The Role of Post-Operative Radiation Therapy for Endometrial Cancer

An ASTRO Evidenced-Based Guideline

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**Conflict of Interest Disclosure Statement:**

Before initiation of this guideline all members of the guideline panel were required to complete disclosure statements. These statements are maintained at the American Society for Radiation Oncology (ASTRO) headquarters in Fairfax, VA and pertinent disclosures are published with the report. The ASTRO Conflict of Interest Disclosure Statement seeks to provide a broad disclosure of outside interests. Where a potential conflict is detected, remedial measures to address any potential conflict are taken and will be noted in the disclosure statement. Ann Klopp, MD, PhD has research funding from the Ovarian Cancer Research Foundation and the MD Anderson Cancer Center Endometrial and Ovarian Spore. Benjamin Smith, MD has received research grants from Conquer Cancer Foundation and Cancer Prevention and Research Institute of Texas. He also serves as a consultant for Conquer Cancer Foundation. Catheryn Yashar, MD serves as a consultant to and owns stock in Cianna Medical. The guideline panel chairs as well as the chair of the guideline subcommittee reviewed these disclosures and
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INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy and the incidence is rising (Figure 1).\textsuperscript{1,2} This increase in incidence is likely attributable to the rising rates of obesity in the United States which are strongly linked to the development of endometrial cancer.\textsuperscript{1,3} Endometrial cancer has been classically divided into two biological entities, type I and type II. Type I endometrial cancer, which has a favorable prognosis, is typically endometrioid and associated with obesity and estrogen exposure. Type II endometrial cancers, which include serous, clear cell, and carcinosarcoma histology, are less common and have a worse prognosis. It is increasingly recognized that the histologic subtypes of endometrial cancer are biologically distinct and may require different treatment approaches.
The optimal adjuvant treatment for endometrial cancer remains poorly defined despite the prevalence of the disease and a large number of completed prospective studies. This ambiguity can be attributed to inadequate power in many of these studies due to heterogeneity in patients, low recurrence rates in early endometrial cancer, and competing risk of death from other causes in women with endometrial cancer. The goal of this article is to provide evidence-based guidelines for adjuvant radiation in the treatment of endometrial cancer.

**METHODS AND MATERIALS**

**Process**

The Guidelines Subcommittee of the Clinical Affairs and Quality Council in accordance with established ASTRO policy recruited a guideline panel of recognized experts in endometrial cancer including radiation oncologists, gynecologic oncologists, and radiation physicists in academic settings, private practice, and residency. The Panel provided guidance on the use of radiation therapy for patients with endometrial cancer. In February 2011, the ASTRO Board of Directors approved the *Post-operative Radiation Therapy for Endometrial Cancer Guideline* proposal and Panel membership. Next, the Panel participated in a series of communications by electronic mail and conference telephone calls to draft the guideline. The members of the Panel were divided into subgroups, according to their areas of expertise, to address the key questions. Next, all members of the Panel evaluated the responses to the questions assigned to the subgroups. The initial draft of the manuscript was reviewed by three expert reviewers and ASTRO legal counsel. A revised draft was placed on the ASTRO Web site in May 2013 for a six-
week period of public comment. Following integration of feedback, the document was submitted for approval to the ASTRO Board of Directors, August 2013.

**Literature Review**

An analytic framework, based on the identified population, interventions, comparators, and outcomes (PICO) was used to refine the search. Next, the population was defined as women of all races, age 18 years or older, with stage I-IV endometrial cancer of any histologic grade. A search was conducted for studies that compared (1) patients who were treated with pelvic radiotherapy alone; (2) patients treated with vaginal brachytherapy alone; (3) patients who were not treated with radiation; (4) patients who were treated with chemotherapy alone; and (5) patients who were treated with vaginal brachytherapy and pelvic radiotherapy. To assess the interventions employed by the studies, a literature search based on the following outcomes was conducted: survival rates, local and distant recurrence rates, toxicity, and overall assessment of quality of life. Finally, additional studies with the following characteristics were included as well: English language only; women ≥ 18 year old with an initial presentation of stage I-IV endometrial cancer of any histology who received no adjuvant radiation therapy; vaginal cuff radiation and/or pelvic radiation (with or without para-aortic radiation). Our exclusion criteria included trials of preoperative radiotherapy, patients with distant metastasis, and patients with unresected gross residual disease after hysterectomy. Literature searches were performed on electronic databases that included “English only” literature from 1980-2011: MEDLINE PubMed (1980 to 2011), EMBASE (1980 to 2011), and the Specialized Register of the Cochrane Gynaecological Cancer Review.
Group (CGCRG). Additionally, reference lists of previous systematic reviews and other relevant papers were searched. Randomized clinical trials, non-randomized clinical trials, observational studies, abstracts, and conference proceedings were searched as well.

The initial search yielded 1,077 abstracts. The articles were reviewed for inclusion by the ASTRO staff and co-chairs of the guideline. Next, 148 articles were excluded due to small sample size, distant metastatic disease, medically inoperable patients, management of recurrences, and not being clinically relevant to the key clinical questions (KQ). A second assessment resulted in the exclusion of 599 articles due to duplicate studies, sarcoma, studies involving less than 10 patients and studies not being clinically relevant to the key clinical questions. Finally, 330 articles were fully abstracted to provide supporting evidence for the clinical guideline recommendations.

Grading of Evidence, Recommendations and Consensus Methodology

When available, high-quality evidence formed the basis of the recommendation statements in accordance with the Institute of Medicine (IOM) standards. Guideline statements were developed based on the body of evidence categorized by the American College of Physicians (ACP) Strength of Evidence Rating. The ACP’s ratings consist of high quality, moderate quality, low quality or insufficient evidence to determine net benefits or risks. Guideline recommendation statements were developed and included evidence ratings. The level of consensus on the guideline recommendation statements among the panelists was evaluated through a modified Delphi approach. The survey was sent by an ASTRO staff to the Panel members. Panelists rated the agreement with each recommendation pertaining to the key clinical questions on a five-point Likert scale,
ranging from strongly disagree to strongly agree, as depicted in Table 7 (higher score corresponds with stronger agreement); a pre-specified threshold of $\geq 75\%$ of raters was determined to indicate when consensus was achieved.\textsuperscript{4}

**Risk Factors**

Various clinical and pathologic factors are prognostic for disease recurrence and cancer-related mortality. Patients with these risk factors are at higher risk of recurrence including locoregional failure and may benefit from a locoregional treatment such as radiation therapy (external beam radiation and/or brachytherapy).

**Older Age**

Older women with endometrial cancer have higher rates of disease recurrence.\textsuperscript{5,6} Many studies have incorporated age into eligibility criteria to identify patients at sufficiently high risk who require additional treatment.

**Histology**

The most common histology, accounting for approximately 80\% of cases is endometrioid adenocarcinoma, which resembles normal or hyperplastic endometrial glandular tissue in its differentiated features.\textsuperscript{7} Serous endometrial cancer accounts for 5\%-10\% of uterine cancers, but is responsible for a much higher percentage of deaths from uterine cancer.\textsuperscript{8} Clear cell carcinoma typically occurs in older women and has a poor prognosis.\textsuperscript{9} Large and small cell undifferentiated carcinoma are rare and exhibit high rates of distant
metastasis. This guideline focuses on the most common histology, endometrioid endometrial cancer.

Grade

Prognosis correlates strongly with tumor grade. High-risk histologies such as serous, clear cell and carcinosarcoma are considered high-grade. Endometrioid tumors are graded on the basis of percentage of tumor cells with a solid growth pattern. Tumors that are architecturally grade 1 or 2 may have their grade increased by one if they have marked nuclear pleomorphism, coarse chromatin, or prominent nucleoli.\(^\text{10}\)

Myometrial and cervical invasion

The depth of myometrial invasion (MI) is an independent predictor of lymph node involvement and overall survival and is one of the most important prognostic indicators.\(^\text{11,12}\) Tumors that involve endocervical stroma are classified by the International Federation of Gynecology and Obstetrics (FIGO) as stage II. In the updated 2009 FIGO staging system, involvement of endocervical glands without cervical stromal invasion does not qualify disease as stage II. This modification to the staging system was made because patients with endocervical gland involvement have a relatively good prognosis, similar to that of patients with tumors of similar grade and depth that are confined to the fundus.\(^\text{13}\) Presumably, invasion of endocervical stroma gives malignant cells access to regional routes of spread, placing regional nodes at greater risk of involvement.
Lymphovascular space invasion (LVSI)

LVSI is a strong independent predictor of lymph node involvement and survival. In a study from Mayo Clinic that included patients with ≤ 50% invasion and grade 1 or 2 tumors, of which 57% had a lymphadenectomy and only 5% had positive nodes, patients without LVSI had a 5-year cancer-related survival rate of 98%, compared to 77% for patients with LVSI ($p < .0001$). In another study from Cleveland Clinic, 131 patients with stage I endometrial cancer with LVSI were analyzed; those who had a lymphadenectomy and were observed had an approximately 20% vaginal recurrence risk, but no patients had a pelvic nodal relapse. LVSI has been found to predict for isolated para-aortic lymph node metastasis. In addition, GOG-99 identified LVSI as one of the critical criteria which identify patients at “high intermediate risk” who benefit from pelvic radiation therapy. The extent of LVSI has also been reported to have prognostic value: extensive LVSI is more highly correlated with lymph node involvement than focal LVSI.

Tumor size

Larger tumors are associated with a higher risk of nodal involvement. Patients with tumors smaller than 2 cm with minimal invasion, endometrioid histology, and low or moderate grade have very low rates of nodal involvement. In a series of 187 patients with clinical stage I endometrial cancer that underwent lymphadenectomy, patients with these pathological characteristic had no nodal metastasis identified. In another series, tumor size greater than 2 cm was associated with a 26.3% risk of nodal metastasis as compared to 6.3% in patients with tumor size less than 2 cm. However, tumor size in
this series was not independently predictive of node metastasis when well-established factors such as depth of invasion and grade were included in the model.\(^{20}\)

*Risk factors for radiotherapy complications*

In addition to the clinical and pathological risk factors discussed above, other patient factors should be considered when deciding whether to recommend radiation. Previous peritonitis, inflammatory bowel disease, prior bowel surgery, or collagen vascular diseases may put patients at high risk for complications from external beam radiation therapy (EBRT). Patients who have undergone extensive lymphadenectomy are at higher risk for developing chronic lower extremity lymphedema which can be compounded by EBRT. Smoking and underweight patients have a modestly increased risk of bowel complications\(^{21}\).

KQ1: Which patients with endometrioid endometrial cancer require no additional therapy after hysterectomy?

*Outcomes for low-risk patients*

Tumors that are stage I, grade 1 or grade 2, with < 50% invasion, and which lack high-risk features such as LVSI or cervical glandular involvement, are generally considered low risk. The absolute risk of recurrence in these patients is less than 5%.\(^{22}\) When recurrence does occur, the vaginal cuff is the most frequent site.\(^{22}\) Sorbe et al conducted a randomized trial of vaginal brachytherapy vs. no further treatment in patients with low risk endometrial cancer (grade 1 or 2 endometrioid cancer with < 50% invasion).\(^{22}\) These
patients did not have routine nodal dissection but did have node sampling of enlarged
nodes. This study reported a non-significant reduction in vaginal recurrence in the group
receiving brachytherapy (3.1 vs. 1.2%, \( p = 0.11 \)) after a median follow-up of 68 months
(Table 1). These findings suggest that brachytherapy is not indicated in these low risk
patients after hysterectomy.

Vaginal cuff brachytherapy

The most common site of relapse in women with early stage endometrial cancer, who do not receive adjuvant radiotherapy is the vaginal cuff. Vaginal cuff brachytherapy reduces the risk of recurrence in the vagina and causes significantly less toxicity than pelvic radiotherapy. However, EBRT is needed to treat the parametrial tissues and draining lymphatics. Patients treated with EBRT using pelvic radiotherapy have higher rates of diarrhea and bowel symptoms in the acute and late setting than patients who receive only vaginal cuff brachytherapy. Patients treated with external beam had a higher need to remain close to a toilet and, as a consequence, more limitation of daily activities because of bowel symptoms and decreased social functioning. Side effects of vaginal cuff irradiation are generally limited to vaginal complications and mild urinary side effects. Nine percent of patients in a randomized trial receiving brachytherapy developed grade 1 and 2 vaginal toxicity as compared to 1.5% of patients in the observation arm. Grade 1 and 2 urinary side effects were also slightly more common after vaginal irradiation (2.8% vs. 0.6%, respectively \( p = 0.063 \)) but brachytherapy did not impact the rates of GI toxicity. In addition, brachytherapy may in
theory have a lower risk of second malignancies due to the smaller region treated, though this must be assessed in future studies.

**KQ 1 Guideline statement:** Which patients with endometrioid endometrial cancer require no additional therapy after hysterectomy? Following total abdominal hysterectomy with or without node dissection, no radiation therapy is a reasonable option for patients with 1) no residual disease in the hysterectomy specimen despite positive biopsy (low quality evidence)\(^1\) or 2) grade 1 or 2 cancers with either no invasion or less than 50% myometrial invasion, especially when no other high risk features are present (high quality evidence). Vaginal cuff brachytherapy may be considered in patients with negative node dissection with 1) grade 3 cancers without myometrial invasion (low quality evidence) or 2) grade 1 or 2 cancers with less than 50% myometrial invasion and higher risk features such as age greater than 60 and/or LVSI (moderate quality evidence). See Table 7 for consensus/ percent agreement.

**KQ2:** Which patients with endometrioid endometrial cancer should receive vaginal cuff radiation?

Vaginal cuff radiation therapy for patients with intermediate risk or high-intermediate risk endometrial cancer

Patients with intermediate risk endometrial cancer have a higher risk of vaginal recurrence than low risk patients and may benefit from vaginal cuff brachytherapy.

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\(^1\) This grading system has been adopted from the American College of Physicians (ACP) process for grading quality of evidence. See Appendix A.
Variable definitions have been used to define intermediate risk endometrial cancer, including stage I or II disease with risk factors such as myometrial invasion, higher grade, LVSI and older age. The PORTEC and GOG studies have defined a subset of these patients who have “high-intermediate risk” disease. These definitions are listed in Table 4.

A number of studies have investigated whether adjuvant pelvic radiation, vaginal cuff brachytherapy, or observation is optimal for stage I and II patients with endometrial cancer. Three studies have compared vaginal cuff brachytherapy to pelvic radiation with or without additional brachytherapy (Table 1). The first study conducted by the Norwegian Radium Hospital enrolled all clinical stage I endometrial cancers. All patients received brachytherapy followed by a randomization to pelvic radiation or no additional therapy. The addition of external beam radiation decreased local recurrence (7% vs. 2%, p < 0.01). Among the subset with deeply invasive grade three tumors (19%, 100 of 540 patients enrolled), the overall survival appeared to be higher in the group that received pelvic radiation although no statistical analysis of this was reported.

More recently, the PORTEC-2 study compared vaginal cuff brachytherapy to pelvic radiation for patients with high-intermediate risk endometrial cancer. Eligibility for this study required that patients greater than 60 years have deeply invasive grade 1 or 2 disease or minimally invasive grade 3 disease. Patients with endocervical gland involvement were eligible at any age. Similar to PORTEC-1, patients with deeply invasive grade 3 were not eligible. Clinically suspicious pelvic or para-aortic lymph nodes were removed, but no routine lymphadenectomy was done. In fact, patients with staging lymphadenectomy were specifically excluded. The primary endpoint, vaginal
recurrence, was equivalent in external beam and brachytherapy only arms (1.6% vs. 1.8%, \( p = 0.7 \)). Patients treated with external beam radiation had lower rates of pelvic recurrence (0.5% vs. 3.8%, \( p = 0.02 \)), but similar to the ASTEC study (Table 4), absolute rates of pelvic recurrence were low in the non-pelvic radiation therapy (RT) arm. A central pathology review was performed after patients were randomized, demonstrating that 79% of patients enrolled in the study had grade 1 cancers, and 14% would have been ineligible for the trial based on favorable features. These results suggest that the use of vaginal cuff radiation may be equivalent to pelvic radiation in patients with intermediate risk findings such as deeply invasive grade 1 disease. However, PORTEC-2 included very few patients with deeply invasive grade 2 disease and none with deeply invasive grade 3 disease; therefore, this study does not provide evidence for using vaginal cuff brachytherapy in place of pelvic radiation in these patients. The impact of pelvic radiation on quality of life was also investigated in PORTEC-2. Patients in the vaginal cuff group reported better social functioning (\( p < .002 \)) and lower symptom scores for diarrhea and fecal leakage which resulted in the need to stay close to the toilet, and limited daily activities (\( p < .001 \)).

The most recently reported study comparing pelvic radiation to vaginal irradiation was published by Sorbe et al. Patients were eligible if they had “medium risk” endometrial cancer, which included aneuploidy as a risk factor, as well as grade and depth of invasion. External beam radiation was followed by additional brachytherapy in this study. Five-year locoregional relapse rates were 1.5% after external beam radiotherapy and 5% after vaginal irradiation alone (\( p = 0.013 \)).
A number of studies have been reported in which patients with stage I and II endometrial cancer with intermediate or high risk features have been treated with vaginal cuff brachytherapy with favorable outcomes. A list of these studies with recurrence rates is shown in Table 2.

Vaginal cuff brachytherapy technique

A variety of techniques have been used for delivery of vaginal cuff brachytherapy. Variables include type of applicator, length of vagina treated, dose per fraction, and prescription depth. Details of the approach have been recently reviewed. Most critical is the use of an applicator that fits snugly in the vaginal apex. In most cases, the upper third of the vagina is treated. For patients at high risk of vaginal recurrence due to serous or clear cell histology or extensive LVSI, a longer length of vagina may be treated. The dose is generally prescribed to the surface or to 5 mm depth but should be reported to both depths.

Dose has been shown to impact vaginal toxicity. Sorbe et al reported a significant reduction in vaginal length when 5 fractions of 5 Gy, rather than 2.5 Gy, were prescribed to 5 mm. There was no difference in rates of vaginal recurrence between the two groups. Seven Gy × 3 prescribed to 5 mm depth is a commonly used fractionation scheme. However, given that the effective dose to the vaginal surface is higher with this regimen than the higher dose regimen in the Sorbe trial, this regimen may be associated with excessive toxicity. Effective lower dose regimens (6 Gy × 5 or 4 Gy × 6 prescribed to the vaginal surface) have been reported with excellent vaginal control rates and minimal vaginal toxicity.
**KQ2 Guideline statement:** Which patients with endometrioid endometrial cancer should receive vaginal cuff radiation? Vaginal cuff brachytherapy is as effective as pelvic radiation therapy at preventing vaginal recurrence for patients with 1) grade 1 or 2 cancers with greater than or equal to 50% myometrial invasion or 2) grade 3 tumors with less than 50% myometrial invasion (moderate quality evidence). Vaginal cuff brachytherapy is preferred to pelvic radiation in patients with these risk factors particularly in patients who have had comprehensive nodal assessment (low quality evidence). See Table 7 for consensus/percent agreement.

**KQ3: Which women should receive post-operative external beam radiation?**

*Pelvic Radiation*

Pelvic radiation offers the advantage of treating the vagina in addition to the regional lymphatics at risk. As a result, the decision to deliver pelvic radiation is closely tied to the risk of involved pelvic nodes. Risk factors for pelvic nodal metastasis include deep myometrial invasion, high grade, and the presence of lymphovascular space invasion. However, grade 2 or higher diarrhea affects 50-80% of patients receiving pelvic radiation during and in the immediate post-treatment period. The degree to which IMRT can reduce these symptoms is the focus on an ongoing randomized RTOG study.

*Lymphadenectomy and pelvic radiation*
Vaginal cuff brachytherapy rather than pelvic radiation is often recommended for patients who have undergone an extensive node dissection with negative nodes since pelvic nodal recurrence risk is thought to be lower. Although retrospective studies suggested that lymphadenectomy improves survival,\textsuperscript{31,32} two randomized trials have reported no difference in survival or local recurrence among patients who had a node dissection (Table 3).\textsuperscript{33,34} Node dissection does increase the risk of toxicity from pelvic radiation, which may influence the risk-benefit ratio. A limited or selected lymphadenectomy in which 10 to 12 lymph nodes are retrieved from the pelvic and low para-aortic region may be sufficient in determining the lymph node status, without the unnecessary increase in morbidity associated with more aggressive lymph node dissections.\textsuperscript{35,36} Alternatively, the diagnostic benefits of node dissection may be captured with sentinel node evaluation, without the toxicity of systematic lymphadenectomy. However, the standard approach remains nodal dissection and in practice decisions about radiation therapy are often made after lymphadenectomy has been performed.

\textit{Evidence for pelvic radiation in intermediate and high-intermediate risk endometrial cancer}

Several trials investigated the benefit of pelvic radiation in patients with early stage endometrial cancer. These studies enrolled slightly different populations of patients. PORTEC-1 enrolled 704 patients with endometrial cancer who were randomized after hysterectomy to receive pelvic radiation therapy (46 Gy) or no further treatment.\textsuperscript{5} Patients were eligible if they had deeply invasive grade 1 or 2 disease or minimally invasive grade 2 or 3 disease. Patients with deeply invasive grade 3 disease and patients
with stage II disease were not included. Pelvic radiation resulted in a reduction in the rate of local recurrence (4% in the radiotherapy group and 14% in the control group, \( p < 0.001 \)). 5-year overall survival rates were similar in the two groups: 81% (radiotherapy) and 85% (controls), \( p = 0.31 \). Central pathology review was performed after randomization, demonstrating that the majority of cancers were low grade (60% grade 1 as compared to 21% on initial evaluation).

GOG-99 was another randomized study conducted to compare pelvic radiation to no additional therapy for patients with stage I endometrial cancer. This study compared adjuvant pelvic radiation therapy to no adjuvant treatment in 392 women with stage I or II adenocarcinoma of any grade with myometrial invasion. Similar to PORTEC-1, pelvic radiation decreased local recurrence but there was no significant difference in overall survival in the two groups. The authors identified a “high intermediate risk” subset of 132 patients (one-third of the study group) who accounted for two-thirds of the cancer-related deaths in the trial. For patients in this group who had no adjuvant treatment, the 4-year survival rate was 72%; in contrast, for patients in this group who had pelvic radiation therapy, the 4-year survival rate was 88%, similar to that of patients in the low intermediate risk group. Patients in the low intermediate risk group had excellent local control and survival rates with or without adjuvant radiation therapy. GOG-99 differs from PORTEC-1 in that patients with deeply invasive grade 3 cancers were included. In addition, patients in GOG-99, unlike PORTEC-1, received lymph node dissection and underwent central pathology review at the time of randomization. It is important to note that neither of these studies was adequately powered to detect a difference in survival.
More recently, the ASTEC study group investigated the benefit of pelvic radiation in patients with early stage endometrial cancer; the primary endpoint was overall survival. Patients with any histology of clinically uterine confined disease were eligible. This included patients with pathologic findings of deeply invasive grade 3 cancers, cervical involvement and positive nodes. A subset of patients on this study received node dissection and approximately 50% of patients on the control arm received vaginal brachytherapy. The rate of pelvic recurrence in the control arm, 6.1%, was lower than the control arm on GOG-99 and PORTEC-1. This is likely due at least in part to the use of brachytherapy in 50% of the patients in the control arm. Overall survival was not different between the 2 arms. Additionally, this trial lacked central pathology review and may thus have included a lower risk group of patients. There was no evidence that the efficacy of pelvic radiation differed in patients who did or did not undergo lymph node dissection.

The details of three randomized studies comparing pelvic radiation to vaginal brachytherapy are discussed above in key question 2. In general, these studies demonstrate that vaginal radiation provides a comparable reduction in vaginal recurrence as pelvic radiation and that pelvic recurrence rates are low among intermediate risk patients treated with vaginal cuff brachytherapy. However, due to the small number of higher risk patients in these studies, these studies do not provide support for replacing pelvic radiation with vaginal cuff brachytherapy in patients at high risk for pelvic recurrence. Further evidence to address this question may come from the ongoing GOG 0249 study which is randomizing high intermediate risk patients to pelvic radiation vs. vaginal cuff brachytherapy followed by chemotherapy (Table 6).
Studies conducted using the SEER database have also addressed the benefit of pelvic radiation in endometrial cancer. The advantage of these studies is the inclusion of a large enough number of individuals to potentially detect a survival benefit. A disadvantage of this approach is that the SEER data generally provides less information about treatment and outcomes than is acquired with patients enrolled on randomized trials. Among 21,249 women, of whom 19.2% received pelvic radiation, patients with invasion of the outer half of the myometrium had significantly better overall survival when pelvic radiation was delivered. In an updated analysis, delivery of vaginal brachytherapy and pelvic radiation together was associated with improved survival among patients with intermediate risk endometrial cancer.\(^{38}\)

**Salvage radiation therapy in early stage endometrial cancer**

Reserving RT for salvage has the potential to prevent overtreatment of patients.\(^{39}\) However, evaluation of the outcome of patients receiving salvage therapy on the randomized trials (GOG-99 and PORTEC-1) as well as large single institution series suggests that this is not an effective treatment strategy. For the GOG-99 series, there were 202 patients in the no additional therapy arm, and among those, 13 failed at the vaginal cuff. Five of those 13 patients went on to die of their endometrial cancer.\(^6\) In PORTEC-1, the three year overall survival for the 46 control patients who relapsed and were treated with salvage radiation was 51%, with better outcomes in the subset of vaginal only recurrence.\(^{40}\) In a large single institution series of 91 patients treated for pelvic recurrence after surgery alone, the 5 year overall survival was 43%.\(^{41}\) Nine percent of those patients
had grade 4 complications from salvage therapy, which most often consisted of external beam pelvic radiation and vaginal brachytherapy. The high rate of recurrence and complications after salvage suggests that adjuvant RT cannot be replaced by reserving RT for the treatment of recurrences.

**KQ 3 Guideline Statement (A):** Which women should receive post-operative external beam radiation? Patients with grade 3 cancer with greater than or equal to 50% myometrial invasion or cervical stroma invasion may benefit from pelvic radiation to reduce the risk of pelvic recurrence (high quality evidence). Patients with grade 1 or 2 tumors with greater than or equal to 50% myometrial invasion may also benefit from pelvic radiation to reduce pelvic recurrence rates if other risk factors are present such as age greater than 60 years and/or LVSI (high quality evidence).

**Evidence for external beam radiation in high-risk endometrial cancer**

High-risk endometrial cancer has been variably defined in the literature. In some studies, deeply invasive grade 3 endometrial cancers through stage III have been defined as high-risk. In other studies this group is defined as stage III or IV with disease confined to the peritoneum. Postoperative radiation has tended to be considered standard in this group although a comparative study of adjuvant radiation versus no treatment for this group of patients has not been conducted. Several prospective randomized trials have been performed comparing radiation therapy to chemotherapy in high-risk patients (Table 5).
Adjuvant radiation therapy was compared to chemotherapy in GOG-122. This study randomized 388 patients with stage III or IV (including peritoneally confined with 2 cm or less residual disease) endometrial cancer to adjuvant chemotherapy (doxorubicin and cisplatin for 8 cycles) or whole-abdominal radiation therapy. Whole-abdominal radiation therapy was delivered to 30 Gy in 20 fractions with an additional boost of 15 Gy delivered to the pelvis or pelvis and para-aortic (PA) regions in the case of positive PA nodes or positive pelvic nodes with no PA nodal dissection. In the final analysis, rates of progression-free survival after adjusting for stage were significantly higher in the chemotherapy arm than in the whole-abdominal radiation therapy arm (5-year progression-free survival [PFS] rate, 50% vs. 38%). The proportion of patients with stage IV disease was higher in the chemotherapy arm, so the reported results were “stage-adjusted.” As a result of this limitation, the evidence derived from this trial was classified as “moderate” rather than “high” (Table 7). In the absence of this adjustment, the study would have revealed no significant difference between the two arms (PFS 42% vs. 38%, p value not reported). The overall survival curves are similar until approximately 2 years of follow-up when patients in the chemotherapy arm may have been successfully salvaged by radiation or other means, resulting in splitting of the curves and a significant overall survival (OS) benefit. A major limitation of the study was the inclusion of patients with intraperitoneal disease, including unresected lesions up to 2 cm. These patients are unlikely to benefit from radiation therapy because the dose to the whole abdomen is limited to 30 Gy which is not an adequate dose to treat microscopic disease. Gross disease within the peritoneum is difficult, if not impossible to treat to tumoricidal doses without excessive toxic effects. Additionally, gross disease may have gone
undetected and untreated as CT scans were not required. As a result, radiation therapy doses were inadequate for many patients. GI toxicity was also worse in the chemotherapy arm than in the radiation arm, despite the large volume radiation fields. Despite the limitations of this study, it established a role for chemotherapy in the treatment of endometrial cancer.

Maggi et al conducted a randomized trial comparing adjuvant chemotherapy to adjuvant radiation therapy for high-risk endometrial cancer. The study enrolled 345 patients with deeply invasive grade 3 tumors and stage I-III endometrial cancer limited to the pelvis. Chemotherapy consisted of 5 cycles of cisplatin, doxorubicin, and cyclophosphamide. Patients on the radiation therapy arm received 45-50 Gy to the pelvis. There was no significant difference in overall or progression-free survival between the pelvic radiation therapy and chemotherapy arms, but there was a non-significant trend towards delayed metastasis in the chemotherapy arm and delayed pelvic relapse in the radiation therapy arm. This study enrolled a more homogeneous group of patients than GOG-122; patients with uterine serous carcinoma or peritoneal disease were not included. Additionally, the radiation therapy was more similar to the current standard pelvic or extended field radiation therapy.

The next randomized study comparing chemotherapy to pelvic radiation therapy for high-risk endometrial cancer was conducted by the Japanese Gynecologic Oncology Group (JGOG). In this trial, patients were randomized to cyclophosphamide, doxorubicin, and cisplatin or pelvic radiation therapy. This study enrolled patients with stage 1C endometrial cancer with > 50% invasion through stage IIIC endometrial cancer. The majority (77.4%) of the registered patients had stage IC or II lesions, and only 11.9%
had stage IIIC lesions. There was no significant difference between the chemotherapy and radiation therapy groups in overall or progression-free survival or pattern of relapse. A small high-risk subset was identified that had improved progression-free survival with chemotherapy. However, the study was not stratified for analysis of this subset, nor was this a planned subset analysis, which limits the utility of this observation. Rates of pelvic recurrence have been reported to range from 30-50% of patients with node positive endometrial cancer who are treated with chemotherapy without external beam.\textsuperscript{45-47} This finding suggests that adjuvant radiation therapy should be combined with adjuvant chemotherapy in patients with stage III disease. Patients with lower grade lesions have excellent outcomes following external beam radiation alone which may be appropriate treatment, especially for patients with comorbidities which increases the risk of complications from adjuvant chemotherapy.\textsuperscript{46} The ongoing GOG-0258 study is comparing pelvic radiation with concurrent and adjuvant chemotherapy with chemotherapy without pelvic radiation in patients with high-risk endometrial cancer. The results of this study should shed light on the benefit of pelvic radiation in this setting (Table 6).

Other pathologic findings can sway decisions regarding indications for pelvic radiation. Cervical stromal invasion is considered a high-risk feature for local recurrence and patients are generally treated with pelvic radiation following total abdominal hysterectomy with cervical stromal invasion. On the other hand, ovarian involvement is generally considered a high-risk feature for peritoneal dissemination. Decisions about radiation therapy may be tailored in some cases based on pathologic risk factors for pelvic recurrence.
KQ 3 Guideline statement (B): Which women should receive post-operative external beam radiation? The best available evidence at this time suggests that a reasonable option for adjuvant treatment of patients with positive nodes, or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum includes external beam radiation therapy as well as adjuvant chemotherapy (moderate quality evidence). Chemotherapy (moderate quality evidence) or radiation therapy alone (low quality evidence) may be considered for some patients based on pathologic risk factors for pelvic recurrence. See Table 7 for consensus/percent agreement.

KQ4: When should brachytherapy be used in addition to external beam radiation?

Rationale for vaginal cuff brachytherapy after pelvic radiation

The use of supplemental vaginal cuff brachytherapy following pelvic external beam radiation is widely employed, albeit with differing doses of external beam and vaginal brachytherapy boost given at different institutions. A vaginal brachytherapy boost is often incorporated into clinical trials with the goal of decreasing vaginal recurrence. However, there have been no randomized trials to measure the benefit of brachytherapy after external beam. In this section, we will review available evidence regarding the role of vaginal brachytherapy after pelvic radiation.

Evidence for vaginal cuff brachytherapy after pelvic radiation
The rate of vaginal recurrence after pelvic radiation alone is low. In the pelvic RT arm of PORTEC-1 and 2, the rate of vaginal recurrence was 2.3% and 1.6%. Among patients with deeply invasive grade 3 tumors, which were included in a non-randomized cohort of patients who received 46 Gy of pelvic radiation, 2% vaginal apex recurrences were reported. Sorbe et al reported a similar 1.9% rate of vaginal recurrence among patients treated with pelvic radiation 46 Gy followed by vaginal cuff brachytherapy (equivalent of 29.3 to 35.3 Gy at the vaginal surface). The Norwegian Radium Hospital study also included patients who were treated with vaginal brachytherapy and pelvic radiation therapy. However, pelvic radiation was delivered with a midline block after 20 Gy, limiting the dose and therefore the comparison to some other series. Low rates of vaginal recurrence following pelvic radiation have also been reported in patients with intermediate and high-risk endometrial cancer. In the JGOG study which randomized patients to pelvic radiation vs. chemotherapy, 1% of women treated with 45-50 Gy of pelvic radiation developed vaginal recurrence. The low rate of vaginal recurrence in patients receiving pelvic radiation without brachytherapy leaves little margin for improvement with the addition of brachytherapy.

Several retrospective studies have compared outcomes among patients with endometrial cancer treated with pelvic radiation with and without brachytherapy. Rossi et al compared outcomes in patients with IIIC endometrial cancer treated with various approaches utilizing SEER data. The study found that among the subgroup of patients coded in SEER as having “direct local extension”, the 5-year OS rate was 34% for patients who received no radiation, 47% for external beam, and 63% for external beam and vaginal brachytherapy. The use of external beam or external beam and vaginal
Brachytherapy was associated with higher rates of survival compared with no adjuvant therapy ($p < 0.001$). Furthermore, in this subgroup, adding vaginal brachytherapy to external beam proved superior to external beam alone ($p = 0.002$). The lack of available information about the rate of vaginal relapse as well as the definition of direct extension hinders interpretation of this finding, which may be accounted for by confounding factors which cannot be evaluated in SEER data. Further study on the added value of a vaginal brachytherapy boost is needed in the stage III population. Randall et al compared vaginal relapses in 154 patients with stage I endometrial cancer treated with or without 30-50 Gy LDR brachytherapy after pelvic radiation. Local failure rates in patients receiving external beam vs. external beam followed by brachytherapy were not significantly different (6 vs. 7.7%, $p = 0.74$). Greven et al compared 270 patients with stage I or II endometrial cancer treated with EBRT with (97 patients) or without brachytherapy (173 patients). The median dose of external beam radiation was 48.5 Gy in patients treated without brachytherapy and 45.8 Gy in patients treated with brachytherapy. Brachytherapy was delivered with a wide range of applicators and doses. No difference in 5-year pelvic control rates was detected (96% vs. 94%, $p=NS$). The presence of cervical involvement has been cited as a predictor of vaginal recurrence and thus an indication for vaginal brachytherapy after pelvic radiation. However, Greven et al found no difference in 5 year pelvic disease control with or without brachytherapy after pelvic radiation among the patients stage II endometrial cancer (93% vs. 90%, $p = NS$). Similarly, Scotti et al noted that there was no difference in vaginal relapse among the patients with cervical involvement who did (136 patients) or did not (93 patients) receive brachytherapy.
Some studies have reported higher rates of toxicity among patients receiving both brachytherapy and external beam. Greven et al reported a non-significant increase in grade 3 or 4 small bowel complications in patients treated with a vaginal brachytherapy application in the study described above (1.7% vs. 4.1%). Additionally, this study documented more vaginal complications consisting of atrophy, stenosis, and adhesions in the patients treated with a brachytherapy. However, because these were not recorded with a uniform scoring system in all patients, it is not possible to reach firm conclusions about the relative effects on vaginal toxicity. Randall et al did detect a significantly higher rate of complications among patients receiving cuff brachytherapy (18.6% EBRT + cuff vs. 3.8% EBRT, $p = 0.01$). The higher effective cuff doses (30-50 Gy vaginal cuff boost (VCB) with LDR) used in this study may not reflect expected toxicity with the current fractionated HDR of 5-6 Gy prescribed to the vaginal surface for 2-3 fractions. The addition of brachytherapy to pelvic radiation also increased the risk of second primary cancers in a SEER study. The 30-year cumulative incidence of secondary bladder cancers was 1.25% for patients who did not receive radiation, 2.14% for patients who received brachytherapy only, 2.71% for patients who received EBRT only, and 3.48% for patients who received both in combination ($p < 0.001$).

**KQ4 Guideline statement:** **When should brachytherapy be used in addition to external beam radiation?** Prospective data is lacking to validate the use of vaginal brachytherapy after pelvic radiation and retrospective studies show little conclusive evidence of a benefit, albeit with small patient numbers. Use of vaginal brachytherapy in patients also undergoing pelvic external beam radiation may not generally be warranted,
unless risk factors for vaginal recurrence are present (low quality evidence). See Table 7 for consensus/percent agreement.

**KQ5: How should radiation therapy and chemotherapy be integrated in the management of stage I-III endometrial cancer?**

**Rationale for combining chemotherapy and external beam radiation in patients with high-risk endometrial cancer**

Combined-modality treatment may be the optimal approach to minimize the risk of pelvic and distant recurrence. Feasibility of this approach was tested by the RTOG-9708 study which treated patients with stage III endometrial cancer with chemoradiation (50 mg/m² on days 1 and 28) followed by adjuvant chemotherapy (four cycles of cisplatin and paclitaxel given at four-week intervals). Toxicity was acceptable and 98% of patients were able to complete the planned treatment regimen. Overall survival and disease-free survival rates at 4 years were 85% and 81%, respectively. Pelvic recurrence rate was only 2% at 4 years. This regimen (using carboplatin/paclitaxel instead of cisplatin/paclitaxel) has been employed as one arm of GOG-0258, which is comparing combined-modality treatment to chemotherapy alone for patients with high-risk endometrial cancer.

**Evidence for chemoradiation approaches**

Hogberg et al reported on the role of combined radiation therapy and chemotherapy delivered using a sequential approach for patients with high-risk
endometrial cancer. These investigators reported merged data from two independent randomized studies: one was conducted in Milan at the Instituto Mario Negri (MANGO), and the other was conducted by the Nordic Society for Gynaecologic Oncology (NSGO)/European Organization for Research and Treatment of Cancer (EORTC). There were differences in the eligibility criteria and the chemotherapy regimen used; however, both studies included patients with high-risk stage I-III endometrial cancer with no residual tumor following hysterectomy. The NSGO/EORTC allowed patients with papillary serous and clear cell carcinoma whereas the Italian study excluded these high risk histologies. Patients were randomized in each trial to radiation therapy alone or radiation therapy with adjuvant chemotherapy. The Italian (MANGO) trial independently showed no progression-free survival benefit to chemotherapy (HR=0.61, CI 0.33–1.12, p= 0.10). However, in the combined dataset, the patients who received combined-modality treatment had a 36% reduction in recurrence and improved cancer-specific survival (hazard ratio (HR) 0.55, CI 0.35–0.88; p=0.01). Surprisingly, the benefit was limited to the endometrioid histology subgroup, as there was no benefit to chemotherapy seen in the NSGO/EORTC trial for patients with papillary serous/clear cell histology (HR= 0.83 (95% CI 0.42–1.64), P = 0.59).

Kuoppala et al compared adjuvant radiation therapy to radiation with cisplatin (50 mg/m²), epirubicin (60 mg/m²) and cyclophosphamide. Patients were eligible if they had grade 3 endometrial cancer with any invasion and any grade with deep invasion or stage II or IIIA endometrial cancer. The majority, 87%, had stage I or II cancer. Chemotherapy consisted of three courses of cisplatin, epirubicin, and cyclophosphamide which were integrated with split course radiation therapy. The addition of chemotherapy
to RT did not improve overall survival or lower the recurrence rate (disease-specific five-year survival of 84.7% with radiation alone vs. 82.1% with the addition of chemotherapy, p=0.148). These results may differ from those reported by Hogberg et al on account of the lower risk population, the integration of chemotherapy with radiation or differences in the chemotherapy regimens used.

Combined modality therapy was also used in GOG-184. This study compared two adjuvant chemotherapy regimens following radiation therapy in patients with stage III or IV endometrial cancer. Patients received six cycles of cisplatin and doxorubicin or the same regimen with the addition of paclitaxel. The addition of paclitaxel did not significantly improve relapse-free survival (62% of patients recurrence-free at 36 months with cisplatin and doxorubicin as compared to 64% with the addition of paclitaxel).

Hematologic and neurologic toxicity was higher in patients receiving paclitaxel (p<0.01). Chemotherapy was completed by over 80% of patients after receiving pelvic or pelvic or extended field radiation, similar to the percent of patients completing chemotherapy on GOG-122. This suggests that initial delivery of radiation does not compromise successful delivery of adjuvant chemotherapy. The initial delivery of radiation may contribute to improved locoregional control. The 5-year locoregional recurrence rate was 9% in GOG-184, compared to an 18% incidence of pelvic failure in the GOG-122 chemotherapy only arm.

The optimal sequencing of combined-modality treatment remains unknown. A retrospective study at Duke University and the University of North Carolina compared the outcome of 356 women treated with different sequences of chemotherapy and radiation therapy. After controlling for stage, age, grade, race, histology, and
cytoreduction status but not institution, in an attempt to address the question of sequencing, a subgroup analysis of 83 patients found that overall survival was best in patients treated with chemotherapy followed by radiation therapy followed by additional chemotherapy referred to as a "sandwich" regimen. The retrospective nature, small patient number and complex modeling performed are significant limitations of this study. This strategy has the advantage of ensuring that radiation therapy does not compromise the ability to deliver adjuvant chemotherapy. A disadvantage is that radiation therapy is delayed beyond the immediate postoperative period which may negatively impact local control based on observations in other disease sites.

Extended field radiation includes the para-aortic nodes in addition to the pelvis. This is recommended for patients with positive para-aortic nodes (PAN) or patients at high risk for PAN. Patients with positive pelvic nodes have an approximately 50% risk of having PAN positive. As a result, patients with positive pelvic nodes who have had few or no nodes dissected from the para-aortics may also need to be treated with extended field radiation, in particular with IMRT in order to reduce the risk of toxicity. In some situations growth factor support may be required if chemotherapy is given after extended-field radiation, particularly if a 4-field technique is used.

**KQ 5 Guideline statement: How should radiation therapy and chemotherapy be integrated in the management of stage I-III endometrial cancer?** The best available evidence suggests that concurrent chemoradiation followed by adjuvant chemotherapy is indicated for patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum (moderate quality evidence). Alternative sequencing
strategies with external beam radiation and chemotherapy are also acceptable (low quality evidence). See Table 7 for consensus/percent agreement.
Table 1: Randomized Studies comparing different vaginal brachytherapy (VBT) and external beam radiation therapy (EBRT) by risk category in endometrial cancer patients

<table>
<thead>
<tr>
<th>ELIGIBILITY</th>
<th>INTERVENTION</th>
<th>DOSAGE</th>
<th>OUTCOMES</th>
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<tr>
<td><strong>Low Risk Patients</strong></td>
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<tr>
<td><strong>Vaginal Brachytherapy (VBT) Alone vs. Surgery Alone (No additional Treatment)</strong></td>
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<tr>
<td>Intravaginal Brachytherapy in FIGO Stage I Low-Risk Endometrial Cancer</td>
<td><strong>Low Risk</strong>: Stage IA, IB, grade 1-2, endometrioid endometrial carcinoma, &lt; 50% myometrial invasion (MI)</td>
<td><strong>645</strong> patients with endometrial cancer randomly assigned to surgery and VBT (S + VBT) or surgery alone (S)</td>
<td>3-6 fractions of 3 to 8 Gy</td>
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<tr>
<td>Intravaginal High-Dose-Rate Brachytherapy for Stage I Endometrial Cancer: A Randomized Study of two dose per fraction levels</td>
<td><strong>Low Risk</strong>: Stage IA, IB, endometrioid histologic type, FIGO tumor Grades 1–2, nuclear Grades 1–2, &lt; 50% MI, diploid DNA profile, and pathologically negative lymph nodes</td>
<td><strong>290</strong> patients randomized to 2.5-Gy per fraction or 5.0-Gy per fraction x 2 to the vaginal cuff</td>
<td>2.5 Gy per fraction or 5 Gy per fraction at 5mm from the surface of the applicator</td>
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<td><strong>Intermediate/ High Risk</strong></td>
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<td><strong>VBT vs. EBRT</strong></td>
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<td>Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-randomized study</td>
<td>Stage IC grade 1 or 2, IB grade 3; age &gt; 60; Stage IIA, any age, &gt; 50% MI (considered high intermediate risk)</td>
<td><strong>427</strong> patients were randomized to EBRT or VBT.</td>
<td><strong>Pelvic EBRT</strong>: 46 Gy in 23 fractions; <strong>VBT</strong>: 21 Gy high-dose rate in three fractions or 30 Gy low-dose rate</td>
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<td>Table</td>
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<td>Inferiority, randomised trial. Lancet. 2010 Mar 6;375(9717):816-23; Nout, RA et al.</td>
<td>5-year OS&lt;br&gt;VBT: 84.8% (95% CI 79.3-90.3);&lt;br&gt;EBRT: 79.6% (95% CI 71.2-88.0); (HR 1.17, 0.69-1.98; p=0.57).</td>
<td></td>
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<tr>
<td>External Pelvic and Vaginal Irradiation vs. Vaginal Irradiation Alone as Postoperative Therapy in Medium-Risk Endometrial Carcinoma- A Prospective Randomized Study. (Int J Gynecol Cancer 2012;82(3): 1249-1252); Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B.</td>
<td>527 patients with endometrial cancer randomly assigned to VBT or VBT + adjuvant EBRT&lt;br&gt;EBRT: median dose, 46 Gy; range 6-50 Gy&lt;br&gt;VBT: total doses delivered were 17.7-20.0 Gy&lt;br&gt;5-year Locoregional Relapse&lt;br&gt;EBRT +VBT: 1.5%&lt;br&gt;VBT: 5% (p=0.013)</td>
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<td>Patients with stage I, endometrioid, grade 3 &gt; 50% MI, pathologically negative lymph nodes (considered intermediate risk)</td>
<td>540 patients randomly assigned to surgery + VBT with or without pelvic RT&lt;br&gt;External RT: 40 Gy pelvic RT over a course of 4 weeks; 5 fractions per week&lt;br&gt;5-year Survival&lt;br&gt;VBT Alone: 91%&lt;br&gt;VBT + External RT: 89%</td>
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**VBT Alone vs. VBT + EBRT**

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<th>Description</th>
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<td>TITLE, JOURNAL</td>
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<tr>
<td>Intravaginal high-dose-rate brachytherapy for Stage IB (FIGO Grade 1, 2) endometrial cancer. Int J Radiat Oncol Biol Phys. 2002 Jul 1;53(3):707-13</td>
</tr>
<tr>
<td>High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. Int J Radiat Oncol Biol Phys. 2000 Jan</td>
</tr>
</tbody>
</table>
### Exclusions:
carcinosarcoma or clear cell, pts. receiving external beam irradiation and more than or less than 3 HDR treatments


**Low Risk:** FIGO 1988 Stage IB Grade1

- **N=191** Patients were treated postoperatively after (TAH/BSO) with outpatient adjuvant HDR brachytherapy for low-risk endometrial cancer
- **4-year Survival:** 95%
- **4-year Relapse Free Survival:** 98%
- **4-year Vaginal Control Rate:** 100%

### Long-Term Survival of Intermediate Risk Endometrial Cancer (Stage IG3, IC, II) Treated with Full Lymphadenectomy and Brachytherapy without Teletherapy. Gynecol Oncol. 2001 Aug;82(2):371-4

**Intermediate Risk:** Stages: I, Grade 3, FIGO 1988 Stage IC and Stage II

- **N=265** Patients with intermediate risk endometrial cancer not treated post-operatively
- **N=66** Patients treated with HDR vaginal brachytherapy alone
- **5-year OS:** 84% (95% CI 78–91%)
- **5-year Progression-Free Survival (PFS):** 97% (95% CI 91–100%)
- **Distant recurrence:** 3%


**Intermediate Risk:** Stages: IB, IC

- **N=87** Patients with low-to intermediate-risk endometrial adenocarcinoma treated with HDR Intravaginal Brachytherapy
- **5-year Actuarial DFS:** 94%
- **5-year Complication Free Survival:** 97%


**High Risk:** Stages: IB-IIIB

- **N=382** Patients treated with Vaginal Brachytherapy Alone
- **5-year Vaginal Control Rate:** 98% (95% CI, 96-99%)
- **5-year Pelvic Control Rate:** 96% (95% CI, 94-98%)
- **5-year Combined Vaginal/Pelvic Control Rate:** 95% (95% CI, 93–98%)
- **5-year DFS:** 93% (95% CI, 90-96%)
- **5-year OS:** 93% (95% CI, 90-96%)
<table>
<thead>
<tr>
<th>Study</th>
<th>Author(s)</th>
<th>Study Details</th>
<th>Patient Details</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal brachytherapy alone is sufficient adjuvant treatment of surgical stage I endometrial cancer. Int J Radiat Oncol Biol Phys. 2005 Aug 1;62(5):1379-84</td>
<td>Solhjem MC</td>
<td><strong>High Risk</strong>: FIGO 1988 Stage IA, IB, IC, grade 3; any MI or any MI with Grade 2 disease if the tumor size was 2 cm</td>
<td>N=100 Patients with Stage I endometrial cancer treated with postoperative adjuvant HDR Intravaginal Brachytherapy Alone</td>
<td>3-year DFS: 93.3% 3-year OS: 97.9%</td>
</tr>
<tr>
<td>High-risk surgical stage 1 endometrial cancer: outcomes with vault brachytherapy alone. Gynecologic Oncology 2003 May; 89 (2): 288–294</td>
<td>Rittenberg P</td>
<td><strong>High Risk</strong>: FIGO 1988 Stage 1C patients with surgically staged endometrial cancer with greater than 50% MI</td>
<td>N=359 Patients treated with HDR vaginal vault brachytherapy alone</td>
<td>2-year Survival: 97% 5-year Survival: 95% Recurrence Rate (all stage I): 2.3% Recurrence Rate (stage IC): 7.2%</td>
</tr>
<tr>
<td>Patterns of failure in endometrial carcinoma stage IB grade 3 and IC patients treated with postoperative vaginal vault brachytherapy. Gynecol Oncol. 1999 Oct;75(1):103-7</td>
<td>Chadha M</td>
<td><strong>High Risk</strong>: FIGO 1988 stages: IB Grade 3, or any Stage IC</td>
<td>N=124 Patients treated with postoperative HDR vaginal vault brachytherapy alone</td>
<td>5-year DFS: 87% 5-year OS: 93%</td>
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</table>
**Table 3: Prospective randomized studies of pelvic lymphadenectomy in endometrial cancer patients**

<table>
<thead>
<tr>
<th>TITLE, JOURNAL</th>
<th>AUTHOR</th>
<th>ELIGIBILITY CRITERIA</th>
<th>TREATMENT</th>
<th>OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC Trial). Lancet 2009; 375:125-36.</td>
<td>ASTEC Committee</td>
<td>Histologically proven endometrial carcinoma preoperatively confined to the corpus</td>
<td><strong>N=1408</strong> Patients randomized to lymphadenectomy or standard surgery</td>
<td><strong>5-year OS</strong> Standard surgery: 81% (95% CI 77–85%) Lymphadenectomy: 80% (95% CI 76–84%); ( p=0.13 ) <strong>5-year Recurrence-Free Survival (RFS)</strong> Standard surgery: 79% (95% CI 75–83%) <strong>5-year RFS</strong> Lymphadenectomy: 73% (95% CI 69–77%); ( p=0.16 )</td>
</tr>
<tr>
<td>Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008; 100(23):1707-16.</td>
<td>Panici, P</td>
<td>Preoperative stage I endometrial cancer</td>
<td><strong>N=514</strong> Patients were randomized to with and without pelvic lymphadenectomy</td>
<td><strong>5-year DFS</strong> Lymphadenectomy: 81% <strong>5-year DFS</strong> No lymphadenectomy: 81.7% (HR for relapse 1.10, 95% CI 0.70-1.71; ( p = 0.68 ) <strong>5-year OS</strong> Lymphadenectomy: 85.9% <strong>5-year OS</strong> No lymphadenectomy: 90.0% (HR for death from any cause 1.20, 95% CI 0.70-2.07; ( p = 0.50 )</td>
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Table 4: Prospective randomized studies of endometrial cancer patients treated with or without external beam radiation therapy (EBRT)

<table>
<thead>
<tr>
<th>Intermediate/ High Risk</th>
<th>External Beam Radiotherapy vs. Observation (No additional treatment)</th>
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<tr>
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<td>TITLE, JOURNAL, FIRST AUTHOR, ELIGIBILITY CRITERIA, TREATMENT, OUTCOMES</td>
</tr>
<tr>
<td>Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis.</td>
<td><strong>Blake, P.</strong> Patients with histologically confirmed endometrial cancer, macroscopically confined to the uterine corpus including <em><strong>Intermediate Risk</strong></em>: Stage IA, IB G3, and IC, IIA, grade 1, 2; Subtypes other than papillary serous and clear cell. <strong>Early Stage, High Risk</strong>: IC G3, IIA G3, IIB, all papillary serous and clear cell subtypes. <strong>N=905</strong> Patients randomized to EBRT or observation</td>
</tr>
<tr>
<td>Surgery and postoperative radiotherapy versus surgery alone for patients with stage I endometrial carcinoma: multicentre randomized trial. PORTEC Study Group. Post-Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000; 355 (9213): 1404-11.</td>
<td><strong>Creutzberg, C.L., et al</strong> Stage 1 endometrial carcinoma, grade 1, &gt;50% MI, grade 2 with any invasion, or grade 3 with &lt; 50% invasion <strong>High Intermediate Risk</strong>: 2 of 3: invasion in the outer half of the myometrium, grade 3 histology, and age &gt; 60 years. <strong>N=715</strong> Patients randomized to postoperative RT or no further treatment (control)</td>
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</tbody>
</table>

Keys HM

Myometrial invasion with adenocarcinoma of any grade and no evidence of lymph node involvement

**High Intermediate Risk:** Any age with one of the following risk factors: Grade 2-3 disease, MI ≥ 66%, LVSI Present, age ≥ 50 with 2 high risk features, age ≥ 70 with 1 high risk feature

**N=392** Patients randomized to no additional treatment (NAT) or whole pelvic RT (50.4 Gy)

**4-year survival (NAT):** 86%

**4-year survival (RT):** 92% (Relative hazard (RH): 0.86; p=0.557).

**Recurrence:** 44 total

**2-year cumulative incidence of recurrence (CIR):**

NAT: 12%

RT: 3% (RH: 0.42; p=0.007)
### Table 5: Prospective randomized studies of combined modality regimens in endometrial cancer patients

<table>
<thead>
<tr>
<th>TITLE</th>
<th>FIRST AUTHOR</th>
<th>ELIGIBILITY CRITERIA</th>
<th>TREATMENT</th>
<th>OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined modality regimens</strong></td>
<td>Hogberg T</td>
<td>Patients with stage I-III endometrial cancer with no residual tumor or prognostic factors implying high risk</td>
<td>N=534 Patients from two randomised clinical trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III) randomized to adjuvant RT with or without sequential chemotherapy.</td>
<td><strong>NSGO/EORTC:</strong> 5-year PFS: RT + Chemo: 0.79; RT: 0.72 (HR 0.64, 95% CI 0.41-0.99); p=0.04 &lt;br&gt; 5-year OS: RT + Chemo: 0.83; RT: 0.76 (HR 0.66, 95% CI 0.40-1.08); p=0.10 &lt;br&gt; 5-year Cancer Specific Survival (CSS): RT + Chemo: 0.88; RT: 0.79 (HR 0.51, 95% CI 0.28-0.90); p=0.02</td>
</tr>
<tr>
<td>Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer - Results from two randomised studies. European Journal of Cancer 46 2010; 2422-2431</td>
<td></td>
<td>Surgically staged high-risk endometrial cancer: Randomized study of adjuvant radiotherapy alone vs. sequential chemoradiotherapy. Gynecologic Oncology 110 2008; 190-195.</td>
<td>Kuoppala T</td>
<td>High risk endometrial cancer patients with stage IA-B G 3, Stage IC-III A G 1-3</td>
</tr>
</tbody>
</table>
Final analysis of RTOG 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high risk endometrial cancer. Gynecologic Oncology 103 2006; 155-159.

Grade 2/3 endometrial adenocarcinoma with >50% MI, stromal invasion of the cervix, or extrauterine disease.

Exclusions: papillary serous or clear cell histology, no prior radiation therapy or chemotherapy

N=46 Patients with high risk endometrial cancer enrolled in single arm phase 2 study of Pelvic radiation therapy with concurrent cisplatin and adjuvant carboplatin and taxol.

4-year OS: 85%
4-year DFS: 81%
4-year Pelvic Recurrence rate: 2%
4-year Regional Recurrence rate: 2%
4-year Distant Recurrence rate: 19%

EBRT vs. Chemotherapy


Maggi R

Patients had to have histologically confirmed endometrioid, adenoacanthoma or adenosquamous carcinoma and had to have had surgery as primary treatment. Stage Ic G3, IIa-bG3 with deep MI (50% or more) or stage III disease.

Exclusions: Previous neoadjuvant therapy or adjuvant brachytherapy

N=345 Patients randomized to EBRT or adjuvant Chemotherapy (CT)

Overall survival CT group:
3-year OS (CT): 76% (CI=70–83%)
5-year OS (CT): 66% (CI=59–73%)
7-year OS (CT): 62% (CI=55–70%)

Overall Survival EBRT group:
3-year OS (RT): 78% (CI=71–84%)
5-year OS (RT): 69% (CI=61–76%)
7-year OS (RT): 62% (CI=54–71%)

Disease-Free Survival CT group:
3-year DFS (CT): 68% (CI=61–75%)
5-year DFS (CT): 63% (CI=55–70%)
7-year DFS (CT): 60% (CI=52–67%)

Disease-Free Survival EBRT group:
3-year DFS (RT): 69% (CI=62–77%)
5-year DFS (CT): 63% (CI=55–70%)
7-year DFS (CT): 56% (CI=46–63%)


Randall ME

Patients with Stage III or IV endometrial carcinoma of any histology were eligible for this trial. Patients must have undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy, surgical staging, tumor resection, and have no single site of residual tumor more than 2 cm

N=296 Patients were randomized to whole- abdominal irradiation or Doxorubicin-Cisplatin (AP)

Adjusted PFS: 0.71 HR favoring AP (95% CI, 0.55-0.91; p<0.01).

Adjusted 60-month DFS: 50% of patients receiving AP 38% of patients receiving WAI.

Adjusted Death HR: 0.68 Hazard Ratio favoring AP (95% CI, 0.52-0.89).
### Table 6: Future trials

<table>
<thead>
<tr>
<th>TITLE</th>
<th>TRIAL OBJECTIVE</th>
<th>ELIGIBILITY</th>
<th>TREATMENT ARMS</th>
<th>PRIMARY ENDPOINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III Randomized Study of Adjuvant Chemoradiotherapy Comprising Cisplatin and Tumor Volume-Directed Radiotherapy Followed by Carboplatin and Paclitaxel Versus Carboplatin and Paclitaxel Alone in Patients With Stage I-IVA Endometrial Carcinoma (GOG-0258).</td>
<td>A multicenter study to determine if treatment with cisplatin and volume directed radiation followed by carboplatin and paclitaxel (4 cycles) reduces the rate of recurrence or death when compared to chemo with carboplatin and paclitaxel (6 cycles) in patients with Stage III-IVA Endometrial Cancer</td>
<td>Surgical Stage III/IVA endometrial carcinoma including clear cell and serous papillary. <strong>Expected Enrollment:</strong> 804</td>
<td><strong>Arm I:</strong> Cisplatin IV on days 1 and 29 plus EBRT once daily. <strong>Arm II:</strong> Patients receive paclitaxel IV over 3 hours and carboplatin IV day 1. Treatment repeats every 21 days for 6 courses in the absence of disease progression or unacceptable toxicity.</td>
<td>Compare the recurrence-free survival of patients with stage I-IVA endometrial carcinoma treated with both regimens. <strong>Secondary Outcome(s):</strong> Compare overall survival, acute and late adverse effects of patients with stage I-IVA endometrial carcinoma treated with both regimens.</td>
</tr>
<tr>
<td>Phase III Randomized Study of Pelvic Radiotherapy Versus Vaginal Cuff Brachytherapy, Paclitaxel, and Carboplatin in Patients With High-Risk Stage I or II Endometrial Carcinoma (GOG-0249).</td>
<td>A multicenter study to compare the recurrence free survival of patients with high risk stage I/II endometrial carcinoma treated with pelvic radiotherapy vs. vaginal cuff brachytherapy, paclitaxel, and carboplatin</td>
<td>Stage I with high intermediate risk factors: (e.g., grade 2 or 3 tumor, presence of lymphovascular space invasion, and/or outer half MI; Stage II with or without risk factors; Stage I/II with serous or clear cell with or without other risk factors</td>
<td><strong>Arm I:</strong> Conventional or intensity-modulated pelvic RT once daily, 5 days a week, for 5-6 weeks (total of 25-28 fractions) in the absence of disease progression or unacceptable toxicity. Patients with stage II disease or stage I disease with a confirmed diagnosis of clear cell and/or papillary serous histology may also undergo 1 or 2 intravaginal (i.e., vaginal cuff) brachytherapy boost treatments. <strong>Arm II:</strong> Patients undergo vaginal cuff brachytherapy comprising 3-HDR brachytherapy treatments over approximately 2 weeks or 1 or 2 LDR brachytherapy treatments over 1-2 days. Patients receive paclitaxel IV over 3 hours and carboplatin IV over 30-60 minutes on day 1. Chemotherapy repeats every 21 days.</td>
<td><strong>Primary Outcome(s):</strong> 5-year actuarial overall survival; 5-year actuarial failure-free survival (with failure defined as relapse or death due to endometrial carcinoma or to treatment complications). <strong>Secondary Outcome(s):</strong> Quality of life; Severe treatment related morbidity; 3, 5-year rates of vaginal, pelvic and distant relapse.</td>
</tr>
</tbody>
</table>
### Trial Comparing Concurrent Chemoradiation and Adjuvant Chemotherapy with Pelvic radiation therapy therapy Alone in High Risk and Advanced Stage Endometrial Carcinoma: PORTEC-3.

**Principal Investigators:** CL Creutzberg, MD

- **Study:** A study to compare the five-year overall survival and failure free survival rates with the addition of concurrent and adjuvant chemo to postop radiation therapy of patients with high risk and advanced endometrial carcinoma.
- **Expected Enrollment:** 500

**Arm I:**
- **Patients receive:** External beam pelvic radiotherapy (standard arm; 48.6 Gy in 1.8 Gy fractions).

**Arm II:**
- **Patients receive pelvic radiotherapy with concurrent chemotherapy (2 cycles of cisplatin) followed by adjuvant chemotherapy (4 cycles of carboplatin and paclitaxel; experimental arm).**

### PORTEC-4:

**Randomised Phase III Trial Comparing Vaginal Brachytherapy (two doses schedules: 21 or 15 Gy HDR in 3 fractions) and Observation after Surgery in patients with Endometrial Carcinoma with High-Intermediate Risk Features**

- **Study:** A multicenter study to establish vaginal recurrence and 5-year vaginal control including treatment for relapse in patients with high-intermediate risk endometrial carcinoma, treated after surgery with vaginal brachytherapy (21 Gy or 15 Gy in 3 fractions), in comparison with no additional treatment.
- **Expected Enrollment:** 500

**Arm I:**
- **Patients receive:** Vaginal brachytherapy (21 Gy or 15 Gy in 3 fractions).

**Arm II:**
- **Patients receive:** No additional treatment

### EORTC 55991: A randomised trial of adjuvant treatment with radiation plus chemotherapy versus radiation alone in high risk endometrial carcinoma.

- **Study:** A multicenter study to compare relapse free survival of patients treated with either radiation alone or radiation and chemotherapy given sequentially.
- **Patients must have:** Histologically proven endometrial cancer, of one of the following types: Clear cell carcinoma; Serous papillary carcinoma; Undifferentiated (anaplastic) carcinoma; Poorly differentiated (FIGO grade 3)

**Arm I:**
- **Patients received:** External pelvic RT

**Arm II:**
- **Patients received:** External pelvic RT followed or preceded by chemotherapy

**Primary Outcome(s):** Overall survival of patients treated with either radiation alone or radiation and chemotherapy given sequentially.
Table 7: Grading of Evidence, Recommendations and Consensus Methodology

<table>
<thead>
<tr>
<th>Guideline Recommendation</th>
<th>Percent (%) Agreement</th>
<th>Strength of Recommendation</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ1. Which patients with endometrioid endometrial cancer require no addition therapy after hysterectomy?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Following total abdominal hysterectomy with or without node dissection, no radiation therapy is a reasonable option for patients without residual disease in the hysterectomy specimen despite positive biopsy</td>
<td>94</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>Following total abdominal hysterectomy with or without node dissection, no radiation therapy is a reasonable option for patients with grade 1 or 2 cancers with either no invasion or less than 50% myometrial invasion.</td>
<td>100</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Vaginal cuff brachytherapy may be considered in patients with grade 3 tumor without myometrial invasion</td>
<td>94</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>Vaginal cuff brachytherapy may be considered in patients with grade 1 or 2 tumors with less than 50% myometrial invasion and higher risk features such as age greater than 60 and/or LVSI.</td>
<td>94</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>KQ2. Which patients with endometrioid endometrial cancer should receive vaginal cuff radiation?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal cuff brachytherapy is as effective as pelvic radiation therapy at preventing vaginal recurrence for patients with 1) grade 1 or 2 tumors with greater than or equal to 50% myometrial invasion or 2) grade 3 tumors with less than 50% myometrial invasion.</td>
<td>100</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Vaginal cuff is preferred to pelvic radiation in patients with the above risk factors particularly in patients who have had comprehensive nodal assessment.</td>
<td>94</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td><strong>KQ3. Which women should receive post-operative external beam radiation?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with grade 3 cancer with greater than or equal to 50% myometrial invasion or cervical stroma invasion may benefit from pelvic radiation to reduce the risk of pelvic recurrence.</td>
<td>94</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Patients with grade 1 or 2 tumors with greater than or equal to 50% myometrial invasion may also benefit from pelvic radiation to reduce pelvic recurrence rates if other risk factors are present such as age greater than 60 years and/or LVSI.</td>
<td>88</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>The best available evidence at this time suggests that reasonable options for adjuvant treatment of patients with positive nodes, or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum includes external beam radiation therapy as well as adjuvant chemotherapy.</td>
<td>100</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Chemotherapy without external beam radiation may be considered for some patients with positive nodes, or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum based on pathologic risk factors for</td>
<td>59</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
 Radiation therapy without chemotherapy may be considered for some patients with positive nodes, or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum based on pathologic risk factors for pelvic recurrence.

**KQ4. When should brachytherapy be used in addition to external beam radiation?**

Prospective data is lacking to validate the use of vaginal brachytherapy after pelvic radiation and most retrospective studies show no evidence of a benefit, albeit with small patient numbers. Use of vaginal brachytherapy in patients also undergoing pelvic external beam radiation is not generally warranted, unless risk factors for vaginal recurrence are present.

**KQ5. How should radiation therapy and chemotherapy be integrated in the management of stage I-III endometrioid endometrial cancer?**

The best available evidence suggests that concurrent chemoradiation followed by adjuvant chemotherapy is indicated for patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum.

Alternative sequencing strategies with external beam radiation and chemotherapy are also acceptable.

*Percent agreement refers to the number of raters who indicate either agree or strongly agree divided by the total number of raters for the round.*
APPENDIX A:

American College of Physicians (ACP) Process for Assigning Strength of Recommendation and Grading of Quality of Evidence

Strong Recommendation
Evidence suggests that the benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus.

Weak Recommendation
Evidence suggests that the benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or non-uniform consensus.

High Quality Evidence
Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change our confidence in the estimate of effect.

Moderate-Quality Evidence
Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In
addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case–control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on our confidence in the estimate of effect and may change the estimate.

**Low Quality Evidence**

Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on our confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose–response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.
References


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54. Greven K, Winter K, Underhill K, Fontenesci J, Cooper J, Burke T. Preliminary analysis of RTOG 9708: Adjuvant postoperative radiotherapy combined with


