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Radiation Therapy for Endometrial Cancer: An ASTRO Clinical Practice Guideline

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FULL-TEXT GUIDELINE

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Radiation Therapy for Endometrial Cancer: An ASTRO Clinical Practice Guideline

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Adherence to this guideline does not ensure successful treatment in every situation. This guideline should not be deemed inclusive of all proper methods of care or of all factors influencing the treatment decision, nor is it intended to be exclusive of other methods reasonably directed to obtaining the same results. The physician must make the ultimate judgment regarding therapy considering all circumstances presented by the patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. This guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials. This guideline is based on information available at the time the task force conducted its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may, over time, be a basis for ASTRO to revisit and update the guideline.

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Abstract

Purpose: With the results of several recently published clinical trials, this guideline informs on the use of adjuvant radiation therapy (RT) and systemic therapy in the treatment of endometrial cancer. Updated evidence-based recommendations provide indications for adjuvant RT and the associated techniques, the utilization and sequencing of adjuvant systemic therapies, as well as the impact of surgical staging techniques and molecular tumor profiling.

Methods: The American Society for Radiation Oncology (ASTRO) convened a multidisciplinary task force to address 6 key questions that focused on the adjuvant management of patients with endometrial cancer. The key questions emphasized the 1) indications for adjuvant RT, 2) RT techniques, target volumes, dose-fractionation, and treatment planning aims, 3) indications for systemic therapy, 4) sequencing of systemic therapy with RT, 5) impact of lymph node assessment on utilization of adjuvant therapy, and 6) impact of molecular tumor profiling on utilization of adjuvant therapy. Recommendations were based on a systematic literature review and created using consensus-building and ASTRO's Guideline Methodology for quality of evidence grading and strength of recommendation.

Results: The task force recommends RT (either vaginal brachytherapy or external beam radiation therapy [EBRT]) be given based on the patient's clinical-pathologic risk factors to reduce risk of vaginal and/or pelvic recurrence. When EBRT is delivered, intensity modulated radiation therapy with daily image guided radiation therapy is recommended to reduce acute and late toxicity. Chemotherapy is recommended for patients with FIGO stage I-II with high-risk histologies and those with FIGO stage III-IVA with any histology. When sequencing chemotherapy and RT, there is limited data and no prospective data to support an optimal sequence. Sentinel lymph node mapping is recommended over pelvic lymphadenectomy for surgical nodal staging, and use of adjuvant therapy should be based on the pathologic ultrastaging status with isolated tumor cells treated as node negative and micrometastasis treated as node positive. The available data on molecular characterization of endometrial cancer is compelling and should be increasingly considered when making recommendations for adjuvant therapy.

Conclusions: These recommendations guide evidence-based best clinical practices on the use of adjuvant therapy for endometrial cancer.

Preamble

As the leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy — ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplemental Materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members — ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and inclusive multidisciplinary group of experts considering race, ethnicity, gender, experience, practice setting, and geographic location. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force, as well as a patient representative.

Methodology — ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix E2 in Supplemental Materials for a list of abbreviations used in the guideline.

Consensus Development — Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree." A prespecified threshold of ≥75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates — Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden, or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

1. Introduction

Endometrial cancer is the most frequently diagnosed gynecologic malignancy in the United States.[3] Endometrial cancer is surgically treated and staged with total hysterectomy, bilateral salpingo-oophorectomy (TH-BSO) with or without lymph node assessment. Despite most patients being diagnosed at an early stage, those with risk factors for recurrence and those with advanced stage disease are routinely recommended to undergo adjuvant therapy to reduce the risk of recurrence, and in some scenarios, improve overall survival (OS). There are several high-quality randomized controlled trials (RCTs) which have evaluated the impact of adjuvant therapy in patients with endometrial cancer, including several recently published trials. Despite these trials, questions remain regarding the relative roles and sequencing of external beam radiation therapy (EBRT), vaginal brachytherapy (VBT), and systemic therapies, making application to clinical practice challenging.

In 2014, the American Society for Radiation Oncology (ASTRO) published a guideline on postoperative radiation therapy for endometrial cancer.[4] Since publication, several trials across risk groups and stages of endometrial cancer have reported on the role of adjuvant radiation therapy (RT) and systemic therapy. Additionally, trials on the accuracy of surgical staging techniques (like sentinel lymph node [SLN] mapping and pathologic ultrastaging) have changed the landscape of surgical management, and research on how these surgical techniques should impact adjuvant therapy selection continues. Four distinct molecular subsets of endometrial cancer have been identified as *polymerase epsilon (POLE)* ultramutated, microsatellite instability hypermutated, copy number low, and copy number high with quite varied prognoses.[5] The prognostic and predictive use of molecular profiling of endometrial cancer is now recognized and its impact on adjuvant therapy selection is increasing with ongoing trials aiming to confirm this influence on endometrial cancer management. As a result, a revised ASTRO guideline acknowledging these important updates and the possible impact these advancements may have in the adjuvant treatment of endometrial cancer is warranted.

2. Methods

2.1. Task force composition

The task force consisted of a multidisciplinary team of radiation oncologists, medical oncologists, and gynecologic oncologists, a medical physicist, a radiation oncology resident, and a patient representative. This guideline was developed in collaboration with the American Brachytherapy Society, American Society of Clinical Oncology, and the Society of Gynecologic Oncology, who provided representatives and peer reviewers.

2.2. Document review and approval

The guideline was reviewed by 16 official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment in May 2022. The final guideline was approved by the ASTRO Board of Directors and endorsed by the European Society for Radiotherapy and Oncology (others TBD).

2.3. Evidence review

A systematic search of human participant studies retrieved from the Ovid MEDLINE database was conducted for English publications from January 2000 (for RCTs, meta-analyses, and prospective studies) and January 2015 (for retrospective studies) through August 2021. The inclusion criteria required studies to involve adults (age ≥18 years), with a diagnosis of nonmetastatic endometrial carcinoma (stages I-IVA). Retrospective studies were limited to more recent publications (for KQ2-KQ6) to reflect modern treatment techniques while KQ1 excluded all retrospective studies. For all publication types the literature review included studies with ≥25 participants. For specific subquestions where there was limited data available, expert opinion was relied upon to support recommendations as reflected in the low-to-moderate quality of evidence cited in these cases.

The following concepts were searched using Medical Subject Heading (MeSH) terms and key search terms: *endometrial cancer, endometrial carcinoma, endometrial neoplasms/radiotherapy, uterine cancer, radiation therapy, systemic therapy, antineoplastic agents, chemotherapy, adjuvant therapy, intensity modulated radiation therapy, external beam radiation therapy, brachytherapy, sentinel lymph node, molecular markers, p53, microsatellite instability, mismatch repair, polymerase E, POLE, treatment outcome, survival, recurrence, quality of life and patient reported outcome.* Additional terms specific to the KQs and hand searches supplemented the electronic searches. Preclinical studies, large registry/database studies, review articles, comments, and editorials were excluded from literature search. Health economics and cost analyses, dosimetric/contouring studies, studies focused on diagnostic methods were also excluded.

The data used by the task force to formulate recommendations are summarized in evidence tables available in the Supplementary Materials, Appendix E4. References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the evidence tables are included in the text but were not used to support the recommendations. The outcomes of interest are listed in Table 2 and include vaginal control, locoregional control, distant metastases rate, OS, acute and late toxicity, and quality of life.

See the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the number of articles screened, excluded, and included in the evidence review, and Appendix E3 in Supplemental Materials for the complete literature search strategy which includes the evidence search parameters and inclusion/exclusion criteria.

2.4. Scope of the Guideline

The scope of this guideline focuses on the adjuvant management of endometrial cancer and emphasizes the evolving impact that uterine risk factors and disease stage (KQ1-4), surgical staging procedures (KQ5), and molecular tumor profiling (KQ6) have on adjuvant therapy. This guideline discusses the indications for adjuvant VBT, EBRT, and systemic therapy and includes sequencing of these therapies, as well as the impact that surgical nodal staging procedures and molecular tumor profiling decisions may have regarding adjuvant therapy.

Determining which patients benefit from adjuvant therapy in endometrial carcinoma requires consideration of patient and uterine risk factors including age, tumor histology, grade, lymphovascular space invasion (LVSI), and tumor stage. Variable definitions have been used in the literature to define intermediate-, high-intermediate and/or high-risk endometrial carcinoma based on combinations of these factors. For this guideline, specific risk factors are used rather than choosing a particular risk grouping definition. Intermediate-risk factors of recurrence include age ≥60 years and/or focal LVSI. A high-risk factor of recurrence is substantial LVSI, especially without surgical nodal staging, defined as bilateral pelvic sentinel lymph node mapping or

lymphadenectomy. Additionally, all stages from studies reported prior to 2009 are converted to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system for ease and consistency of interpretation. In this guideline, high-risk histologies refer to nonendometrioid histologies such as serous carcinoma, clear cell carcinoma, carcinosarcoma, dedifferentiated carcinoma, undifferentiated carcinoma, or mixed histology carcinoma (combination of histologies that include a high-risk histology). Grade 3 endometrioid carcinoma was not included in this high-risk definition.

Racial disparities in endometrial cancer are noted at all stages of diagnosis and treatment.[6] Black patients have a higher incidence of nonendometrioid histologies, are diagnosed at more advanced cancer stage, are less likely to receive timely surgery and adjuvant therapy, and have poorer survival irrespective of stage or histology.[7,8] Disparities are routinely multifactorial, but social determinants of health including insurance coverage, access to specialty care, financial toxicity, and racism are major drivers. Healthcare equality is paramount to improve receipt of standard of care therapy and patient outcomes, but the complexity of this topic and implementation of solutions is beyond the scope of this guideline.

Additionally, there are many topics that are important to the multidisciplinary management of endometrial cancer which are beyond the scope of this guideline. The details and recommendations regarding primary surgical management of endometrial cancer (except as related to KQ5) are outside of the focus of this guideline. The guideline also does not address endometrial cancers that are metastatic, inoperable, or recurrent, nor management of nonepithelial histologies (ie, sarcomas) as these topics were determined to be beyond the scope of this guideline. This guideline addresses only the subjects specified in the KQs (Table 2).

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	**What are the indications for adjuvant RT in patients with endometrial cancer?**			
	Adult patients with endometrial cancer	• Adjuvant RT (VBT or EBRT)	• Surgery alone	• Local control • Locoregional control • Overall survival • Pelvic control • Vaginal control • Distant metastases
2	**What are the appropriate dose-fractionation regimens, target volumes, and normal tissue constraints for patients receiving adjuvant RT for endometrial cancer?**			
	Adult patients with endometrial cancer undergoing adjuvant RT	• Adjuvant VBT • Adjuvant EBRT	• N/A	• Acute and late toxicity • Patient-reported side effects • Quality of Life
3	**What are the indications for systemic therapy in patients with nonmetastatic endometrial cancer?**			
	Adult patients with nonmetastatic endometrial cancer	• Adjuvant systemic therapy • Adjuvant RT with systemic therapy	• Surgery alone • Adjuvant RT without systemic therapy	• Local control • Locoregional control • Overall survival • Pelvic control • Vaginal control • Distant metastases
4	**What is the appropriate sequencing of systemic therapy with RT in patients with endometrial cancer?**			
	Adult patients with endometrial cancer receiving adjuvant	• Adjuvant RT (VBT or EBRT) sequenced with systemic therapy	The different sequences of the chemotherapy compared to each other	• Local control • Locoregional control • Overall survival

	systemic therapy and RT		• "Sandwich" systemic therapy • Sequenced systemic therapy • Concurrent systemic therapy • Combination of above	• Pelvic control • Vaginal control • Distant metastases
5	**How should the performance of, and type of, lymph node assessment influence adjuvant RT decisions in patients with endometrial cancer?**			
	Adult patients with endometrial cancer undergoing surgical staging including lymph node assessment	• Surgery with sentinel lymph node mapping or biopsy • Surgery with lymph node dissection	• Surgery with lymph node dissection • Surgery without sentinel mapping, biopsy, or lymph node dissection	• Local control • Locoregional control • Overall survival • Pelvic control • Vaginal control • Distant metastases • Detection rate of nodal metastases
6	**How should molecular markers influence adjuvant RT and systemic therapy decisions in patients with nonmetastatic endometrial cancer?**			
	Adult patients with nonmetastatic endometrial cancer	• Adjuvant therapies with molecular markers	• Adjuvant therapies without molecular markers	• Local control • Locoregional control • Overall survival • Pelvic control • Vaginal control • Distant metastases

Abbreviations: EBRT = external beam radiation therapy; KQs = key questions; PICO = Population, Intervention, Comparator, Outcome; RT = radiation therapy; VBT = vaginal brachytherapy.

3. Key Questions and Recommendations

3.1. KQ1: Indication for adjuvant RT (Table 3)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ1 and Figures 1 and 2.

What are the indications for adjuvant RT in patients with endometrial cancer?

Table 3 Indications for adjuvant RT

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with FIGO stage IA, grade 1 or 2 endometrioid carcinoma without intermediate* or high-risk factors,† adjuvant RT is **not** recommended.	Strong	Moderate [9,10]
2. For patients without high-risk factors† and with either FIGO stage IB, grade 1 or 2 endometrioid carcinoma or myoinvasive FIGO stage IA, grade 3 endometrioid carcinoma, vaginal brachytherapy is recommended.	Strong	Moderate [11-13]

3. For patients with high-risk factors† and who have FIGO stage IB, grade 1 or 2 or myoinvasive FIGO stage IA, grade 3 endometrioid carcinoma, EBRT is conditionally recommended.	Conditional	Moderate 12-15
4. For patients with FIGO stage IB, grade 3 or FIGO stage II endometrioid carcinoma, EBRT is recommended.	Strong	High 14,16-20
5. For patients with myoinvasive FIGO stage IA high-risk histology‡ endometrial carcinoma, vaginal brachytherapy with or without chemotherapy is conditionally recommended.	Conditional	Low 21
6. For patients with FIGO stage IB or II high-risk histology‡ endometrial carcinoma, EBRT with chemotherapy is conditionally recommended.	Conditional	Moderate 19,22
7. For patients with FIGO stage III or IVA endometrial carcinoma of any histology, EBRT with chemotherapy is conditionally recommended to decrease locoregional recurrence.	Conditional	Moderate 19,23-25

Abbreviations: EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; KQ = key question; LVSI = lymphovascular space involvement; RT = radiation therapy.

* Intermediate-risk factors include age ≥60 years, focal LVSI.

† High-risk factors include substantial LVSI, especially without surgical nodal staging.

‡ High-risk histologies include serous carcinoma, clear cell carcinoma, carcinosarcoma, mixed histology carcinoma, dedifferentiated carcinoma, or undifferentiated carcinoma.

FIGO Stage I-II Endometrioid Carcinoma

Early-stage, low-grade endometrial carcinoma historically has a very favorable prognosis with low rates of disease recurrence. An RCT enrolled patients with low-risk endometrial carcinoma (FIGO stage IA, grade 1 or 2 endometrioid carcinoma) to VBT versus no further treatment following TH-BSO and sampling of enlarged lymph nodes and reported no significant difference in vaginal recurrence.[9] The prospective population-based Danish Cancer Endometrial Study showed that 4.1% of patients with low-risk endometrial carcinoma developed locoregional recurrence following no adjuvant treatment.[10] Based on these findings, for patients with FIGO stage IA, grade 1 or 2 endometrioid carcinoma, adjuvant RT is not recommended in the absence of uterine risk factors. Given that VBT is generally very well tolerated with low rates of clinically significant acute and chronic morbidity, it is reasonable to offer VBT to patients with myoinvasive FIGO IA, grade 1 or 2 disease with uterine risk factors for recurrence. A patient and physician survey reported that patients (especially those who were treated with VBT) may have a relatively low local control benefit threshold to choose VBT.[26] Therefore, patients with FIGO stage IA, grade 1 or 2 endometrioid carcinoma with uterine risk factors may be considered for VBT to reduce the risk of vaginal recurrence. In the rare scenario of FIGO stage IA, grade 1 or 2 with substantial LVSI, especially without surgical nodal staging, EBRT could be considered to reduce the risk of locoregional recurrence. Similarly, patients with grade 3 endometrioid carcinoma without myoinvasion or without residual disease in the hysterectomy specimen following positive endometrial biopsy may be treated with or without VBT. (Figure 1)

Several RCTs with slightly different eligibility criteria compared EBRT to no adjuvant treatment in patients with early-stage endometrial cancer.[14-16,18] All showed a reduction in locoregional recurrence rate with EBRT. The Norwegian trial randomized stage I patients to VBT alone or EBRT with VBT boost. They found that EBRT decreased the risk of nonvaginal pelvic recurrences while only the group with FIGO stage IB, grade 3 disease had improved OS.[27] PORTEC-1 enrolled patients with FIGO stage I endometrioid carcinoma (grade 1 with ≥50% myoinvasion, grade 2 with any myoinvasion, or grade 3 with <50% myoinvasion) following TH-BSO and

biopsy of suspicious nodes and randomized them to EBRT versus no further treatment.[15] EBRT significantly reduced the rate of locoregional recurrence (4% with EBRT vs 14% with observation). Patients with FIGO stage IB, grade 3 endometrioid carcinoma were ineligible for PORTEC-1, but they were registered in a separate database, all treated with EBRT.[17] The 5-year locoregional recurrence rate was 14% for FIGO stage IB, grade 3 patients who received EBRT. The Gynecologic Oncology Group (GOG) 99 study is a similarly designed study that randomized patients with myoinvasive FIGO stage IA, FIGO stage IB, and occult stage II to EBRT versus no adjuvant treatment following TH-BSO and selective bilateral pelvic/para-aortic lymphadenectomy.[14] Similarly, EBRT reduced locoregional recurrence compared to no adjuvant treatment. Both PORTEC-1 and GOG 99 performed post-hoc analyses of a high-intermediate risk subset and found the locoregional recurrence risk reduction to be greatest in these groups.[14,15] These definitions vary though as PORTEC defined this group by age ≥60 years with myoinvasive FIGO stage IA, grade 3 or age ≥60 years with FIGO stage IB, grade 1 or 2. GOG defined their group as any age with all 3 risk factors [grade 2 or 3, presence of LVSI, and outer third myometrial invasion], age ≥50 years with any 2 of these risk factors, or age ≥70 years with any 1 risk factor).[14] A pooled analysis of 2 trials (MRC ASTEC/NCIC CTG EN.5) reported on patients with intermediate- or high-risk endometrial carcinoma (defined as FIGO stage IA, grade 3; FIGO stage IB, all grades; endocervical glandular involvement; FIGO stage I serous or clear cell histology). These studies randomized patients to EBRT versus observation following surgery.[16] With VBT used in approximately 50% of patients in the observation arm, the cumulative incidence of isolated vaginal or pelvic initial recurrence rates were 6.1% in the observation arm and 3.2% in the EBRT arm. There was no significant difference in the primary endpoint of OS.[16] A meta-analysis of trials confirmed that EBRT reduces the risk of locoregional recurrence in FIGO stage I endometrioid carcinoma, without a significant difference in OS.[18]

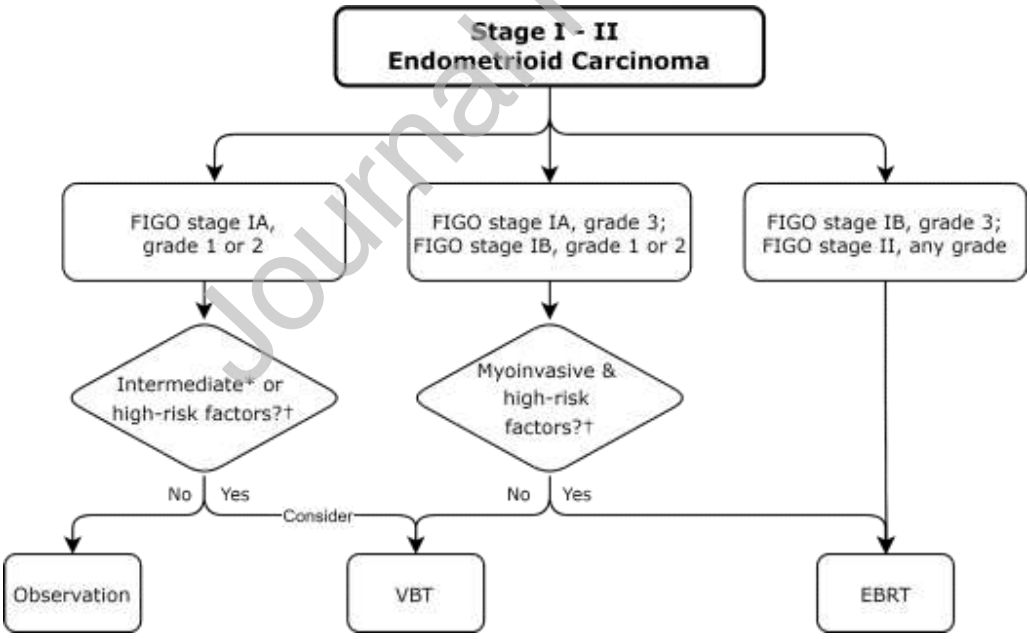
About 70% to 75% of recurrences in PORTEC-1 and GOG 99 were in the vagina which supports the hypothesis that VBT may be a sufficient adjuvant therapy to reduce the risk of recurrence while limiting treatment-related morbidity.[14,15] PORTEC-2 was a noninferiority RCT of PORTEC-defined high-intermediate risk patients who were randomized to VBT versus EBRT following TH-BSO without routine lymph node assessment.[11] With the primary endpoint of vaginal recurrence, the study showed that VBT was noninferior to EBRT. Additionally, patients in the VBT arm had improved quality of life relative to EBRT.[11,28] There was a significantly higher rate of pelvic recurrence with VBT but no difference in isolated pelvic recurrence, any locoregional recurrence, distant metastasis, disease-free survival (DFS) or OS. Long-term follow-up showed no significant difference in 10-year vaginal recurrence rate, distant metastasis, DFS, or OS.[12] The pooled analysis of PORTEC-1 and PORTEC-2 supported use of a 3-tiered LVSI scoring method [no LVSI, focal LVSI (defined as a single focus of LVSI around the tumor), and substantial LVSI (defined as diffuse or multifocal LVSI recognized around the tumor)].[29] They found substantial LVSI to be the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis, and OS. They also found that EBRT reduced the risk of pelvic recurrence.[13] Additional data suggests that substantial LVSI remains an adverse prognostic factor among patients who underwent staging lymphadenectomy.[30] The PORTEC-1 and -2 specimens were further quantitatively analyzed for LVSI to determine a clinically meaningful threshold. They found that patients with ≥4 LVSI-involved vessels (substantial LVSI) in at least one hematoxylin and eosin slide resulted in clinically meaningful LVSI and 26.3% rate of pelvic lymph node recurrence compared to 6.7% with 1 to 3 foci (focal LVSI) and 3.3% with no LVSI.[31] Other systems for LVSI stratification have been described, but this definition of substantial LVSI has the strongest evidence.

Another trial randomized patients to VBT versus EBRT plus VBT following TH-BSO and nodal sampling of enlarged nodes with “medium-risk” FIGO stage I endometrioid carcinoma with one of the following risk factors:

grade 3, ≥50% myoinvasion, or DNA aneuploidy.[32] Similar to PORTEC-2, the VBT group experienced lower toxicity and higher locoregional recurrence rates but no difference in recurrence-free survival (RFS) or OS compared to EBRT plus VBT group.[33] Based on these findings, for patients with FIGO stage IB, grade 1 or 2 endometrioid carcinoma or FIGO stage IA, grade 3 endometrioid carcinoma, VBT is recommended for those age ≥60 years and may be considered for those <60 years in the absence of substantial LVSI.[11-13] EBRT is conditionally recommended for patients with myoinvasive FIGO stage IA, grade 3 or FIGO stage IB, grade 1 or 2 when substantial LVSI is identified, especially when surgical nodal staging has not been performed.[12,13,31] (Figure 1)

GOG 249 randomized patients with high-intermediate and high-risk FIGO stage I and II endometrioid carcinoma or FIGO stage I-II serous or clear cell carcinoma with negative peritoneal cytology to VBT and chemotherapy versus EBRT.[20] VBT and chemotherapy was not superior to EBRT for RFS or OS and resulted in greater acute toxicity with a higher rate of lymph node recurrence.[20] Based on these findings and the aforementioned Norwegian trial, for patients with FIGO stage IB, grade 3 or FIGO stage II endometrioid carcinoma, EBRT is recommended (Figure 1). While a VBT boost after EBRT is often delivered in practice in patients with uterine risk factors, there have been no RCTs to support the routine addition of VBT to EBRT. VBT alone may be considered for select patients with microscopic FIGO stage II node-negative patients without significant uterine risk factors,[34,35] or select FIGO stage IB, grade 3 endometrioid carcinoma with negative bilateral surgical nodal assessment and no LVSI.[36] Select patients with FIGO stage II who undergo a radical hysterectomy and surgical staging can be considered for observation. How to define these selected patients for whom adjuvant therapy may be de-escalated is not well-established.

Figure 1 Stage I-II Endometroid Carcinoma



Abbreviations: EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; VBT = vaginal brachytherapy.

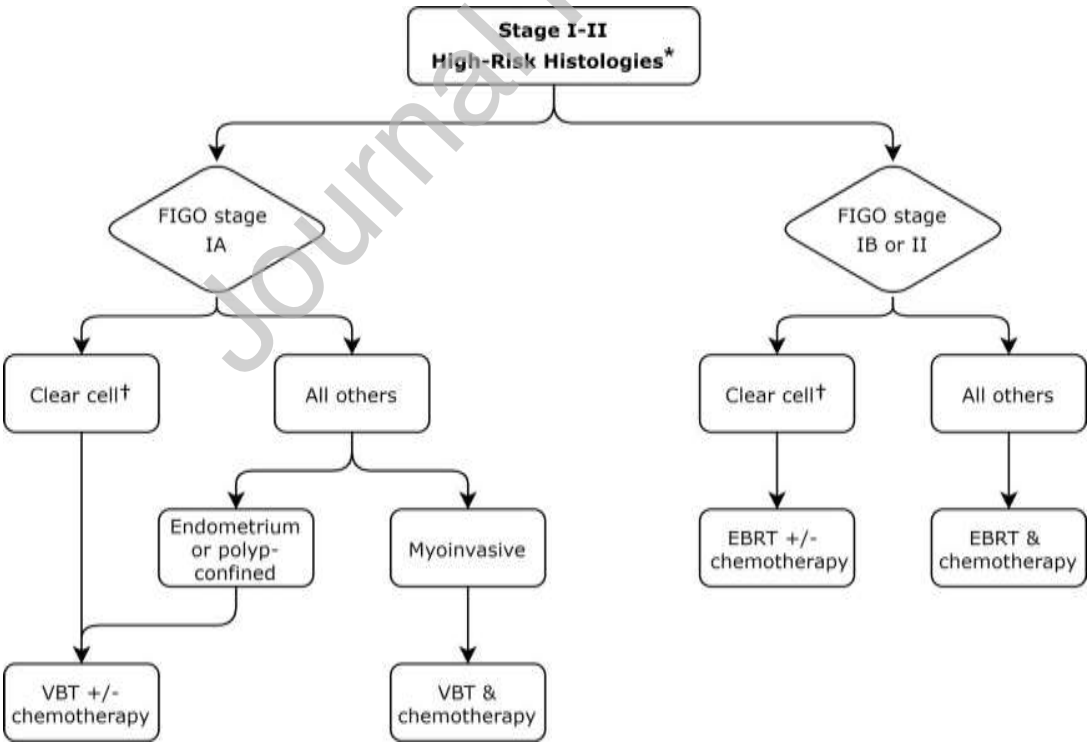
* Intermediate-risk factors include age ≥60 years and focal LVSI.

† High-risk factors include substantial LVSI, especially without surgical nodal staging.

FIGO Stage I-II High-Risk Histologies

Although high-risk histologies have been included in some trials, there have been no RCTs evaluating the role of RT specifically in early-stage high-risk histologies, and studies that did include high-risk histologies are underpowered to draw specific conclusions. A systematic review of patients with stage I endometrial serous carcinoma (predominantly FIGO stage IA) treated with VBT and chemotherapy showed local control of 97.5% and DFS of 88%.[21] In GOG 249 (which included 15% serous and 5% clear cell carcinoma), vaginal and distant recurrence rates were similar between VBT and chemotherapy compared with EBRT though pelvic and/or para-aortic nodal recurrences were more common with VBT and chemotherapy compared to EBRT.[20] PORTEC-3 randomized patients with high-risk and advanced stage endometrial carcinoma to EBRT alone versus EBRT with concurrent chemotherapy followed by adjuvant chemotherapy.[19] EBRT with concurrent chemotherapy followed by adjuvant chemotherapy improved RFS and OS compared to EBRT alone, especially in patients with FIGO stage III or serous carcinoma.[19] As outlined in Figure 2, given the lack of high-risk histology-specific trials, VBT with or without chemotherapy is conditionally recommended for myoinvasive FIGO stage IA high-risk histology endometrial carcinoma. EBRT is an alternative option, especially in the presence of substantial LVSI without surgical nodal assessment. For FIGO stage IB or II high-risk histology endometrial carcinoma, EBRT with chemotherapy is conditionally recommended. High-risk histology endometrial carcinoma confined to a polyp or without myometrial invasion were not included or were under-represented in trials, so treatment with VBT with or without chemotherapy may be considered and individualized for the patient. Clear cell carcinomas may behave differently than some of the other high-risk histologies depending on the molecular classification and are further discussed in KQ6.

Figure 2 High-Risk Histologies



Abbreviations: EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; VBT = vaginal brachytherapy.

* Serous carcinoma, clear cell carcinoma, carcinosarcoma, mixed histology carcinoma, dedifferentiated or undifferentiated carcinoma.
† Molecular profiling may influence alternate treatment pathway selection.

FIGO Stage III-IVA All Histologies

Several studies have demonstrated that EBRT results in low rates of locoregional recurrence in FIGO stage III-IVA endometrial carcinoma.[19,23-25] GOG 258 showed no difference in RFS between EBRT with concurrent chemotherapy followed by adjuvant chemotherapy (similar to the regimen used in PORTEC-3) compared with chemotherapy alone for 6 cycles in FIGO stage III-IVA endometrial carcinoma.[23] EBRT with concurrent chemotherapy followed by adjuvant chemotherapy was associated with a lower incidence of 5-year vaginal recurrence (2% vs 7%) and pelvic/para-aortic nodal recurrence (11% vs 20%) but more distant recurrence (27% vs 21%) than chemotherapy alone.[23] As previously described, PORTEC-3 demonstrated improved OS with EBRT with concurrent chemotherapy followed by adjuvant chemotherapy compared to EBRT alone among FIGO stage III patients.[19] Only 4 of 330 patients treated with EBRT with concurrent chemotherapy followed by adjuvant chemotherapy developed locoregional recurrence as the first site of recurrence as most recurrences were distant.[19] RTOG 9708 was a single-arm phase II trial of high-risk endometrial carcinoma evaluating EBRT with concurrent and adjuvant chemotherapy and is the regimen from which the PORTEC-3 and GOG 258 regimens evolved. Locoregional control proved to be excellent in this study.[25] Another RCT of patients with high-risk endometrial carcinoma randomized patients to EBRT versus chemotherapy and found no difference in OS or PFS. EBRT decreased locoregional recurrence and chemotherapy decreased distant metastases.[24] These data support the use of EBRT with chemotherapy to decrease locoregional recurrence in patients with FIGO stage III or IVA endometrial carcinoma of any histology.

3.2. KQ2: Adjuvant RT techniques, target volumes, dose-fractionation regimens, and normal tissue constraints (Table 4)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ2.

What are the appropriate techniques, target volumes, dose-fractionation regimens, and normal tissue constraints for patients receiving adjuvant RT for endometrial cancer?

Table 4 Adjuvant RT techniques, target volumes, dose-fractionation regimens, and normal tissue constraints

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with endometrial carcinoma undergoing adjuvant EBRT, IMRT is recommended to reduce acute and late toxicity.	Strong	Moderate [37-41]
2. For patients with endometrial carcinoma undergoing adjuvant EBRT using IMRT, a vaginal ITV is recommended for treatment planning with daily IGRT for treatment verification.	Strong	Moderate [37,38]

3. For patients with endometrial carcinoma undergoing adjuvant EBRT, a dose of 4500-5040 cGy at 180-200 cGy per fraction is recommended.	Strong	Moderate [11,14-16,19,37,38]
4. For patients with endometrial carcinoma undergoing adjuvant vaginal brachytherapy alone, treating the proximal third to half of the vagina (typically 3-5 cm) is recommended.	Strong	Moderate [11,20]
5. For patients with endometrial carcinoma with cervical stromal involvement and/or close or positive vaginal margins, postoperative vaginal brachytherapy as a boost following EBRT is conditionally recommended.	Conditional	Expert Opinion

Abbreviations: EBRT = external beam radiation therapy; IGRT = image guided radiation therapy; IMRT = intensity modulated radiation therapy; ITV = internal target volume; RT = radiation therapy.

Pelvic EBRT

The dosimetric benefits and feasibility of pelvic intensity modulated radiation therapy (IMRT) are well documented and demonstrate decreased volumes of bladder, rectum, bowel, and bone marrow receiving clinically significant doses of RT.[42-46] Clinical benefits also have been demonstrated in retrospective and prospective studies. Retrospective data show lower rates of acute and late toxicity with use of IMRT compared to 3-dimensional (3-D) conformal radiation therapy,[47-49] with comparable clinical outcomes, specifically survival and disease control.[39] RTOG 0418 was a phase II study that demonstrated the feasibility of IMRT, a favorable rate of acute grade ≥2 gastrointestinal toxicity, and that higher bone marrow dose corresponded to greater hematologic toxicity in patients with postoperative endometrial and cervical cancer.[37,40] RTOG 1203 (TIME-C) was a phase III RCT of patients with postoperative endometrial and cervical cancer, randomized patients to 3-D conformal radiation therapy or IMRT with a primary endpoint of patient-reported acute gastrointestinal toxicity.[38] The study demonstrated that IMRT was associated with significantly lower rates of acute patient-reported gastrointestinal and urinary toxicity and improved quality of life. Together, these findings support the use of IMRT techniques in the postoperative treatment of endometrial cancer.[38,41] A 3-D conformal radiation therapy technique is also acceptable, and may be appropriate in certain circumstances, for example when there is uncertainty regarding the appropriate target volume or the treating center does not possess the technical or personnel resources to safely deliver IMRT.

Accurate target volume definition is critical for the appropriate application of IMRT. While bony landmarks were historically used for field design, the adoption of IMRT technique necessitates a more detailed understanding and delineation of the clinical target volumes and normal structure volumes based on cross-sectional imaging. Contouring atlases have been created defining postoperative target volumes as well as the normal female pelvic organs, and these primary sources should be referenced for more information.[50,51]

The position of the proximal vagina, residual parametria, and paravaginal tissues can be highly variable depending on status of rectal and bladder filling. Therefore, a vaginal internal target volume (ITV) should be created to account for the full range of organ movement and deformation. Full bladder and empty bladder scans are obtained at simulation and co-registered in the treatment planning software. The vaginal ITV encompasses the positions of the vagina, residual parametria, and paravaginal tissues on both scans.[37,38,40,41] If the patient has a distended rectum at the time of simulation, the vaginal ITV should include the anterior rectum to account for the predicted location of the target when the rectum is empty for a daily treatment. Alternatively, adding a

generous margin around the vaginal clinical target volume to account for potential inter-fraction motion also is acceptable.

Even with careful attention to target volume delineation and planning, organ motion between fractions remains a significant issue.[52] Treatment delivery is further complicated by the fact that the proximal vagina and surrounding tissues are relatively mobile, potentially on the order of several centimeters, while pelvic lymph nodes are relatively fixed. A specified bladder filling regimen may help the patient's daily anatomic reproducibility. Image-guided radiation therapy using orthogonal kilovoltage images and routine volumetric imaging, such as cone beam CT, is recommended to ensure precise delivery of treatment.[37,38] Daily volumetric imaging has the benefit of ensuring the vaginal ITV is included in target and bladder filling is reasonably reproduced. If the vagina is outside of the planning target volume on routine volumetric imaging, then replanning and/or resimulation with creation of a larger target volume should be performed.

Adjuvant EBRT should be delivered to a total dose of 4500 to 5040 cGy at 180 to 200 cGy per fraction, based on doses used in prospective studies.[11,14-16,37,38,40,41,53] Selective sites of residual nodal disease may receive additional dose using either a sequential or a simultaneous integrated boost. In general, a 200 cGy equivalent dose (EQD2) of 5500 to 6500 cGy should be considered for gross nodes based on size, location, and dose per fraction with careful attention to dose delivered to nearby organs at risk, though evidence for a specific nodal boost dose is limited. For patients receiving adjuvant pelvic IMRT for endometrial cancer, there are limited data to support specific dose constraints or planning aims. As a result, it is reasonable to follow the normal tissue planning aims from those utilized in RTOG 1203 given that these planning aims resulted in significantly lower toxicity (Table 5).[38] The literature search for this guideline was performed with an aim to provide evidence-based recommendations for specific planning aims, but there was insufficient evidence to support making recommendations.

Table 5 TIME-C planning aims for adjuvant treatment of endometrial cancer

Organ at risk	Ideal dose limit	Variance allowed
Bowel Space	Up to 30% receives 4000 cGy	No more than 70% receives 4000 cGy
Rectum	Up to 80% receives 4000 cGy	<100% receives 4000 cGy
Bladder	Up to 35% receives 4500 cGy	No more than 70% receives 4500 cGy
Bone Marrow	Up to 37% receives 4000 cGy Up to 90% receives 1000 cGy	No more than 60% receives 4000 cGy No more than 90% receives 2500 cGy

Abbreviations: IMRT = intensity modulated radiation therapy; TIME-C = RTOG 1203, Standard vs. IMRT Pelvic Radiation for Post-Operative Treatment of Endometrial and Cervical Cancer.
Planning aims used in RTOG 1203 (TIME-C) trial protocol.[54]

Vaginal Brachytherapy

As described previously, VBT significantly decreases the risk of vaginal recurrence which is the predominant site of failure for patients with early-stage endometrial cancer without multiple risk factors. The delivery of VBT has evolved with predominant usage of high-dose-rate brachytherapy. Practice patterns vary widely in the United States which includes quite a variation of dose-fractionation regimens, length of vagina treated, and dose specification depth for both monotherapy and boost treatments.[55] The technical aspects of VBT are very important yet are beyond the scope of this guideline. These factors are described in other technical documents developed by the American Brachytherapy Society (ABS) and can be referenced for more detailed procedural information.[56,57]

Historically, dose-fractionation regimens for adjuvant VBT have been prescribed to deliver 6000 to 6500 cGy low-dose-rate equivalent to the vaginal surface. More contemporary lower dose regimens have also shown to be effective at decreasing the risk of recurrence.[58] A thorough summary of these dose-fractionation options, including discussion of the supporting evidence, has been generated by the ABS and should be used as a more complete reference on this topic.[59] When adjuvant VBT alone is used, the vaginal treatment length should include the proximal third to proximal half of the vagina length, which typically corresponds to a treatment length of 3 to 5 cm[11,20] as the proximal vagina is the predominant location of recurrence. Routine treatment of the entire length of the vagina is not advised because of greater risk of vaginal stenosis with longer treatment length, especially when prescribe to 5 mm depth.[60] For patients believed to be at an increased risk of local recurrence due to LVSI or high-risk histology, a longer treatment length of vagina may be considered. Though commonly performed in practice, there is limited data supporting a VBT boost following EBRT. The primary indications where a VBT boost is conditionally recommended after EBRT are close or positive vaginal margins following surgery or cervical stromal involvement. An EBRT or interstitial brachytherapy boost may be an option in the event of close or positive parametrial or other margins inaccessible to VBT.

For VBT, organs at risk include the bladder, rectum, sigmoid colon, bowel, and vagina. There is a lack of high-quality data on normal tissue dose constraints for VBT as the recommended doses are relatively low in the absence of EBRT and rarely exceed normal tissue planning aims established by the definitive treatment of cervical cancer.[61] As a result, no specific planning aims to organs at risk can be recommended when VBT is used as monotherapy. Doses to the adjacent critical organs should be monitored with VBT alone and especially when combined with EBRT. Three-dimensional based planning using CT is optimal for VBT treatment planning. A comparison of 2-D versus 3-D CT-based treatment planning demonstrated decreased dose to critical organs without compromising the dose delivered to the clinical target volume, as planning can be customized according to individual patient anatomy.[62]

3.3. KQ3: Indications for systemic therapy (Table 6)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ3.

What are the indications for systemic therapy in patients with nonmetastatic endometrial cancer?

Table 6 Indications for systemic therapy

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with FIGO stage I-II endometroid adenocarcinoma, systemic therapy is not recommended.	Strong	High [19,20,63]
2. For patients with myoinvasive FIGO stage I-II endometrial cancer with high-risk histologies,* systemic therapy is conditionally recommended.	Conditional	Moderate [19,22,23]
3. For patients with FIGO stage III-IVA endometrial cancer of any histology, adjuvant systemic therapy is recommended.	Strong	High [19,22,23,64]

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; KQ = key question.
* High-risk histologies include serous carcinoma, clear cell carcinoma, carcinosarcoma, mixed histology carcinoma, dedifferentiated or undifferentiated carcinoma.

FIGO Stage I-II Endometrioid Adenocarcinoma

The role of adjuvant chemotherapy in high-intermediate risk and high-risk early-stage endometrial cancer has been evaluated in 2 RCTs.[20,53] PORTEC-3 included patients with FIGO stage I, grade 3 endometrioid cancers with >50% myometrial invasion and/or LVSI and FIGO stage II-III endometrioid cancers. Patients were randomized to EBRT alone or EBRT with concurrent chemotherapy followed by sequential chemotherapy. The trial reported a significant improvement in RFS and OS for the entire study population with the addition of chemotherapy. However, on subset analysis by stage, there was no difference in RFS or OS for FIGO stage I-II patients with the addition of chemotherapy.[19]

GOG 249 included patients with FIGO stage I endometrial cancer with high-intermediate and high-risk factors and patients with FIGO stage II endometrial cancer.[20] Adjuvant treatment was randomized to EBRT alone or VBT followed by 3 cycles of paclitaxel and carboplatin. There was no difference in 5-year RFS or OS between the 2 treatment arms. Similarly, on subgroup analysis, there was no difference in RFS or OS for FIGO stage I-II endometrioid patients. Chemotherapy also did not decrease the rate of distant metastases.[20] A meta-analysis was performed to evaluate the addition of chemotherapy to RT in patients with FIGO stage I-II high-risk endometrial cancer. This analysis found no significant difference in RFS or OS with the addition of chemotherapy. The effect of reducing distant metastases was equivocal between groups.[63]

Considering adjuvant endocrine therapy, a Cochrane meta-analysis was conducted to evaluate the role of adjuvant progesterone for endometrial cancer and included over 4500 patients in 7 RCTs. The study concluded that the use of adjuvant progesterone therapy did not improve clinical outcomes.[65] Therefore, based on high-quality RCTs[19,20,53] and meta-analysis,[63] the routine use of adjuvant systemic therapy in the form of either chemotherapy or endocrine therapy for stage I-II endometrioid endometrial cancer is not recommended.

FIGO Stage I-II Endometrial Cancer with High-Risk Histologies

Approximately 15% of patients who are diagnosed with endometrial cancer will have a type II endometrial cancer which is comprised of serous carcinoma, clear cell carcinoma, carcinosarcoma, mixed histology carcinoma, dedifferentiated carcinoma, and undifferentiated carcinoma. These histologic subtypes are associated with a worse prognosis and are responsible for approximately 40% of all endometrial cancer-related deaths.[66] In patients with early-stage disease, there is a higher risk of recurrence and death as compared to endometrioid histology. Due to the limited number of patients, clinical trials in this patient population have been limited, and there is a lack of consensus regarding use of systemic therapy. Noninvasive (endometrial only or polyp-confined) high-risk histology patients were not included in the RCTs that investigated chemotherapy.[19,20,22,23] However, it is reasonable to consider chemotherapy for these patients given their high-risk histology, but prospective data are lacking to provide evidence.

In the Nordic Society of Gynecologic Oncology/European Organization for the Research and Treatment of Cancer (NSGO/EORTC) trial, patients were randomized to EBRT alone or EBRT followed by sequential chemotherapy. The chemotherapy arm resulted in significantly improved PFS, but there was no difference in OS. Interestingly, when outcomes were analyzed by histology, there was negligible treatment effect. The trial concluded that the data did not support the use of chemotherapy for serous and clear cell carcinomas.[67]

The GOG conducted 2 trials that included patients with early-stage nonendometrioid histologies.[20,23] GOG 258 randomized patients to either EBRT with concurrent chemotherapy (2 cycles of cisplatin) followed by 4

cycles of sequential chemotherapy (paclitaxel and carboplatin) or to chemotherapy alone for 6 cycles (paclitaxel and carboplatin).[23] Although the study included patients with FIGO stage I-II nonendometrioid histology with positive peritoneal cytology, there were too few patients enrolled to draw any conclusions. For the overall patient population, the study concluded that EBRT with concurrent chemotherapy followed by sequential chemotherapy did not improve RFS as compared to chemotherapy alone. In GOG 249, patients with serous carcinoma comprised 15% of the those enrolled, yet they accounted for 29% of the recurrences.[20] Clear cell carcinoma comprised only 5% of the accrual. On subgroup analysis, there was no difference in RFS between EBRT alone and VBT with chemotherapy arms, yet the study was likely underpowered given the relatively few patients enrolled with high-risk histologies.[20]

In PORTEC-3, patients with serous carcinoma had significantly lower RFS and OS than the other histological subtypes. There was a significantly greater improvement in RFS and OS among patients with serous carcinoma with the addition of chemotherapy with a 5-year survival improvement from 52.8% to 71.4%.[19]

There are several retrospective studies that have evaluated the role of chemotherapy in patients with early stage high-risk histologies.[68-70] In a retrospective study of FIGO stage I-II serous carcinoma, there was improved OS with the addition of chemotherapy among patients who were surgically staged.[68] Another large retrospective study of patients with high-risk endometrial cancer showed that chemotherapy was associated with a worse DFS as compared to observation, VBT, or EBRT. A similar trend was observed with the serous carcinoma group but did not reach statistical significance.[69] A multicenter study pooled patients with FIGO stage I nonendometrioid histologies and demonstrated that adjuvant chemotherapy was associated with improved local control (96% vs 84%) and DFS (84% vs 69%) as compared to no adjuvant therapy.[70]

The role of chemotherapy for FIGO stage I-II clear cell carcinoma remains unclear. While clear cell carcinomas are often classified together with other high-risk histologies, their patterns of failure and response to adjuvant therapy seem to differ. Therefore, treatment recommendations may differ for serous and clear cell carcinomas as outlined in Figure 2. One retrospective study showed no OS benefit from chemotherapy in patients with clear cell carcinoma of any stage.[68] A study of adjuvant therapy for FIGO stage I-II clear cell carcinoma and serous carcinoma demonstrated similar clinical outcomes despite significantly less use of chemotherapy among clear cell carcinoma patients.[71] Molecular analysis of clear cell carcinomas suggest features representative of all molecular subtypes of endometrial cancer. Therefore, it is possible that prognosis may align more with the molecular subtyping than the histology itself.[72]

Uterine carcinosarcoma is a less common endometrial cancer variant comprising <5% of cases but is responsible for 16.4% of endometrial cancer related deaths.[73] Although prospective data is limited by patient numbers, GOG conducted a prospective randomized trial of whole abdominal radiation (WAI) versus chemotherapy (cisplatin and ifosfamide) in patients with FIGO stage I-IV carcinosarcoma (about half were FIGO stage I-II).[22] Five-year survival rates were 65% and 45% for patients with FIGO stage I and stage II disease, respectively. The study did not find a statistically significant advantage in recurrence rate or OS for adjuvant chemotherapy over WAI, likely because of small numbers. However, given the observed differences in recurrence and survival endpoints, the authors favored the use of combination chemotherapy in future trials.[22] In summary, although systemic therapy is often recommended for patients with endometrial cancer with high-risk histologies, the quality of the data is low, and the routine use of adjuvant chemotherapy is only conditionally recommended.

FIGO Stage III-IVA Endometrial Cancer with Endometroid or High-Risk Histologies

Patients with FIGO stage III-IVA endometrial cancers are a heterogeneous group who are at high risk for local recurrence, distant metastases, and cancer-related death. Given the high rates of relapse, advanced endometrial cancer has been treated in a variety of combinations of RT, chemotherapy, or combined modality adjuvant therapy.

Historically, WAI was used to treat FIGO stage III or IV endometrial cancer after surgery. WAI was effective at decreasing risk of pelvic recurrence but less successful at preventing distant metastases. GOG 122 was a RCT comparing WAI to chemotherapy alone (cisplatin and doxorubicin) in patients with FIGO stage III or IV endometrial cancer with <2 cm of residual disease after surgery. This study demonstrated improved PFS and OS with chemotherapy compared with WAI establishing chemotherapy as part of the standard therapy for patients with advanced disease.[64] Unfortunately, the efficacy of RT in this study was limited by the low doses used and the associated high local failure rates because of this WAI technique. Two other similarly designed RCTs randomized patients to EBRT alone (not WAI) or chemotherapy alone and both showed no difference in PFS or OS.[24,74]

As previously described, the PORTEC-3 trial demonstrated that patients with FIGO stage III endometrial cancer who were randomized to EBRT with concurrent chemotherapy followed by sequential chemotherapy had improved 5-year RFS and OS compared to EBRT alone, and these results were most significant for patients with FIGO stage III or serous carcinoma.[19] In contrast, the GOG 258 trial demonstrated no differences in RFS between EBRT with concurrent chemotherapy followed by sequential chemotherapy and chemotherapy alone.[23] There were lower rates of vaginal recurrences (2% vs 7%) and pelvic and para-aortic relapses (11% vs 20%) with chemoradiation compared to chemotherapy alone, but there were more distant recurrences (27% vs 21%) with EBRT with concurrent chemotherapy followed by sequential chemotherapy compared with chemotherapy alone. The authors concluded that the combination of EBRT and chemotherapy was not superior to chemotherapy alone for advanced stage endometrial cancer, and that chemotherapy is important for preventing distant relapses.[23]

Therefore, based on high-quality RCTs,[19,23,53,64] the routine use of adjuvant chemotherapy for FIGO stage III-IVA endometrial cancer is recommended with the aim of decreasing distant recurrence. EBRT is effective in reducing locoregional recurrences but may not impact survival.

3.4. KQ4: Sequencing of systemic therapy with RT (Table 7)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ4 and Figures 2 and 3.

What is the appropriate sequencing of systemic therapy with RT in patients with endometrial cancer?

Table 7 Sequencing of systemic therapy with RT

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with FIGO stage III-IVA endometrial cancer receiving RT, EBRT with concurrent chemotherapy followed by adjuvant chemotherapy is conditionally recommended.	Conditional	Moderate [19,23,25]

2. For patients with FIGO stage III-IVA endometrial cancer receiving RT, sequential chemotherapy followed by RT is conditionally recommended.	Conditional	Expert opinion
3. For patients with FIGO stage I-II endometrial cancer with high-risk histologies* receiving EBRT and chemotherapy, either sequential or concurrent treatment is recommended.	Strong	Moderate [19,23]
4. For patients with endometrial cancer receiving vaginal brachytherapy and chemotherapy, either sequential or concurrent treatment is recommended. Implementation remark: It is preferrable not to administer brachytherapy on the same day as chemotherapy.	Strong	Expert opinion

Abbreviations: EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; KQ = key question; RT = radiation therapy.

* High-risk histologies include serous carcinoma, clear cell carcinoma, carcinosarcoma, mixed histology carcinoma, dedifferentiated or undifferentiated carcinoma.

The optimal sequencing approach for chemotherapy and RT has not been evaluated in a RCT, resulting in heterogeneity in treatment approaches for locally advanced endometrial cancer.[75] EBRT with concurrent chemotherapy followed by sequential chemotherapy was evaluated in one phase II prospective trial (RTOG 9708) and 2 large phase III prospective RCTs (PORTEC-3 and GOG 258).[19,23,25] All studies used a similar regimen of EBRT with 2 cycles of concurrent cisplatin followed by 4 cycles of platinum and taxane chemotherapy. These studies were not designed to conclude that a particular sequencing regimen is optimal. The regimen used in PORTEC-3 demonstrated an OS benefit compared to EBRT alone, especially among FIGO stage III and serous carcinoma patients.[19] In GOG 258, there was no difference in RFS between chemotherapy alone and EBRT with concurrent chemotherapy followed by sequential chemotherapy. The incidence of vaginal, pelvic, and para-aortic recurrence was higher in the chemotherapy group, highlighting the importance of EBRT in improving locoregional control.[23] In contrast, distant recurrence was more common with EBRT with concurrent chemotherapy followed by sequential chemotherapy compared with chemotherapy alone. The timing of doublet chemotherapy initiation and number of high-dose chemotherapy cycles may be the reasons why the distant metastasis rate was lower in the chemotherapy alone arm. These data indicate that each regimen has benefits regarding patterns of failure. As a result, using the regimen of EBRT with concurrent chemotherapy followed by sequential chemotherapy as performed in these RCTs is the rationale supporting the sequencing of RT and chemotherapy despite the design of these studies comparing to EBRT or chemotherapy alone.[19,23] The combined schedule of EBRT with 2 cycles of cisplatin followed by 4 cycles of carboplatin and paclitaxel has the advantage that both treatments (chemotherapy and EBRT) are started soon after surgery, overall treatment time is shorter, and it is the most published schedule with complete follow-up, toxicity, and quality-of-life data from 2 large RCTs.[19,23] The disadvantage of this sequencing is that high-dose chemotherapy is delayed and with fewer cycles.

Distant metastasis remains the most common site of recurrence in patients with locally advanced endometrial cancer.[19,23] This is particularly true of patients with fallopian tube, ovary, and serosal involvement, or those with common iliac or para-aortic nodal disease.[76-78] Therefore, in patients with a high-risk of distant recurrence, an early initiation of high-dose doublet chemotherapy may be preferred. With the known locoregional control benefit of RT, sequencing RT to follow chemotherapy also should be considered for patients

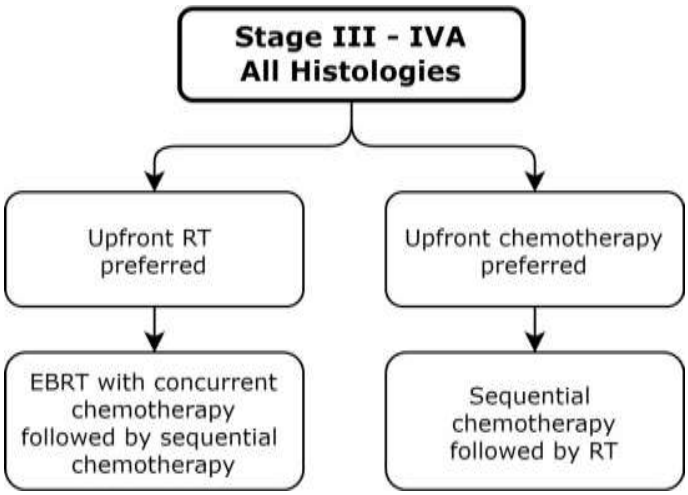
who have not progressed following chemotherapy. This sequence serves to treat microscopic distant disease already present as well as subclinical disease that may seed distantly. Since distant recurrence is the most common site of recurrence, the benefits of delivering chemotherapy first may outweigh the risks. Also, if EBRT is given first, particularly when extended field irradiation is used, a greater portion of bone marrow will be irradiated which may decrease the patient's hematologic tolerance of subsequent chemotherapy. Bone marrow dose can be limited with IMRT which has been shown to decrease hematologic toxicity.[38] Sequential chemotherapy followed by EBRT is supported by a retrospective study that reported improved DFS and OS with sequential chemotherapy followed by EBRT compared to EBRT alone or chemotherapy alone in patients with FIGO stage III endometrial cancer.[79] For patients where chemotherapy is prioritized,[23] it is reasonable to sequence chemotherapy for up to 6 cycles followed by volume-directed EBRT if there is no development of distant metastases and locoregional control remains important for the patient.

Chemotherapy followed by RT then by further chemotherapy, also known as the "sandwich" regimen, has been described in phase II trials and retrospective series with limited patient numbers and relatively short follow-up.[80-83] The regimen generally is well-tolerated with similar results to the aforementioned sequencing options, but there are no randomized trials that include this regimen. There is concern about the biologic implications of a significant lapse in time between the 2 chemotherapy courses and the potential for development of chemoresistance. Additionally, there is the potential psychological toll of stopping and restarting chemotherapy (eg, hair loss). As a result, there was not sufficient evidence to make a recommendation regarding the "sandwich" regimen.

A large multicenter retrospective study specifically evaluated the impact of sequencing approaches in patients with FIGO stage IIIC endometrial cancer treated with adjuvant chemotherapy and RT.[75] The sequencing approaches were EBRT with concurrent chemotherapy followed by sequential chemotherapy, chemotherapy with VBT, chemotherapy followed by EBRT, EBRT followed by chemotherapy, and "sandwich" regimen. The sequence and type of adjuvant therapy were not associated with RFS or OS. Similar to the randomized studies, the most common site of first recurrence was distant metastasis.[19,23] Patients who received VBT alone with chemotherapy had a higher rate of nodal recurrence compared to patients treated with EBRT, emphasizing the role of EBRT for locoregional control in locally advanced endometrial cancer.[75]

Numerous studies have shown that the most common location of pelvic recurrence is the vagina for early-stage disease.[14,15] VBT is a low morbidity therapy unlikely to decrease chemotherapy tolerance or cause hematologic toxicity. Therefore, when VBT is delivered in conjunction with chemotherapy, it can be delivered safely during or after chemotherapy.[84] Early initiation of VBT is likely to reduce the risk of a vaginal recurrence. There have not been any prospective trials investigating optimal sequencing of VBT and chemotherapy nor regarding the safety or efficacy of VBT on the same day as chemotherapy. Delivery of VBT and chemotherapy on the same day is not preferred and may pose unnecessary risk to the patient given that these are adjuvant therapies. VBT may be delivered before chemotherapy, in between cycles of chemotherapy, or after chemotherapy, with care not to delay chemotherapy if the patient is at high risk of distant recurrence. There are, however, no RCTs that have found VBT and chemotherapy superior to either EBRT alone[20] or EBRT with concurrent and sequential chemotherapy.[19,23]

Figure 3 Stage III-IVA Endometroid Carcinoma



Abbreviations: EBRT = external beam radiation therapy; RT = radiation therapy.
Chemotherapy alone is also an option based on GOG 258.[23]

3.5. KQ5: Adjuvant RT decisions based on lymph node assessment (Table 8)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ5.

How should the performance of, and type of, lymph node assessment influence adjuvant RT decisions in patients with endometrial cancer?

Table 8 Adjuvant RT decisions based on lymph node assessment

KQ5 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with endometrial cancer, use of bilateral sentinel lymph node mapping is recommended over standard pelvic lymphadenectomy, to accurately detect subclinical nodal metastases, decrease morbidity, and guide selection of adjuvant therapy.	Strong	Moderate 85-89
2. For patients who have undergone hysterectomy and no pelvic nodal assessment, surgical restaging or pelvic RT is conditionally recommended for any myoinvasion with LVSI or deep myoinvasion.	Conditional	Expert Opinion
3. For patients who have undergone hysterectomy and pelvic nodal assessment with isolated tumor cells present, it is conditionally recommended that uterine risk factors be used to guide adjuvant therapy.	Conditional	Low 85-87,90-96
4. For patients who have undergone hysterectomy and pelvic nodal assessment with nodal micrometastases or macrometastases (FIGO stage IIIC), adjuvant therapy is recommended.	Strong	High 19,23-25

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; KQ = key question; LVSI = lymphovascular space involvement; RT = radiation therapy.

In patients with apparent uterine-confined endometrial carcinoma, surgical staging remains the gold standard for detecting microscopic disease outside the uterus. SLN mapping with a cervical injection of dye with or without radiocolloid has emerged as a feasible and reliable strategy to surgically stage patients with newly diagnosed endometrial cancer.[85,87-90] SLN mapping is best performed by following a structured surgical algorithm that emphasizes bilateral pelvic nodal mapping. Key elements of the SLN mapping algorithm include peritoneal and serosal evaluation and washings, bilateral detection of pelvic SLNs, a side-specific lymphadenectomy if there is no SLN mapping on a hemipelvis, and removal of any suspicious or grossly involved nodes regardless of mapping. Several retrospective and prospective studies comparing SLN mapping to the historical pelvic lymphadenectomy for staging demonstrated that SLN mapping increased the accuracy of surgical staging.[85-90] This is due to greater surgical precision by removing fewer but more relevant nodes and the added value of pathologic ultrastaging with serial sectioning and immunohistochemistry staining of SLNs. The concept of SLN mapping for endometrial cancer emphasizes quality (bilateral relevant pelvic SLN mapping) over quantity (the total count of lymph nodes) as a surgical metric. Emerging data from patient-reported outcomes surveys also show a decrease in lower extremity lymphedema rates with SLN and potential for less pelvic lymphocele formation as compared to lymphadenectomy.[97,98] Bilateral SLN mapping rather than standard lymphadenectomy is recommended for the surgical staging of endometrial cancer.[85-89]

There is no definitive evidence that pelvic lymphadenectomy for apparent uterine-confined disease decreases the risk of death from uterine cancer.[99-102] However, the utility of surgical staging, including bilateral pelvic nodal assessment, is known to provide prognostic information to accurately assign FIGO stage and guide adjuvant therapy.[99,102-104] In patients who have not undergone pelvic nodal assessment, decision making for surgical restaging or consideration of EBRT has been based on assessment of uterine pathologic risk factors.[105] Studies demonstrate that in cases where final pathology reveals >50% myoinvasion or any myoinvasion with LVSI, patients have approximately 10% or greater risk of pelvic lymph node positivity. These patients may benefit from surgical restaging or EBRT.[106,107] RCTs have demonstrated improved pelvic control with the use of adjuvant RT for patients with adverse uterine pathologic risk features.[11,13-15,27] There is no evidence, however, that the effect of EBRT is different in women who have had a lymphadenectomy.[102]

SLN mapping must be accompanied by pathologic ultrastaging. SLN are considered positive for disease if they contain micrometastases (0.2–2 mm) or macrometastases (>2 mm). Ultrastaging of the SLNs may detect isolated tumor cells (ITCs), defined as a focus of metastatic disease fewer than 200 cells and smaller than 0.2 mm, which are infrequently detected by conventional histologic methods. When ITCs are detected, the lymph node stage is designated as pN0(i+) and thus does not “upstage” the patient to node positive.[108] The presence of ITCs has been shown to be associated with other pathologic uterine risk factors, including microcystic, elongated and fragmented (MELF) pattern with LVSI.[109] In a prospective study, PFS for patients with ITCs was over 95%, similar to node negative patients, and significantly better relative to node positive patients.[94] Additional studies have reported that patients with ITCs, and otherwise low-risk uterine disease, do not have significantly improved RFS with adjuvant therapy, and ITC detection alone may not be clinically relevant.[91,96] Contrastingly, a large multicenter retrospective study evaluated the prognostic impact of nodal micrometastases and found they were associated with worse DFS compared with node negative patients, and this effect was improved with adjuvant therapy.[92] To summarize, in patients with ITCs, the use of adjuvant treatment should be tailored to uterine risk factors and histology, and not only based on the presence of ITCs. Given that many of these published data are

retrospective in nature, further evaluation of the prognostic significance of lymph nodes with ITCs within prospective clinical studies is warranted. In patients with nodal micrometastases and macrometastases, adjuvant treatment is recommended, irrespective of uterine risk factors and histology, as these patients have stage IIIC disease.

Multiple RCTs using adjuvant RT in one or both arms demonstrated excellent pelvic and locoregional control for patients with FIGO IIIC endometrial cancer.[19,23,25,53,110,111] The role of volume-directed EBRT in patients with node-positive endometrial cancer is driven by the balance of competing risk of distant and locoregional failure. GOG 258 demonstrated that chemotherapy alone for 6 cycles had lower rates of distant recurrence whereas EBRT with concurrent chemotherapy followed by sequential chemotherapy had lower rates of vaginal and nodal recurrence.[23] Locoregional recurrence is a potentially life-threatening and quality of life altering diagnosis for patients. Additionally, locoregional recurrences are challenging to salvage and may require escalation of therapy to higher tumoricidal doses of EBRT or incorporation of interstitial brachytherapy. For node-positive patients in whom locoregional control of disease is important, EBRT is recommended.

Cross-sectional imaging may be considered for patients with high-risk histologies or those patients with grade 3 or extrauterine extension of disease. Imaging is advised especially in these high-risk patients for whom a surgical lymph node staging procedure is not performed. Functional imaging with 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) can be used to further assess lymph node status and locations of involved lymph nodes.[112]

3.6. KQ6: Molecular marker influence on adjuvant RT and systemic therapy decisions (Table 9)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ6.

How should molecular markers influence adjuvant RT and systemic therapy decisions in patients with nonmetastatic endometrial cancer?

Table 9 Molecular marker influence on adjuvant RT and systemic therapy decisions

KQ6 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with endometrial cancer considering adjuvant therapy, molecular testing is recommended. Implementation remarks: • Immunohistochemistry is needed to assess for mutations in mismatch repair and *TP53* genes • *POLE* sequencing can be used to identify hypermutated tumors	Strong	Moderate [12,113,114]
2. For patients with myoinvasive FIGO stage IA-IIIC2 *TP53* mutated endometrial cancer, chemotherapy and RT are conditionally recommended.	Conditional	Low [113]

3. For patients with FIGO stage IB-IIIC2 mismatch repair deficiency endometrial cancer, RT without chemotherapy is conditionally recommended.	Conditional	Low [113]
4. For patients with FIGO stage IB-IIIC2 *POLE* mutant tumors, RT without chemotherapy is conditionally recommended.	Conditional	Low [113]

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; KQ = key question; *POLE* = polymerase epsilon; RT = radiation therapy.

Endometrial cancer has been long recognized as a histologically and molecularly heterogenous cancer. More recent progress has defined specific molecular subsets of endometrial cancer which may function as prognostic and increasingly predictive biomarkers. The Cancer Genome Atlas (TCGA) made significant progress at identifying these subsets through the comprehensive molecular analysis of 373 endometrial cancers involving whole exome sequencing, gene expression and copy number analysis.[5] Four distinct subsets of endometrial cancer which spanned histologic subtypes were identified with differing prognosis: *POLE* ultramutated, microsatellite instability hypermutated, copy number low, and copy number high.[5] The copy number high tumors had high rates of *TP53* mutations and had the worst prognosis. Patients with mismatch repair (MMR) deficient cancers and copy number low tumors had intermediate prognoses. *POLE* ultramutated tumors had the best prognosis, with very few relapses reported in these patients.

A workflow for defining these subsets without the need for expensive next generation sequencing techniques was developed by different groups.[12,113] Immunohistochemistry can be performed to identify p53 abnormal cancers. *TP53* is commonly stabilized following mutation so it can be detected with immunohistochemistry within the cell nuclease when mutant. MMR deficient cancers can be identified by noting the absence of the MMR proteins MLH1, MSH2, MSH6, and PMS2 or by detecting the consequence of the absence of functional MMR proteins, the accumulation of repeats of a short sequence of DNA, called microsatellite repeats. This is referred to as microsatellite instability and can be detected with a polymerase chain reaction (PCR)-based assay using DNA from tumors. Detection of *POLE* mutations require sequencing of this single *POLE* gene which, when mutated, causes accumulation of many mutations throughout the genome.

With these molecular classifications of endometrial cancer readily defined, the question of their impact on adjuvant therapy is being addressed. Some of the most informative data collections comes from secondary molecular analyses of the PORTEC studies.[12,113] In PORTEC-3, the primary aim of this study was to determine if the addition of chemotherapy to EBRT for women with high-risk and advanced endometrial cancer improved RFS and OS.[53] The 5-year RFS and OS was significantly improved with the addition of chemotherapy and this was most significant among the stage III and serous carcinoma subgroups.[19] A molecular analysis of these patients was performed to determine which of these molecular subsets derived the benefit from chemotherapy.[113] Interestingly, the only molecular subgroup found to benefit from chemotherapy was among patients whose tumors were p53 abnormal. The 5-year RFS was significantly improved from 36% to 59% with the addition of chemotherapy for patients with p53 abnormal tumors.[113] As a result, combined modality treatment for patients with p53 abnormal or *TP53* mutated myoinvasive FIGO stage IA-IIIC2 endometrial cancer is conditionally recommended.

Among patients with MMR deficiency, there was no difference in survival for patients who did or did not receive chemotherapy. Five-year rates of RFS were 68% for patients who received chemotherapy versus 76% for those that did not.[113] These findings suggest that it is reasonable to consider EBRT alone for patients with MMR

deficiency. Given the response to immunotherapy for patients with metastatic disease with MMR deficiency, adjuvant immunotherapy may improve outcomes in the adjuvant setting. The NRG-GY020 *(NCT04214067)* study is testing this hypothesis by randomizing patients with early-stage endometrial cancer to treatment with and without pembrolizumab.

Patients with the *POLE* ultramutated phenotype, even with high grade and/or advanced stage tumors, have excellent outcomes whether treated with EBRT with concurrent chemotherapy followed by sequential chemotherapy or EBRT alone. In the PORTEC-3 molecular classification series, there were 51 patients in the *POLE* subset, and only one patient (treated with EBRT alone) had disease recurrence.[113] Given these findings, simplifying adjuvant therapy to a single modality approach is reasonable and thus RT alone is an option for patients with *POLE* ultramutated tumors who are eligible for adjuvant therapy based on clinical and pathologic factors. Further study is needed to understand the improved survival in this population, whether attributable to the biologic consequences of the high mutational burden and potential impact on sensitivity to adjuvant therapies. In the combined analysis of PORTEC-1 and -2, the 49 patients with *POLE* ultramutated phenotype had a favorable prognosis with no locoregional recurrences, only 2 distant recurrences, and a 5-year disease-specific survival rate of 100%.[114] An important remaining question is whether these low recurrence rates also will be seen in locally advanced patients who are observed after surgery. Observation following surgery is an arm of the ongoing PORTEC-4a *(NCT03469674)* and the Tailored Adjuvant Therapy in POLE-mutated and p53-wildtype Early-Stage Endometrial Cancer (TAPER) studies *(NCT04705649)*. Until data demonstrating these same excellent outcomes following observation is available, omitting adjuvant therapy is not recommended for patients with uterine risk factors or node positive disease.

Additionally, among those "multiple classifier" patients with both MMR deficiency and p53 abnormal tumors, prognosis clusters closely with the MMR deficiency group. Similarly, patients with both *POLE* ultramutated and p53 abnormal tumors, prognosis clusters closely with the *POLE* ultramutated group.[115]

Among high-risk histologies, p53 abnormal most commonly is associated with serous carcinomas, thus carrying an unfavorable prognosis. Human epidermal growth factor receptor 2 (HER2) is overexpressed in about 30% of uterine serous carcinomas, and HER2 is a target for the humanized monoclonal antibody, trastuzumab. A phase II clinical trial of patients with stage III-IV or recurrent serous carcinoma with HER2 overexpression randomized patients to chemotherapy with or without trastuzumab. The study demonstrated significantly improved PFS and OS without differences in toxicity.[116] HER2 expression is an emerging marker of interest for guiding systemic therapy.

Among clear cell carcinomas, all molecular phenotypes are represented, supporting the use of molecular profiling to better characterize the prognosis and response to adjuvant therapy as represented in Figure 2.[72] A meta-analysis of patients with clear cell carcinoma with MMR deficiency revealed that they appear to have favorable prognosis whereas those with MMR proficiency (either p53 wild-type or p53 abnormal) have a poor prognosis.[117] Another study suggested that clear cell carcinomas with any of the 4 molecular subtypes have prognoses that cluster with other similar histologies with those molecular profiles.[118] A study of patients with carcinosarcoma and *POLE* ultramutation demonstrated that these tumors had a very favorable prognosis while carcinosarcomas that were p53 abnormal or *TP53* mutated and patients with no specific molecular profile had prognoses that were worse than those with endometrioid or serous histologies. There was not a clear determination of how prognosis was impacted by MMR status.[119] These data indicate that molecular profiling of tumors with adverse histologies may be particularly informative regarding prognosis and may help guide adjuvant therapy. Whenever possible, for patients with endometrial cancer considering adjuvant therapy,

molecular testing is recommended.[12,113,114] We await the results of multiple prospective trials on molecular profile-based adjuvant treatment for patients with endometrial cancer.

In clinical scenarios of conflicting clinicopathologic and molecular factors, decisions about adjuvant treatment options should be shared with the patient and risk/benefit analysis of potential over- or under-treatment discussed. Enrollment to molecularly based clinical trials is encouraged to support and develop the molecularly based adjuvant treatment paradigms prospectively.

4. Conclusions/Future Directions

Just as significant evolution of adjuvant therapy in endometrial cancer has occurred since the publication of the 2014 ASTRO endometrial guideline, much more is anticipated in the coming years. The following are conclusions of this guideline:

- The choice of EBRT versus VBT in FIGO stage I endometrial cancer should depend on the performance and method of lymph node assessment and the uterine risk factors including the degree of LVSI and histology, and patient age.
- EBRT decreases the risk of locoregional recurrence, especially in patients with FIGO stage I disease with high-risk features or high-risk histologies, FIGO stage II disease, and FIGO stage III-IVA disease.
- When EBRT is indicated, the use of IMRT is associated with improved patient-reported outcomes and acute and late toxicity. Creation of a vaginal ITV with daily image-guidance ensures accurate daily treatment delivery.
- Systemic chemotherapy should be effectively sequenced with radiation therapy in patients with high-risk histologies of all stages and in FIGO stage III-IVA disease of all histologies to decrease distant and locoregional recurrence, respectively.
- SLN mapping with pathologic ultrastaging improves the accuracy of surgical staging and results in less morbidity than pelvic lymphadenectomy. Adjuvant therapy should be recommended based on the clinical and uterine risk factors, performance of a nodal assessment, and results of that nodal assessment.
- For patients with endometrial cancer considering adjuvant therapy, molecular profiling is recommended and may be used to guide adjuvant therapy.

Future directions in adjuvant management are likely to be driven by further discoveries and thoughtfully designed clinical trials. Equity-focused clinical research, including diverse study teams, inclusive enrollment practices, pragmatic study designs, and targeted dissemination of results, will ensure more equitable cancer treatment for all patients with endometrial cancer. Better understanding of the patterns of failure and long-term outcomes for patients undergoing SLN mapping with pathologic ultrastaging is likely to inform which patients with high-risk uterine risk factors can safely omit EBRT and/or chemotherapy. SLN mapping is a more accurate and less morbid staging procedure, but data will emerge if SLN-staged patients have a lower risk of pelvic recurrences to support de-escalation of adjuvant therapy. Similarly, molecular characterization is moving into the forefront and informing on both prognosis and predictive use of adjuvant therapy for patients with endometrial cancer. Studies prospectively incorporating molecular profiling into their randomization and stratification will be important to evolve the standard of care to molecular profile-guided decision making for adjuvant (and possibly even surgical) management. As more prognostic molecular markers are discovered, a

more complete and personalized treatment plan can be delivered. Future work will methodically evolve from histology, grade, and stage to molecular-based prognostic and predictive utilization of adjuvant therapy.

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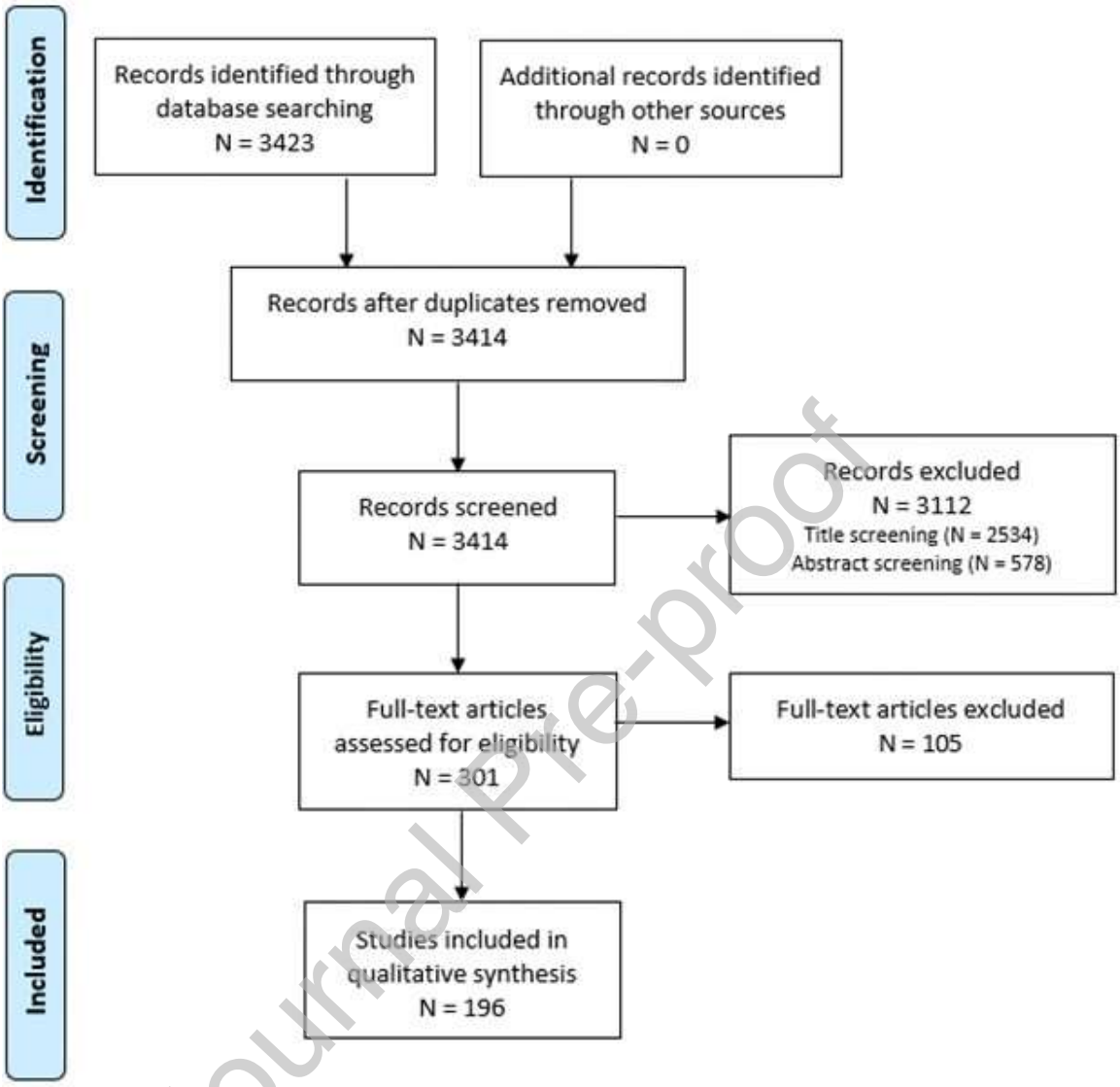
PRISMA Diagram, based on Moher et al.[120]



Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Appendix E1. Peer Reviewers and Disclosures (Comprehensive)

Name	Employment	Disclosure Company/ Organization	Disclosure Category
Junzo Chino, MD *(Content Reviewer)*	Duke Cancer Center – Associate Professor & Director of Brachytherapy	• NanoScint • American Brachytherapy Society	• Stock • International cmt, chair
Carien Creutzberg, MD *(ESTRO Reviewer)*	Leiden University Medical Center – Radiation Oncologist	• Elekta • GSK • Merck • Varian • ESGO • International Gynecological Cancer Intergroup	• Research • Honoraria • Other • Research • Guideline subcmt, co-chair • Endometrial cancer cmt, chair
David Gaffney, MD, PhD *(Content Reviewer)*	University of Utah – Professor, Department of Radiation Oncology	• AstraZeneca • Elekta • Merck • NCI • NRG Oncology	• Advisory board • Research • Consultant (DSMB Chair) • Research/Gyn steering cmt • Gyn Committee, co-chair
Pearly Khaw, BApp Sci, MBBS *(RANZCR Reviewer)*	Peter MacCallum Cancer Center – Lead Radiation Oncologist, Gynae-Tumour Stream	• Australian & New Zealand Gynae-Oncology Group	• Board director
Elizabeth Kidd, MD *(Content Reviewer)*	Stanford Comprehensive Cancer Center – Associate Professor, Department of Radiation Oncology	• TEMPUS	• Research
Panagiotis Konstantinopoulis, MD, PhD *(ASCO Reviewer)*	Dana-Farber Cancer Institute – Associate Professor, Harvard Medical School	• AstraZeneca, Bayer, BMS, GSK, Merck • Alkermes, Artios Pharma, IMV, Kadmon, Mersana • Eli Lilly, Merck KGaA	• All research & advisory boards • Advisory boards • Research
Eric Leung, MD *(CARO Reviewer)*	University of Toronto – Assistant Professor	None	N/A
Constantine Mantz, MD *(Content Reviewer)*	GenesisCare – Chief Policy Officer	None	N/A
Andrea Mariani, MD, MS *(Content Reviewer)*	Mayo Clinic College of Medicine – Professor in Obstetrics and Gynecology	None	N/A
Daniela Matei, MD *(SGO Reviewer)*	Northwestern University Feinberg School of Medicine – Diana Princess of Wales Professor in Cancer Research	• AstraZeneca, Eisai, GSK, Seagen • GOG Foundation • PinotBio	• All advisory board • Honoraria • Research
Mackenzie McGee, MD *(Content Reviewer)*	OSF St. Francis Medical Center – Attending physician; Loyola University Health System – Assistant Professor, Radiation Oncology	None	N/A

Lorraine Portelance, MD *(Content Reviewer)*	University of Miami – Professor, Radiation Oncologist	• Sirtex Medical • ViewRay	• Advisory board • Consultant, other
Matthew Powell, MD *(Content Reviewer)*	Washington University School of Medicine – Professor & Chief Gyn Oncology	• AstraZeneca, Clovis Oncology, Eisai, GSK/Tesaro, Merck, NRG Partner's, Roche/Genentech, SeaGen • NRG Oncology	• All advisory boards & consultant • Uterine Corpus Cmt, chair
Tracy Sherertz, MD *(Content Reviewer)*	Washington Permanente Medical Group – Radiation Oncologist	None	N/A
William Small, Jr., MD *(Content Reviewer)*	Stritch School of Medicine Loyola University Chicago – Professor and Chairman, Radiation Oncology	• ACR	• Board, ASTRO representative
Alexandra Taylor, MD *(ESTRO Reviewer)*	Royal Marsden NHS Foundation Trust – Consultant in Clinical Oncology	• British Gynecological Cancer Society	• Guideline group, co-chair
Theresa Werner, MD *(Content Reviewer)*	Huntsman Cancer Institute, University of Utah – Professor, Oncology & Senior Director of Clinical Research	None	N/A

Abbreviations: ACR = American College of Radiology; ASCO = American Society of Clinical Oncology; CARO = Canadian Association of Radiation Oncology; Cmt = committee; DSMB = data safety monitoring board; ESGO = European Society of Gynecologic Oncology; ESTRO = European Society for Radiotherapy & Oncology; Gyn = gynecologic; N/A = not applicable; NCI = National Cancer Institute; RANZCR = Royal Australian and New Zealand College of Radiologists; SGO = Society of Gynecologic Oncology.

This table represents the reviewers' reported disclosures at the time this document was under review (February-March 2022), not necessarily their disclosures at the time of publication. Dr. Anuja Jhingran served as the Guideline Subcommittee lead reviewer.

Appendix E2. Abbreviations

3-D = 3-dimensional
cGy = centigray
CT = computed tomography
DFS = disease-free survival
EBRT = external beam radiation therapy
FIGO = International Federation of Gynecology and Obstetrics
GOG = Gynecologic Oncology Group
HER2 = human epidermal growth factor receptor 2
IMRT = intensity modulated radiation therapy
ITC = isolated tumor cell
ITV = internal target volume
KQ = key question
LVSI = lymphovascular space involvement
MMR = mismatch repair
OS = overall survival
PFS = progression-free survival
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
POLE = polymerase epsilon
RT = radiation therapy
RCT = randomized controlled trial
RFS = recurrence/relapse/failure-free survival
SLN = sentinel lymph node
TH-BSO = total hysterectomy, bilateral salpingo-oophorectomy
VBT = vaginal brachytherapy
WAI = whole abdominal irradiation

Appendix E3. PICOTS Questions / Literature Search Protocol

Search Limits:

Search Date(s):	3.8.2021 (Updated 8.5.21 to include uterine cancer)
Age Range	Adults (≥18 years old)
Language	English only
Species	Humans
Patient Minimum	≥25 patients
Publication Types	• RCTs • Meta-analyses • Prospective trials • Retrospective studies, excluded for KQ1
Timeframe	Jan 2000 - Aug 2021 Retrospective studies 2015 - Aug 2021

Universal Exclusion Criteria:

1. Metastatic disease
2. Neoadjuvant RT
3. SBRT studies
4. Electronic brachytherapy
5. Non-epithelial tumors of the uterus
6. Pediatric patients
7. Dosimetric studies
8. Large database registry (NCDB, SEER)
9. Pre-clinical/non-human studies
10. Health economics/cost analysis studies
11. Studies available in abstract only
12. Comment or editorial
13. Guidelines or review articles
14. Otherwise not relevant or out of scope

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 1:** What are the indications for adjuvant RT in patients with endometrial cancer?
Definitions	Total Hysterectomy – Bilateral Salpingo-Oophorectomy (TH-BSO) Lymph Node Dissection Sentinel Lymph Node Adjuvant RT Radiation Vaginal brachytherapy (VBT) External beam radiation therapy (EBRT)
Participants/ population	Patients age ≥18 years with endometrial cancer

Intervention(s)/exposure(s)	• Adjuvant RT (EBRT or brachytherapy)
	• Baseline surgery search terms may include:
	  ○ Total hysterectomy
	  ○ Radical hysterectomy
	  ○ Total abdominal hysterectomy

	○ Total robotic hysterectomy ○ Total laparoscopic hysterectomy ○ Simple hysterectomy ○ Extrafascial hysterectomy ○ Vaginal hysterectomy
Comparator(s)/ control	Surgery alone
Outcomes: primary/critical	Overall survival, local control, pelvic control, vaginal control, locoregional control, distant metastases
Outcomes: secondary/ important but not critical outcomes	• Acute and late toxicity • Patient-reported side effects • Quality-of-life assessments
Timing	Adjuvant
Setting/context	Ambulatory/outpatient, hospital/inpatient
Study design	• RCTs: ○ Surgery alone vs. adjuvant RT ○ Comparison of adjuvant RT modalities (VBT & EBRT) • Meta-analyses • Prospective trials
Summary of the key selection criteria	**Inclusion criteria:** Patients age ≥18 years with endometrial cancer • Nonmetastatic, stages I-IVA • With surgical or imaging-based staging (PET, CT, MRI inclusive) **Exclusion criteria:** Retrospective studies and universal exclusion criteria above

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 2:** What are the appropriate dose-fractionation schemes, target volumes, and normal tissue constraints for patients receiving adjuvant RT for endometrial cancer?
Participants/ population	Patients age ≥18 years with endometrial cancer undergoing adjuvant RT
Intervention(s)/ exposure(s)	• Adjuvant Vaginal Brachytherapy • Adjuvant External beam radiation therapy
Comparator(s)/ control	N/A (will be comparing among modalities and techniques)
Outcomes: primary/critical	• Acute and late toxicity • Patient-reported side effects • Quality-of-life assessments
Outcomes: secondary/ important but not critical outcomes	Overall survival, local control, pelvic control, vaginal control, locoregional control, distant metastases
Timing	Adjuvant
Setting/context	Ambulatory/outpatient, hospital/inpatient
Study design	• RCTs: 3-D vs. IMRT • Meta-analyses • Prospective trials • Retrospective studies
Summary of the key selection criteria	**Inclusion criteria:** Patients age ≥18 years with endometrial cancer

	• Nonmetastatic, stages I-IVA • With surgical or imaging-based staging (PET, CT, MRI inclusive) **Exclusion criteria:** See universal exclusion criteria above

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 3:** What are the indications for systemic therapy in patients with nonmetastatic endometrial cancer?
Participants/ population	Patients age ≥18 years with nonmetastatic endometrial cancer
Intervention(s)/ exposure(s)	• Adjuvant systemic therapy • Adjuvant RT with systemic therapy
Comparator(s)/ control	• Surgery alone • Adjuvant RT without systemic therapy
Outcomes: primary/critical	Overall survival, local control, pelvic control, vaginal control, locoregional control, distant metastases
Outcomes: secondary/ important but not critical outcomes	• Acute and late toxicity • Patient-reported side effects • Quality-of-life assessments
Timing	Adjuvant
Setting/context	Ambulatory/outpatient, hospital/inpatient

Study design	• RCTs:
	  ○ Surgery alone vs. surgery with adjuvant systemic therapy
	  ○ Adjuvant RT +/- adjuvant systemic therapy
	  ○ Adjuvant RT vs. adjuvant systemic therapy
	• Meta-analyses
	• Prospective trials
	• Retrospective studies

Summary of the key selection criteria	**Inclusion criteria:** Patients age ≥18 years with endometrial cancer • Nonmetastatic, stages I-IVA • With surgical or imaging-based staging (PET, CT, MRI inclusive) **Exclusion criteria:** See universal exclusion criteria above

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 4:** What is the appropriate sequencing of systemic therapy with RT in patients with endometrial cancer?
Definitions	• Sandwich therapy - systemic therapy given before and after adjuvant RT • Sequenced – before, during and/or after
Participants/ population	Patients ≥18 years of age with endometrial cancer receiving adjuvant Systemic therapy and RT

Intervention(s)/ exposure(s)	Adjuvant RT (EBRT or brachytherapy) sequenced with systemic therapy
Comparator(s)/ control	• The different sequences of the chemotherapy compared to each other ○ Sandwich systemic therapy ○ Sequenced systemic therapy ○ Concurrent systemic therapy ○ Combination of above
Outcomes: primary/critical	Overall survival, local control, pelvic control, vaginal control, locoregional control, distant metastases
Outcomes: secondary/ important but not critical outcomes	• Acute and late toxicity • Patient-reported outcomes • Quality-of-life assessments
Timing	• Adjuvant • Sandwich therapy • Sequenced
Setting/context	Any
Study design	• RCTs ○ Adjuvant RT vs. adjuvant RT sequenced with systemic therapy ○ Adjuvant systemic therapy vs. adjuvant RT sequenced with systemic therapy • Meta-analyses • Prospective trials • Retrospective
Summary of the key selection criteria	**Inclusion criteria:** Patients ≥18 years of age with endometrial cancer • Nonmetastatic, stages I-IVA • Surgical staging (+/- nodes) • Carboplatin, Taxol, concurrent Cisplatin (most common) or other agents **Exclusion criteria:** See universal exclusion criteria above

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 5:** How should the performance of, and type of, lymph node assessment influence adjuvant RT decisions in patients with endometrial cancer?
Definitions	• Sentinel lymph node mapping or biopsy - intraoperative retrieval of dye identified first echelon nodes from the uterine primary • lymph node dissection - removal of lymph nodes from the perivascular fat
Participants/ population	Patients ≥18 years of age with endometrial cancer undergoing surgical staging including lymph node assessment
Intervention(s)/ exposure(s)	• Surgery with sentinel lymph node mapping or biopsy • Surgery with lymph node dissection
Comparator(s)/ control	• Surgery without sentinel mapping, biopsy, or lymph node dissection • Surgery with lymph node dissection
Outcomes: primary/critical	Overall survival, local control, pelvic control, vaginal control, locoregional control, distant metastases, detection rate of nodal metastases

Outcomes: secondary/ important but not critical outcomes	• Patient-reported outcomes • Quality-of-life assessments
Timing	Adjuvant
Setting/context	Any
Study design	• RCTs • Meta-analyses • Prospective trials • Retrospective studies
Summary of the key selection criteria	**Inclusion criteria:** Patients ≥18 years of age with endometrial cancer • Nonmetastatic, stages I-IVA • Surgical staging including nodal assessment **Exclusion criteria:** see universal exclusion criteria above

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 6:** How should molecular markers influence adjuvant RT and systemic therapy decisions in patients with endometrial cancer?
Definitions	• Molecular markers – immunohistochemical markers or mutation analyses • Molecular pathways
Participants/ population	Patients ≥18 years of age with nonmetastatic endometrial cancer
Intervention(s)/ exposure(s)	• Adjuvant therapies with molecular markers ○ Baseline search terms may include m
Comparator(s)/ control	• Adjuvant therapies without molecular markers
Outcomes: primary/critical	Overall survival, local control, pelvic control, vaginal control, locoregional control, distant metastases
Outcomes: secondary/ important but not critical outcomes	• Acute and late toxicity • Patient-reported side effects • Quality-of-life assessments
Timing	Adjuvant
Setting/context	Any
Study design	• RCTs • Meta-analyses • Prospective trials • Retrospective studies
Summary of the key selection criteria	**Inclusion criteria:** Patients ≥18 years of age with endometrial cancer • Nonmetastatic, stages I-IVA • Surgical staging including nodal assessment **Exclusion criteria:** see universal exclusion criteria above

Endometrial and Uterine Cancer Search Strategy

Database(s): Ovid MEDLINE(R) ALL 1946 to August 05, 2021

#	Searches
1	exp Endometrial Neoplasms/
2	(Uterine Neoplasms/ and ((uterine or uterus) adj5 (cancer* or neoplas* or carcinom* or adenocarcinom*)).ab.) not ("uterine cervical" or "uterine cervix").ti.
3	(endometri* adj5 (cancer* or neoplas* or carcinom* or carcinosarcoma* or adenocarcinom*)).ti,ab,kf.
4	((uterine or uterus) adj5 carcinosarcoma*).ti,ab,kf.
5	((uterine or uterus) adj3 (cancer* or neoplas* or carcinom* or adenocarcinom*)).ti,kf. not ("uterine cervical" or "uterine cervix").ti.
6	Mixed Tumor, Mullerian/
7	"malignant mixed Mullerian tumo?r*".ti,ab,kf.
8	or/1-7 [Endometrial cancer]
9	limit 8 to (english language and yr="2000 -Current")
10	(animals not (humans and animals)).sh.
11	9 not 10
12	((mice or mouse or murine or rat or rats or rodent or cells or "in vitro" or "cell line") not "Isolated tumor cells").ti.
13	11 not 12 [Remove animal study]
14	((child or children or adolescent or pediatric* or paediatric*).ti. or (infant* or newborn*).ti,kf.) not childhood.ti.
15	13 not 14 [Remove pediatric patients]
16	case report*.ti,jw.
17	case reports.pt. not (exp clinical study/ or comparative study/ or evaluation studies/ or meta-analysis/ or multicenter study/ or validation studies/ or exp Cohort Studies/ or letter.pt. or (series or cohort or retrospective*).ti,ab.)
18	16 or 17
19	15 not 18 [Remove most case reports]
20	(comment or editorial or news or preprint).pt.
21	19 not 20 [Remove comments editorials news preprints]
22	review.pt.
23	comparative study/ or evaluation studies/ or Clinical Trial/
24	systematic review*.ti,pt. or "cochrane database of systematic reviews".jn. or meta-analysis as topic/ or Meta-Analysis.pt. or (meta-analy* or metaanaly*).ti.
25	23 or 24
26	22 not 25
27	21 not 26 [Remove review articles]
28	Practice Guideline/
29	consensus development conference.pt.

30	consensus development conference nih.pt.
31	(Guideline* or consensus).ti.
32	((consensus or position) adj3 statement*1).ti.
33	(practice adj3 parameter*).ti.
34	or/28-33
35	27 not 34 [Remove guideline]
36	(NCDB or SEER).ti. or ("National Cancer Data Base" or "National Cancer Database").ti,ab,kf. or SEER Program/
37	(unresectable or non-resectable or nonresectable or inoperable or nonoperative or "non-operable" or "stage IVB").ti.
38	35 not 37 [Remove medically inoperable]
39	(sarcoma* not carcinosarcoma*).ti.
40	38 not 39 [Remove uterine sarcomas]
41	exp Radiotherapy/
42	(radiotherap* or irradiat* or radiat* or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or "intensity modulated" or IMRT or EBRT or stereotactic or brachytherapy).ti,ab,kf.
43	exp Radiotherapy Planning, Computer-Assisted/
44	exp Radiation Oncology/
45	or/41-44
46	40 and 45 [Endometrial cancer + radiotherapy]
47	Neoplasm Recurrence, Local/
48	recurrence*.ti,ab,kf.
49	((local* or locoregional or pelvic or vaginal) adj3 (control or failure or progression or progressive)).ti,ab,kf.
50	distant metastas?s.ti,ab,kf.
51	exp TREATMENT OUTCOME/
52	SURVIVAL/
53	exp SURVIVAL ANALYSIS/
54	Survival Rate/
55	Kaplan-Meier.ab.
56	survival.ti,kf.
57	survival.ab. /freq=2
58	exp *"Quality of Life"/
59	("quality of life" or "HR-QOL" or "health-related QOL" or toxicity or toxicities).ti,kf.
60	(toxic* or safety or ((adverse* or side) adj3 (event* or effect*))).ti.
61	exp Radiotherapy/ae [Adverse Effects]
62	patient reported outcome measures/
63	"patient reported".ti,ab,kf.
64	or/47-63 [treatment outcome]
65	46 and 64 [Endometrial cancer + radiotherapy + outcome]

66	exp Hysterectomy/
67	(Salpingo-oophorectom* or ovariectom* or oophorectom* or "TH-BSO" or hysterectom*).ti,ab,kf.
68	exp Pelvic Exenteration/
69	exp Ovariectomy/
70	Lymph Node Excision/
71	(surger* or surgical or hysterectom* or excision* or resect* or dissect* or exenteration* or biops* or lymphadenectom* or laparotom*).ti,ab,kf.
72	lymphadenectom*.ti,ab,kf.
73	("post operative" or postoperative or "post surger*" or postsurger* or "post hysterectom*" or posthysterectom*).ti,ab,kf.
74	exp Sentinel Lymph Node/
75	exp Sentinel Lymph Node Biopsy/
76	((sentinel or lymph) adj node*).ti,kf.
77	"sentinel lymph node*".ti,ab,kf.
78	or/66-77 [surgical treatment]
79	65 and 78 [KQ1: indications for radiation therapy]
80	79 and 36 [NCDB or SEER studies for KQ1]
81	79 not 80 [KQ1 without DCDB or SEER studies]
82	exp radiotherapy, computer-assisted/
83	exp Radiotherapy Dosage/
84	(fraction* or hyperfractionat* or hypofractionat* or accelerat* or dose or dosage).ti,ab,kf.
85	Brachytherapy/
86	brachytherapy.ti,ab,kf.
87	Radiotherapy, Image-Guided/
88	(external adj (radiation or beam or radiotherapy)).ti,ab,kf.
89	("target volume" or "gross tumor volume").ti,ab.
90	Organs at Risk/
91	"organ* at risk*".ti,ab,kf.
92	normal tissue constraint*.ti,ab,kf.
93	(MRI or "magnetic resonance imaging" or "positron emission tomography" or PET or "computed tomography" or CT).ti,kf.
94	or/82-93
95	65 and 94 [KQ2: appropriate dose fractionation schemes, target volumes and normal tissue constraints]
96	95 and 36 [NCDB or SEER studies for KQ2]
97	95 not 96 [KQ2 without DCDB or SEER studies]
98	95 not 79 [KQ2 unique]
99	95 and 79 [KQ2 dups with other KQs]
100	exp Antineoplastic Protocols/
101	exp Antineoplastic Agents/

102	(chemo* or "systemic therapy" or antineoplastic or "anti neoplastic*" or anticancer or "anti cancer").ti,ab,kf.
103	Molecular Targeted Therapy/
104	exp chemoradiotherapy/
105	chemotherapy, adjuvant/ or consolidation chemotherapy/ or induction chemotherapy/ or maintenance chemotherapy/
106	exp Neoplasms/dt [Drug Therapy]
107	(lenvima* or lenvatinib* or platinol* or cisplatin* or "cis-platinum" or paraplatin* or carboplatin* or adriamycin* or doxorubicin* or taxol* or paclitaxel* or taxotere* or docetaxel* or herceptin* or trastuzumab* or avastin* or bevacizumab* or keytruda* or pembrolizumab* or lambrolizumab* or hycamtin* or topotecan* or hycamptamine* or ifex* or ifosfamide* or isophosphamide* or nolvadex* or tamoxifen* or provera* or depoprovera* or medroxyprogesterone* or veramix* or curretab* or cycrin* or farlutal* or gestapuran* or perlutex* or femara* or letrozole* or letoval* or megace* or megestrol* or temsirolimus*).mp.
108	or/100-107 [adjuvant chemotherapy]
109	46 and 108 [adjuvant systemic therapy/chemotherapy, chemotherapy in combination with RT]
110	or/66-73 [surgical treatment]
111	110 and 40 and 108 [postoperative chemotherapy]
112	109 or 111 [KQ3: indications for systemic therapy in patients with non-metastatic endometrial cancer]
113	112 and 36 [NCDB or SEER studies for KQ3]
114	112 not 113 [KQ3 without DCDB or SEER studies]
115	112 not (79 or 95) [KQ3 Unique]
116	112 and (79 or 95) [KQ3 dups with other KQs]
117	(sequencing or sequenced or sequential or concurrent or concomitant or Sandwich).ti,ab,kf.
118	((chemo* or radio* or radiation or brachytherapy or RT or VBT or IMRT or EBRT) adj5 (before or after or during or follow* or combined or combination) adj5 (chemo* or radio* or radiation or brachytherapy or RT or VBT or IMRT or EBRT)).ti,ab,kf.
119	((order or sequence) adj5 (VBT or CT or RT or chemo* or radiation* or radio* or brachytherapy)).ti,ab,kf.
120	or/117-119 [treatment sequence]
121	112 and 120 [KQ4: appropriate sequencing of chemotherapy with radiation therapy]
122	121 and 36 [NCDB or SEER studies for KQ4]
123	121 not 122 [KQ4 without DCDB or SEER studies]
124	121 not (79 or 95 or 112) [KQ4 unique (not KQ1-3)]
125	121 not 124 [KQ4 dups with other KQs]
126	Lymph Nodes/
127	lymph node*.ti,ab,kf.
128	lymphatic mapping.ti,ab,kf.
129	70 or 72 or 74 or 75 or 76 or 77 or 126 or 127 or 128 [lymph node assessment]
130	46 and 129 [KQ5 lymph node assessment]
131	130 and 36 [NCDB or SEER studies for KQ5]
132	130 not 131 [KQ5 without DCDB or SEER studies]

133	130 not (79 or 95 or 112 or 121) [KQ5 unique]
134	130 not 133 [KQ5 dups with other KQs]
135	79 or 95 or 112 or 121 or 130 [KQ1-5]
136	exp DNA Polymerase II/
137	(POLE or "DNA polymerase epsilon").ti,ab,kf.
138	DNA Mismatch Repair/
139	("Mismatch Repair" or mmr).ti,ab,kf.
140	Microsatellite Instability/
141	"Microsatellite Instability".ti,ab,kf.
142	Tumor Suppressor Protein p53/
143	Genes, p53/
144	(P53 or tp53).ti,ab,kf.
145	("No Specific Molecular Profile" or NSMP).ti,ab,kf.
146	or/136-145 [molecular markers]
147	40 and 108 and 146 [KQ6: Endometrial cancer chemo/systemic therapy molecular markers]
148	46 and 146 [KQ6: Endometrial cancer radiation therapy molecular markers]
149	147 or 148 [adjuvant systemic therapy or radiation therapy molecular markers]
150	40 and 64 and 146 [Outcome+ molecular marker]
151	149 or 150 [KQ6 Final]
152	remove duplicates from 135 [KQ1-5]
153	remove duplicates from 151 [KQ6]