carboplatin and paclitaxel alone in women with locally advanced endometrial cancer (stage III-IVA) or stage I/II serous or clear cell endometrial cancer with positive cytology. The rationale for selection of the components of the chemotherapy alone arm are detailed below in the discussion of treatment for patients with distant metastasis. At 60 months, the primary endpoint of recurrence-free survival was nearly identical at 59% for chemoradiotherapy versus 58% for chemotherapy alone. Locoregional and retroperitoneal recurrence was more common in the chemotherapy group while there was a trend toward more distant recurrence with chemoradiotherapy. Rates of toxicity were similar while quality of life was slightly inferior in the chemoradiotherapy arm. Exploratory subgroup analyses failed to identify a subgroup of patients who may have benefitted more from chemoradiotherapy versus chemotherapy alone [76].

The theoretic appeal of chemotherapy for prevention of distant recurrence and RT for locoregional control is conceptually attractive. Findings contradictory to the randomized trial reports from institutional [83] and large database analyses continue to suggest a role for combined modality treatment [84,85]. A recent report of nearly 6000 women utilizing the National Cancer Database found that women with locally advanced endometrial cancer treated by multi-agent chemotherapy prior to radiation therapy had improved overall survival compared with RT followed by chemotherapy. The authors point out that no prospective trials included a treatment arm in which chemotherapy was administered before RT raising the question if chemotherapy should be the

first adjuvant therapy rather than the second or only adjuvant therapy [86].

Despite the recent publication of four large randomized trials detailed above, there is no consensus on the optimal approach to treatment of high-risk endometrial cancer and many patterns of care may be reasonable based on the available evidence. Decisions regarding uterine serous cancers, clear cell, and carcinosarcomas remain challenging as available studies were not adequately powered for subset analyses. Given these uncertainties, adjuvant chemotherapy is often recommended. Newer strategies taking advantage of molecular classification to determine which patients may truly benefit from adjuvant treatment are currently being studied.

5.5. Clinical question 5

What is the preferred treatment for patients with distant metastasis?

5.5.1. Recommendation 5.1. The therapeutic index of carboplatin and paclitaxel favor this regimen for endometrial cancer with distant metastasis (AI).

5.5.2. Recommendation 5.2. In women with uterine serous carcinoma, the tumor should be tested for HER2/neu and if positive by IHC, trastuzumab should be added to paclitaxel and carboplatin regimen (BI).

5.5.3. Literature review. Trials informing current management of patients presenting with distant metastatic disease have typically grouped these patients with stage III, stage IV, and often recurrent endometrial carcinoma. GOG 122 enrolled patients with stage III or IV disease with no residual tumor more than 2 cm and randomized them to whole-abdominal irradiation versus doxorubicin and cisplatin. In this trial, both progression free and overall survival favored chemotherapy and help establish chemotherapy as standard postoperative treatment in patients with advanced or recurrent disease. [79]. GOG 177 also tested the doxorubicin and cisplatin combination with and without paclitaxel in patients with measurable stage III, stage IV or recurrent endometrial carcinoma. The three-drug combination improved response rate, progression-free, and overall survival at a cost of significant neurotoxicity [87]. The GOG subsequently tested paclitaxel, doxorubicin, and cisplatin against what had largely become the community standard of carboplatin and paclitaxel. This trial (GOG 209), which enrolled a population similar to GOG 177 and reported thus far in abstract only, demonstrated non-inferiority of carboplatin and paclitaxel with less toxicity [88]. Based on this, carboplatin and paclitaxel became the standard of care and the backbone for further trials in combination with targeted therapies.

GOG 86P adopted the carboplatin and paclitaxel backbone of GOG 209 and used it as a historical control. This trial compared paclitaxel, carboplatin, and bevacizumab to paclitaxel, carboplatin, and temsirolimus, or ixabepilone, carboplatin, and bevacizumab in stage III or IVA (with measurable disease) or Stage IVB or recurrent (with or without measurable disease) endometrial cancer. Forty percent of patients on this trial had recurrent, chemotherapy naïve disease. Progression free survival, the primary endpoint, was not significantly better in any arm compared to historical controls from GOG 209. The overall survival was significantly increased with the addition of bevacizumab when compared to historical controls treated with carboplatin/paclitaxel [89].

The addition of trastuzumab to carboplatin/paclitaxel significantly improved PFS in select patients. The greatest benefit was seen in the 41 patients with stage III or IV HER2/neu-positive uterine serous carcinoma undergoing primary treatment (9.3 versus 17.9 months; $P = 0.013$; HR, 0.40; 90% CI, 0.20 to 0.80) and a smaller benefit was seen in recurrent uterine serous carcinoma ($n=17$; 83% received 1–2 prior lines of treatment; 9.2 v 6.0 months; HR, 0.14; 90% CI, 0.05 to 0.54; $P = 0.003$) while overall survival data are still immature [90].

5.6. Clinical question 6

What is the preferred treatment for women with uterine carcinosarcoma?

5.6.1. Recommendation 6.1. In the primary setting, paclitaxel and carboplatin is the preferred regimen for these patients (BII) [91].

5.6.2. Literature review. The treatment of uterine carcinosarcoma evolved uniquely in the gynecologic cancer literature. Initially studied with uterine sarcomas, it is now recognized as a dedifferentiated carcinoma and considered a high-risk variant of endometrial adenocarcinoma. During this evolution, carcinosarcomas have been prospectively studied independent of other histologies [92–94]. GOG 261 accrued 536 patients with stage I – IV, persistent or recurrent uterine carcinosarcoma in a randomized controlled trial comparing ifosfamide plus paclitaxel to carboplatin plus paclitaxel. Preliminary results presented in 2019 demonstrated non-inferiority of the experimental carboplatin arm with longer progression free survival. Hematologic toxicity was increased in the carboplatin arm but there was significantly less confusion and genitourinary hemorrhage while quality of life and neurotoxicity were similar. There is broad consensus that these results establish a new standard regimen for women with carcinosarcoma [95].

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Declaration of Competing Interest

The authors of this paper report that they have no conflicts of interest related to any of the content of this manuscript.

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Review Article

Endometrial cancer: A society of gynecologic oncology evidence-based review and recommendations, part II

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HIGHLIGHTS

- Context of recurrence drives treatment options to include combination approaches.
- Surveillance and survivorship should be tailored for endometrial cancer patients.
- Fertility and ovarian preservation can be considered for select patients.
- Primary radiation is reasonable for patients who are not surgical candidates.

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ABSTRACT

In 2014, the Society of Gynecologic Oncology's Clinical Practice Committee published a clinical update reviewing the treatment of women with endometrial cancer. At that time, there had been significant advances in the diagnosis, work-up, surgical management, and available treatment options allowing for more optimal care of affected women.

This manuscript, Part II in a two-part series, includes specific recommendations on treatment of recurrent disease, post treatment surveillance and survivorship, considerations for younger women, and special situations. Part I covered histopathology and molecular pathology, risk factors, presentation and diagnostic approach, surgical approach and adjuvant therapy.

Contents

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1. Treatment of recurrent disease

1.1. Clinical question 1

What are the treatment options for pelvic recurrence?

Recommendation 1.1

In patients not previously radiated, pelvic radiation is recommended and can be used for nodal and/or vaginal recurrences. In general, this should be administered as external beam radiation therapy (EBRT), either 3-D conformal or intensity modulated radiotherapy (IMRT), followed by brachytherapy performed using either an intracavitary or an interstitial technique.

Recommendation 1.2

Prior to radiation, surgical resection may be considered for isolated pelvic tumors that are resectable and not considered curable without resection (CII).

Recommendation 1.3

Chemotherapy may be considered for those with high risk of extra-pelvic relapse (CII).

Literature review

Ten to 15% of patients with intermediate risk endometrial cancer experience a pelvic recurrence after surgery alone [1,2]. Adjuvant radiation decreases the risk of pelvic relapse to less than 5% [1–3]. The majority of recurrences (63–75%) will be vaginal [1]. In PORTEC 1, 89% of patients with vaginal relapse who were treated with curative intent, usually EBRT and vaginal brachytherapy (VBT), and occasionally surgery, achieved complete remission. Five-year overall survival after vaginal recurrence in patients without prior radiation was 65%, compared to 43% for patients with a vaginal recurrence who received prior adjuvant radiation. Treating with EBRT prior to brachytherapy treats lymph nodes and paravaginal tissues that may harbor microscopic disease while at the same time shrinking gross vaginal disease allowing lower doses of radiation to surrounding organs. Additionally, image-guided brachytherapy has demonstrated encouraging results potentially through improved target delineation, local control and normal tissue sparing [4]. EBRT or IMRT can also be used effectively to treat nodal recurrences of endometrial cancer and long-term survival can be achieved [5]. In contrast to isolated vaginal recurrence, only 20% of patients with a pelvic relapse treated with curative intent reached complete remission and survival after pelvic relapse is similar to distant recurrence (3-year OS 8% and 14%, respectively) [6].

Treatment of recurrent endometrial cancer after prior radiation is clearly more challenging. With modern imaging and radiation techniques the dose to the target can be optimized while limiting the dose to surrounding critical organs to minimize morbidity and radiation related complications. Several studies have reported on re-irradiation. Ling and colleagues described 22 patients with a vaginal recurrence who previously received vaginal brachytherapy (55%), pelvic radiation (23%) or both modalities (22%). Treatment for vaginal recurrence was with curative intent. With a cumulative rectosigmoid and bladder dose limited to <75 Gy and <90Gy, treatment was overall well tolerated without grade≥3 radiation related toxicities. Three-year local control was 65% with 41% disease free survival. Most studies report that local control and survival are improved with combined brachytherapy and external beam RT compared with either modality alone [7]. Improved outcomes have also been reported with the use of higher doses of radiation (>80 Gy) [7,8] and image-guided brachytherapy [9–11]. Whether concurrent chemotherapy can further improve disease control and survival is currently being studied in GOG 238 which is a randomized trial of pelvic radiation with or without concurrent weekly cisplatin in women with pelvic-only recurrences of endometrial carcinoma.

While it is encouraging that many vaginal (and some pelvic) recurrences can be salvaged, it is important to note that close surveillance in PORTEC-1 allowed many recurrences to be detected early while still small tumors. Outcomes vary greatly in retrospective studies with and without prior radiation. Two to five-year local control is 44–100%, relapse free survival 26–96%, and overall survival 35–80% [4].

For those patients who have received prior radiation and for whom re-irradiation is not an option, pelvic exenteration may be the only alternative for treatment with curative intent. Unfortunately, 5-year overall survival is 20–60% and the morbidity of the procedure is high [12–15], with the worst outcomes for those with node positive disease.

1.2. Clinical question 2

What are the treatment options for extra-pelvic recurrence?

Recommendation 2.1

Surgery may be considered in select cases where complete surgical resection is feasible and safe. (CII).

Recommendation 2.2

Systemic therapy with either chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or a combination regimen, is recommended for patients with an extra-pelvic recurrence (AI, AII).

Literature review

The role of secondary cytoreductive surgery in recurrent endometrial cancer is not well defined and is mostly based on small retrospective studies and case reports. Bristow et al. identified 35 patients who underwent secondary cytoreductive surgery. Complete cytoreduction was achieved in 66% of patients. Those with no gross residual disease had improved survival (39 months) compared to those with residual disease (13.5 months) which was similar to those treated without surgery (13 months) [16]. Patients with isolated distant metastases such as isolated para-aortic lymph node recurrence may achieve prolonged disease-free survival with surgical resection [17]. Unfortunately, most patients with a distant recurrence present with multifocal disease. While in some cases surgery may be appropriate, most patients will require systemic therapy. Until recently, there were only two Food and Drug Administration (FDA) approved treatment options. These included megestrol acetate hormonal therapy, and pembrolizumab immunotherapy for mismatch repair deficient tumors. Twenty to 30% of endometrial cancers have defective DNA mismatch repair. In 2017, The FDA granted accelerated approval to pembrolizumab (anti PD-1)

as the first tissue agnostic therapy for mismatch repair deficient solid tumors that progressed following prior treatment. A preliminary study including 15 MMR deficient endometrial cancers demonstrated a 53% objective response rate and 73% disease control rate [18]. A recent update showed an ORR 57% and median PFS of 25.7 months amongst 49 patients with dMMR recurrent endometrial cancer [19]. In the KEYNOTE-028 phase IB trial, 24 patients with pretreated PD-L1 positive endometrial cancers, there was a 13% partial response rate with median duration of response not reached and 13% stable disease rate with median duration of response 25 weeks [20].

In September 2019, the FDA approved combination pembrolizumab and lenvatinib for the treatment of recurrent endometrial cancer without microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation [21].

This was based on the results of the advanced endometrial cancer cohort of the single arm phase Ib/II Keynote-146/Study 111. With extended follow-up, the combination demonstrated favorable efficacy with an overall response rate of 38% and median PFS of 7.4 months. The overall response rate in microsatellite stable disease was 37.2% and 63.6% in MSI-H tumors. Sixty-seven percent of patients experienced grade 3 or 4 treatment-related adverse events and 18% discontinued one or both study drugs due to adverse events [20].

Hormonal therapy is an option to control recurrent disease, especially for patients with low grade endometrial cancer and/or for patients unable to tolerate chemotherapy, however duration of response may be limited. Progestin therapy with megestrol acetate was approved over 40 years ago and is overall very well tolerated. GOG 153 evaluated tamoxifen 20 mg twice daily for three weeks alternating with megestrol acetate 80 mg twice daily for three weeks and reported a 27% response rate. Higher response rates are seen in patients with grade 1 disease compared to grade 3 (38% vs 22%), women less than age 60, and in patients with extra-pelvic disease [22]. Although the median progression free survival was 2.7 months, in 53% of responders the response duration was greater than 20 months. A dosing schedule of tamoxifen 40 mg daily with alternating weekly cycles of medroxyprogesterone acetate 200 mg daily was also beneficial with a 33% response rate [23]. Aromatase inhibitors have minimal activity as single agents [24,25], but in combination, letrozole and everolimus demonstrated encouraging activity with an objective response rate of 24–32% and median duration of response of 15 months [26,27]. Combination letrozole and palbociclib is currently being investigated in the PALEO study through the NSGO, and letrozole and ribociclib through NRG Oncology.

Patients with recurrent endometrial cancer who have not received prior chemotherapy are typically treated with chemotherapy or hormonal therapy. Based on GOG 209, carboplatin and paclitaxel is the standard of care for these patients [28]. For patients with recurrence and prior chemotherapy with a long platinum free interval, combination platinum retreatment is reasonable. Several single agents have been tested in the second line. The GOG-129 single arm phase II series evaluated cytotoxic agents in patients with one prior cytotoxic regimen. Response rates were generally less than 15% except for paclitaxel, which was used prior to adoption of paclitaxel in the front-line setting. The GOG-229 series explored a series of the targeted agents in recurrent and persistent endometrial cancer with modest response rates ranging from 0% - 24.5% potentially warranting further investigation [29]. In the MITO END-2 trial, all patients had one prior line of platinum-based chemotherapy and progressed greater than 6 months after completion of prior platinum. This trial showed improved response rate with the addition of bevacizumab to carboplatin/paclitaxel (54% vs 73%) and improved PFS (8.7 vs 13 months, HR 0.57 [0.34, 0.96], $p = 0.036$) [30]. Historically, doxorubicin demonstrated efficacy in endometrial cancer [28]. Although response rates were 19–37% in the first line, when tested in the second line in a phase III trial, doxorubicin demonstrated an objective response rate of 14%, PFS 4.7 months, and OS 10.8 months [28]. Similarly, liposomal doxorubicin demonstrated limited activity with an overall response rate of 9.5% in previously treated metastatic endometrial cancer in the GOG's phase II trial [31].

1.3. Clinical question 3

What pathologic / molecular testing should be considered to guide treatment?

Recommendation 3.1

Pathologic and molecular testing can help guide treatment decisions and identify (on label) targeted treatment options. Mismatch repair status and/or microsatellite instability testing should be performed on all endometrial tumors to 1) screen for Lynch syndrome, and 2) determine eligibility for (future) single agent immunotherapy use (AI). HER2Neu testing is recommended for serous uterine cancers to determine eligibility for trastuzumab (AI, preferred). Hormone receptor status (estrogen and progesterone receptor status) should be performed to evaluate possible candidates for hormonal therapy (AII). Next generation sequencing may help identify other possible targetable mutations (BII).

Literature review

Hormonal treatment for endometrial cancer makes it one of the first cancers to be treated based on molecular features. As discussed in greater detail in the section on extra-pelvic recurrence, with modern advances, tailored treatment continues to hold great promise. Tumors should be tested for mismatch repair proteins / microsatellite instability based on efficacy of anti PD-1 therapy and an FDA approved therapeutic [18,19]. HER2 immunohistochemistry (IHC) testing (with reflex to HER2 FISH testing for equivocal IHC) should be considered to guide the treatment of advanced stage or recurrent serous endometrial cancer based on compelling phase II data [32]. Next Generation Sequencing is CMS approved for advanced solid tumors and may provide a tool to identify targeted mutations which can help guide treatment and highlight patients who may be eligible for targeted therapy basket trials. Part I of this review further discusses the basis of current molecular pathologic recommendations.

2. Post treatment surveillance and survivorship

2.1. Clinical question 1

What is the appropriate follow-up for women after treatment of endometrial cancer?

Recommendation 1.1

A speculum and pelvic examination, in addition to a review of systems to elicit any new symptoms associated with a possible recurrence, should be completed every 3–6 months for 2 years, and every 6–12 months thereafter in patients with endometrial cancer (CIII). It is acceptable to follow patients with low-risk endometrial cancer with less frequency (e.g. every 6–12 months for first 2 years, then yearly thereafter) (CIII).

Recommendation 1.2

Do not perform cytology (Pap tests) of the vaginal cuff in patients with a history of endometrial cancer and no prior history of high-grade cervical dysplasia (CII).

Recommendation 1.3

Imaging (e.g. CT scans, PET/CT scans) should be used if there is a suspicion for recurrent disease (CIII).

Literature review

In addition to detecting treatable, recurrent disease, surveillance provides psychosocial reassurance and may improve quality of life. Prospective data does not guide current recommendations. Given that most

endometrial cancers are early stage when initially diagnosed and treated, and that recurrence is often local and curable, a cost-effective surveillance strategy is desirable. An institutional review of the incorporation of the initial 2011 SGO surveillance guidelines, which focused on physical exam and symptoms as primary surveillance, reported equivalent outcomes with appreciable decrease in surveillance costs [33]. Separate surveillance guidelines set forth by the NCCN and SGO are largely congruent, and the SGO guidelines offer a stratified approach based on low and high-risk characteristics [34]. Although the current NCCN guidelines recommend a physical examination every 3–6 months for 2–3 years, then 6 months or annually it is reasonable for patients with low-risk endometrial cancer to be followed with less frequency [34]. The SGO review recommends a thorough speculum and pelvic examination in addition to a review of systems to elicit any new symptoms associated with recurrence, such as vaginal bleeding, abdominal or pelvic pain, weight loss, headaches, coughing, or lethargy [34]. NCCN supplements this list with bladder or rectal bleeding, decreased appetite, shortness of breath, and swelling in the abdomen or legs.

The SGO recommends against vaginal cytology to aid in the detection of recurrence at the vaginal cuff. Most vaginal recurrences are detected with clinical examination alone, and asymptomatic recurrences are infrequently detected with vaginal cytology [35–37]. The NCCN and SGO recommend that radiologic evaluation such as CT or PET/CT scans be used only if there is concern for recurrence. However, the NCCN notes that for patients with treated stage III-IV disease, CT of the chest, abdomen, and pelvis every 6 months is an option [36]. The NCCN and SGO recommend that CA-125 may be used in surveillance for those patients who have an elevated CA-125 prior to treatment. The SGO notes that the use of CA-125 may also be appropriate in patients with advanced disease or serous endometrial cancer [34].

Although patients may prefer that surveillance care be provided by an oncologist, it is also safe and reasonable for patients with low-risk endometrial cancer to be followed by a gynecologist once two years have elapsed from their treatment [36]. Patients with advanced stage disease and/or high-risk histologic types should be followed by a gynecologic oncologist until five years have elapsed since their treatment, although alternating visits can be considered.

2.2. Clinical question 2

Are there survivorship issues unique to endometrial cancer patients?

Recommendation 2.1

Following treatment, endometrial cancer patients should be counseled on the impact of obesity, lifestyle and nutrition (CIII).

Literature review

One of the most common risk factors for endometrial cancer is obesity, therefore obesity-related comorbidities should be addressed in the survivorship period. Highlighting this, cardiovascular disease is the leading cause of death in endometrial cancer survivors making interventions to address cardiac risk factors a necessary part of a survivorship care plan [38]. Although weight and obesity have not been found to impact the risk of endometrial cancer recurrence [39], obesity affects both quality of life and overall survival.

3. Endometrial cancer considerations for younger women

3.1. Clinical question 1

How should patients considering fertility-sparing options be evaluated?

Recommendation 1.1

Patients who desire fertility sparing treatment should be evaluated by D&C (Preferred) or endometrial biopsy to evaluate grade. (AII).

Recommendation 1.2

An MRI to evaluate for myometrial invasion, lymphadenopathy, and adnexal pathology should also be completed (AII).

Literature review

Although the majority of endometrial cancer patients are postmenopausal, up to 14% of women are premenopausal, and 4% younger than 40 years old [40,41]. This trend is expected to increase with the increasing prevalence of obesity, and though younger women are more likely to be stage I and have low-grade disease, 20% will still be diagnosed with disease beyond the uterus and over half with higher grade disease [41]. This poses a unique treatment challenge in this population where fertility preservation, ovarian conservation, and long-term treatment toxicity must be balanced with the oncologic risk of non-standard treatment [42,43].

The most common risk factors for the development of endometrial cancer in young women are increasing body mass index (BMI), nulliparity, and irregular menstrual cycles [44]. Polycystic ovary syndrome, a common cause of anovulatory cycles associated with excessive endogenous estrogen, has also been associated with an increased risk of endometrial cancer [45,46]. The risk for developing endometrial cancer may be increased as much as 22-fold in women younger than 45 years of age with BMIs that are greater than 35. There may be an increased rate of mutations associated with Lynch syndrome in young women with endometrial cancer. A prospective multi-institutional study found a 9% rate of germline mutations associated with Lynch syndrome in women younger than 50 years old who developed endometrial cancer [47]. Predictors of germline mutation were a first-degree relative with a Lynch-syndrome associated cancer, tumor with loss of MSH2 expression, tumors with high microsatellite instability and lower BMI. Currently, the SGO and American College of Obstetricians and Gynecologists recommend a systematic approach to identifying women with Lynch syndrome that includes either selective or universal tumor testing of endometrial carcinomas for MMR proteins or MSI testing [48].

While hysterectomy is considered standard of care for endometrial cancer, fertility-sparing options should be considered with appropriate counseling for a young patient desiring future fertility. Data on long-term and pregnancy-related outcomes are limited by small sample size. A key principle of the evaluation of patients is ensuring the presence of a grade 1 endometrioid tumor limited to the endometrium; such tumors have a lower risk of extrauterine or nodal metastases. In a Swiss registry study, only 18% of endometrial cancer patients aged 45 years or younger had stage IA, grade 1 disease [49]. For women who wish to pursue fertility-sparing options, dilation and curettage (D&C) is preferred for evaluating the tumor grade. In a review of more than 1400 cases of endometrial cancer, post-hysterectomy grade was higher in 8.7% of cases diagnosed by D&C which was significantly lower compared to 17.4% diagnosed by office endometrial sampling [50]. MRI is preferred for assessment for myometrial invasion and adnexal pathology or alternatively, transvaginal ultrasound if MRI is not available. A meta-analysis demonstrated that MRI has a better sensitivity than ultrasound for detecting deep myometrial invasion [51]. Several authors and the SGO recommend assessment of tumor progesterone status to better identify ideal candidates for conservative treatment [52]. Though there is limited data from fertility-sparing series and reports, a historical review reported response rates to progestin therapy of 72% for progesterone-positive tumors and 12% for progesterone-negative tumors [53]. In parallel with the above work-up, the clinician and patient, in the process of shared decision making, should discuss the likelihood of attaining pregnancy, potentially with consultation from an infertility specialist.

3.2. Clinical question 2

What is the recommended fertility-sparing treatment of endometrial cancer?

Recommendation 2.1

Progestin therapy with oral or intrauterine progestins should be used (AII).

Literature review

Progestins have been the mainstay of conservative hormonal treatment for endometrial cancer in young woman who want to preserve fertility. These progestin-based therapies include the levonorgestrel-releasing intrauterine system (L-IUS), medroxyprogesterone acetate (MPA) and megestrol acetate. Others have suggested combined oral and intrauterine progestins [54] or hysteroscopic resection followed by L-IUS placement [55]. In a systematic review of oncologic outcomes in patients with grade 1 adenocarcinoma treated with progestins, the complete response rate was 48.2%. The risk of recurrence after initial response was 35.4% in women with carcinoma; persistent disease was noted in 25.4% [56]. In patients with hyperplasia, a review and meta-analysis noted that the response rate with the levonorgestrel IUS was higher for complex and atypical hyperplasia compared with oral progestins [57]; however, in a review of patients with complex atypical hyperplasia or early endometrial adenocarcinoma, the treatment with oral or intrauterine progestin was noted to be similarly effective. [58]

3.3. Clinical question 3

How long can a patient be treated conservatively before treatment is considered unsuccesful?

Recommendation: 3.1

Fertility sparing treatment for endometrial cancer is typically continued for 6–12 months (BII).

Recommendation 3.2

Patients will need to be thoroughly counseled about the risks and benefits of fertility sparing endometrial cancer treatment (BIII).

Literature review

The optimal regimen, route and follow-up of progestin therapy is not well defined, as most available data are limited to retrospective series and reviews. Following the initiation of progestin-based therapy, it is recommended to repeat sampling with office biopsy or D&C in 3–6 months. In the review by Gunderson et al., the median time to complete response to progestin therapy was 6 months [56]. Hysterectomy with staging should be considered once childbearing is complete, if patients have documented progression on biopsies, and/or of endometrial cancer is still present after a specified duration of progestin-based therapy. A recent review of patients <45 years of age from the SEER database revealed no difference in survival for patients treated with progestin compared to those undergoing hysterectomy [59].

A systematic review of reproductive outcomes for patients with grade 1 adenocarcinoma treated with progestins showed that nearly 35% of those with a history of carcinoma became pregnant [56]. A case series accompanied by a systematic review noted 65 deliveries with 77 live births; these pregnancies resulted from both assisted reproductive technologies and spontaneous conceptions. One maternal death was seen due to recurrent disease [60]. Though pregnancy outcomes have been promising, it is important each patient understand the high likelihood of needing reproductive technology. Consultation with a Reproductive Endocrinologist concomitant with beginning medical therapy is advised [61].

3.4. Clinical question 4

Can ovarian preservation be considered?

Recommendation 4.1

Ovarian preservation may be considered in premenopausal women with low grade, early stage endometrial cancer with normal appearing adnexa and no evidence of extra-uterine disease (CII).

Recommendation 4.2

Risk-reducing hysterectomy and bilateral salpingo-oophorectomy is the recommended risk-reducing option for women with Lynch syndrome who have completed childbearing with a suggested age of 40 to 45 years old. For women considering hysterectomy with ovarian preservation, complete resection of the fallopian tubes is recommended. (AII).

Literature review

Traditionally, surgeons perform bilateral salpingo-oophorectomy (BSO) in conjunction with hysterectomy to detect occult disease and reduce recurrence risk from continued estrogen production. With an evolving knowledge of the health risks of oophorectomy in premenopausal women [62], there is interest in the impact of ovarian preservation. A recent institutional review showed that in patients with pelvic-confined disease, only 0.8% had microscopic ovarian involvement; all patients with ovarian involvement had FIGO grade 3 disease, deep myometrial invasion and extrauterine involvement of either cervix or lymph nodes [63]. The Korean Gynecologic Oncology Group demonstrated that in a group of women with stage I-II endometrial cancer who had ovarian preservation, there were no recurrences in patients with stage IA disease [64], and ovarian preservation did not have an impact on either recurrence-free or overall survival [65]. Similarly, an analysis of ovarian preservation at the time of hysterectomy for women with early stage endometrial cancer using the National Cancer Database found no excess deaths associated with ovarian preservation [66]. Accumulating data including recent systematic reviews appear to confirm the safety and perhaps benefits of ovarian preservation in younger patients with early-stage endometrial cancer [56]. Earlier reports raised concern for synchronous ovarian malignancy which was reported in a younger patient population to be as high as 25% [67,68]. However, the majority of these patients either had identifiable extrauterine disease at the time of surgery or gross abnormalities of the ovary. For women without gross extrauterine disease and normal appearing adnexa, the risk of ovarian involvement appears to be less than 1% [69].

The recommendation for risk-reducing hysterectomy combined with bilateral salpingo-oophorectomy in young women with Lynch Syndrome largely stems from a study of a retrospective cohort of 315 women with Lynch syndrome. In this study 61 and 47 women underwent risk-reducing hysterectomy and risk-reducing bilateral salpingo-oophorectomy respectively and they were matched with mutation positive women who had not undergone risk reducing surgery. The incidence of both endometrial and ovarian cancer was significantly lower in the patients who had risk reducing surgery. No patients in the surgery groups developed endometrial or ovarian cancer compared to 33% and 5% in the non-surgery group who developed endometrial and ovarian cancer respectively [70]. Risks and benefits of ovarian preservation should be thoroughly discussed inclusive of the implications of surgically induced menopause and the limited data at present regarding lifetime risk of ovarian cancer with specific mutations. If the ovaries are preserved, the complete fallopian tubes should be removed as fallopian tube cancers have been reported [48,71].

3.5. Clinical question 5

Are patients with a personal history of endometrial cancer candidates for estrogen therapy for menopausal symptoms?

Recommendation 5.1

In patients with low grade, early stage endometrial cancer, hormonal therapy can be considered for postmenopausal patients with severe menopausal symptoms not otherwise relieved (CII).

Literature review

Historically the use of estrogen therapy after endometrial cancer treatment raised concerns for increasing risk of cancer recurrence. This concern has largely been resolved by studies demonstrating

the safety of estrogen therapy in postmenopausal women with endometrioid endometrial cancer [72]. In GOG 137, patients with stage I-II endometrial cancer were randomly assigned to estrogen therapy. Due to the publication of the Women's Health Initiative during the study period, the study was terminated prior to meeting its accrual goal. The overall recurrence rate was 2% and although the study could not statistically refute or support the use of estrogen, the investigators concluded that in patients with low grade stage I-II endometrial cancer, hormone therapy appears to be associated with a low risk of endometrial cancer recurrence. Additional case-control studies support these findings [73,74]. Although a meta-analysis notes the safety of hormone replacement [75], there are limited data on the use of hormone replacement in patients with Type II and/or advanced stage endometrial cancers.

4. Special situations

4.1. Clinical question 1

Should surgical staging be completed in all patients who have an incidental diagnosis of endometrial cancer following hysterectomy for another indication?

Recommendation 1.1

Women found to have endometrial cancer incidentally after hysterectomy should have their risk for extrauterine disease and potential for disease recurrence evaluated based on age, histologic cell type, and uterine tumor features. Individualized treatment plans can be based on the findings (B).

Literature review

The need for repeat surgery for the sole purpose of staging in women discovered to have endometrial cancer following a hysterectomy should be considered carefully. A dedicated study will probably never be performed because of the relative rarity of the situation. Comprehensive pathology review is mandatory in order to retrieve as much information as possible about the features of the uterine cancer, including histologic cell type, FIGO grade, depth of myometrial invasion, presence of lymphovascular space invasion, and tumor size. If such a patient has a tumor with endometrioid histology, grade 1 or 2 tumors, small tumor volume, and superficial myometrial invasion, further intervention may not be indicated after hysterectomy because these features are compatible with a low risk of extrauterine disease and recurrence [76]. Patients who have intermediate- or high-risk features for extrauterine spread or recurrence, patients with high-risk histologic cell types, and older patients should be considered for comprehensive surgical staging. If the patient is a good candidate for surgery, comprehensive staging can be beneficial either by helping avoid unnecessary adjuvant therapies or by guiding such therapies.

If the patient is not a good surgical candidate and/or has uterine features suggestive of intermediate to high risk for extrauterine disease or disease recurrence, imaging along with CA 125 can be used to evaluate for extrauterine disease. The addition of PET to CT scan has been found to have improved sensitivity for detecting nodal metastases while maintaining the specificity of CT scan [77]. Adjuvant radiation and/or chemotherapy can be administered based on the outcome of the diagnostic evaluation.

4.2. Clinical question 2

Can radiotherapy be used as a primary treatment modality for endometrial cancer?

Recommendation 2.1

Select women diagnosed with endometrial cancer who are not candidates for surgery can be treated with primary radiation therapy. Some patients may also benefit from chemotherapy (BII).

Literature review

In patients who cannot undergo hysterectomy or surgical staging following a diagnosis of early stage endometrial cancer, primary RT with external beam radiation and intracavitary radiation remains a reasonable option for loco-regional disease control. Several studies evaluated patients in this unique circumstance. The five-year overall survival following primary radiation therapy ranges from 39 to 71% [78,79] but locoregional control and cancer-specific survival can be excellent with rates of 90% and 86% respectively in one study of 45 inoperable clinical stage I patients treated with high-dose rate image-guided brachytherapy [80,81]

Imaging may be used to assess for extrauterine disease. This may allow for consideration of palliative chemotherapy following completion of radiation therapy, or for determination of metastatic disease that may benefit from palliative radiation. Those women who have been diagnosed with high-risk histology, such as grade 3 endometrioid, clear cell, serous and carcinosarcoma, should be considered for palliative chemotherapy. In addition, molecular studies may identify patients who may benefit from palliative treatment with hormones or immunotherapy.

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Declaration of Competing Interest

The authors of this paper report that they have no conflicts of interest related to any of the content of this manuscript.

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