Adjuvant Radiotherapy for Stage I Endometrial Cancer: An Updated Cochrane Systematic Review and Meta-analysis

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Manuscript received April 19, 2012; revised July 23, 2012; accepted July 25, 2012.

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Background  The role of adjuvant radiotherapy in stage I endometrial cancer has changed in recent years. This updated Cochrane systematic review aimed to reexamine the efficacy and toxicity of adjuvant radiotherapy vs no treatment in stage I endometrial cancer.

Methods  We searched various databases including The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and the Specialised Register of the Cochrane Gynaecological Cancer Review Group (CGCRG) for randomized controlled trials that met the predefined inclusion criteria. The primary outcome was overall survival (OS); secondary outcomes were endometrial cancer–specific survival, locoregional recurrence, distant recurrence, and toxicity. Hazard ratios (HRs) were estimated and pooled if possible; otherwise, dichotomous data were extracted. All statistical tests were two-sided.

Results  Of the eight included trials, seven trials (3628 women) compared external beam radiotherapy (EBRT) and no EBRT (or vaginal brachytherapy [VBT]), and one trial (645 women) compared VBT and no additional treatment. EBRT statistically significantly reduced locoregional recurrence compared with no EBRT (or VBT alone) (HR = 0.36, 95% confidence interval [CI] = 0.25 to 0.52; P < .001), but this did not translate into an improvement in OS (HR = 0.99, 95% CI = 0.82 to 1.20; P = .95), endometrial cancer–specific survival (HR = 0.96, 95% CI = 0.72 to 1.28; P = .80), or distant recurrence rates (risk ratio = 1.04, 95% CI = 0.80 to 1.35; P = .77). EBRT was associated with an increased risk of severe acute toxicity, severe late toxicity, and reduced quality of life scores.

Conclusions  EBRT reduces the risk of locoregional recurrence but has no statistically significant impact on cancer-related deaths or OS. However, EBRT is associated with clinically and statistically significant morbidity and a reduction in quality of life.

J Natl Cancer Inst 2012;104:1625–1634

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (1,2). Here, we examined the role of adjuvant radiotherapy after surgery for endometrial carcinoma, a disease that affects mainly postmenopausal women and is one of the most common gynecological cancers. The majority of endometrial carcinomas are diagnosed at stage I in which the cancer is confined to the body of the uterus (3). The initial treatment of stage I disease is usually a hysterectomy and bilateral salpingo-oophorectomy. Previously, it was advocated that a pelvic and/or para-aortic lymphadenectomy should be performed to determine the need for adjuvant therapy. However, two recent randomized trials of pelvic lymphadenectomy vs no lymphadenectomy showed no evidence of benefit for routine lymphadenectomy in patients with stage I endometrial cancer (4,5). The role of adjuvant radiotherapy in stage I endometrial cancer and early disease has changed over recent years. Previously, adjuvant radiotherapy had been offered to some women who had stage I disease based on the perceived “risks of recurrence” including histological type, grade, depth of myometrial invasion, lymphovascular invasion, and age (6). This practice resulted in different policies of routine adjuvant radiotherapy with external beam radiotherapy (EBRT) and/or vaginal brachytherapy (VBT) being offered at various treatment centers throughout the world. More recently, many centers stopped offering adjuvant EBRT to women who have stage I endometrial cancer.

Both pelvic EBRT and vaginal intracavitary VBT may result in acute toxicities and long-term complications, which may cause worsening of quality of life for some patients (7). Therefore, the decision to offer adjuvant radiotherapy must be based on true clinical benefit,
which should outweigh the side effects. Our original review (1) combined data from four randomized controlled trials of EBRT (with or without VBT) vs no EBRT and found no evidence that adjuvant EBRT improved overall survival (OS) or endometrial cancer–related survival, despite a reduction in locoregional recurrence (1,2). Since then, several larger randomized trials of adjuvant radiotherapy in early endometrial carcinoma have been reported, and subsequently, the less toxic VBT is increasingly used for local tumor control, even for high-risk endometrial cancer (8,9). However, there is still uncertainty whether this may result in more locoregional recurrences and a reduction in patient survival. Therefore, there was a need to update the Cochrane systematic review on the benefits and risks of adjuvant radiotherapy to guide the clinical management of stage I endometrial cancer.

Methods

Search Strategy

For the original review (1), we searched MEDLINE and EMBASE databases from January 1, 1966 to February 10, 2006, as well as the Cochrane Register of Controlled Trials, the Specialised Register of the Cochrane Gynaecological Cancer Review Group, abstracts from major international scientific meetings (International Gynecologic Cancer Society, American Society of Clinical Oncology, American Society of Radiation Oncology), and the US National Institute of Health clinical trial register (www.clinicaltrials.gov). Further details on the search strategy and selection criteria can be found in the Appendix of the full review (10). These searches were repeated on May 3, 2011 and January 16, 2012 for this updated review. We searched the reference lists of the relevant articles, and articles in all languages were included in our study. In addition, we searched the MetaRegister of Clinical Trials (www.controlled-trials.com/mrct/) and attempted to contact investigators of past and ongoing trials for further information.

Selection Criteria

We included randomized controlled trials that compared surgery and EBRT with surgery alone (with or without VBT) and excluded nonrandomized trials, trials of preoperative radiotherapy, sarcoma or mixed histology, when group size was less than 10 women, and trials of radiotherapy vs other active treatment such as chemotherapy or hormonal therapy. At least two authors independently selected studies for inclusion, and differences were resolved by discussion.

Data Extraction and Quality Assessment

At least two authors extracted data to prespecified data collection forms. We assessed the risk of bias (selection, detection, attrition, and reporting bias) in the included studies using the Cochrane Collaboration’s tool in the Cochrane Handbook (10). For time-to-event outcomes, we extracted hazard ratios (HR) and their associated variances, or we estimated them where possible using the methods described by Parmar and colleagues (11). Where this was not possible, we extracted dichotomous data. The data extraction was discussed and agreed by the authors, and, if necessary, the authors of the trials were contacted for clarification. We also contacted the authors of included trials for all data relevant to the primary and secondary outcomes.

Statistical Analysis

We carried out statistical analysis using the Cochrane Review Manager Software 5.1 (RevMan 5.1, Cochrane IMS, Copenhagen) (12). The generic inverse variance facility was used to combine time-to-event data to produce hazard ratios, and we produced summary risk ratios (RR) with 95% confidence intervals (CI) using the Mantel Haenszel method for dichotomous data. The random effects model with inverse variance weighting was used for all meta-analyses (13).

The staging system has undergone revision since the quoted studies have been reported (14). For the purposes of this review, we used the (before the year 2010) International Federation of Gynecology and Obstetrics staging, which defines stage IA as cancer that does not invade the myometrium and is confined to the endometrium, stage IB as cancer that invades less than one half of the muscle wall of the uterus, and stage IC as cancer that invades more than one half of the muscle wall of the uterus (3). The initial protocol stated that we would carry out subgroup analyses by prognostic factors if possible. As the definitions and inclusion of patients with high risk factors varied between the studies, we grouped women by the investigators’ definitions of intermediate and high risk. When this was not possible, we defined women as intermediate risk if they had stage IC or grade 3 and as high risk if they had stage IC and grade 3. We also included high–intermediate risk women from GOG 99 in the high-risk subgroup analysis. In GOG 99, the risk factors were considered as grade 3, stage IC, increasing age, and presence of lymphovascular invasion (15). High–intermediate risk was defined as 1) at least 70 years of age with only one of the other risk factors, 2) at least 50 years of age with any two of the other risk factors, or 3) any age with all three of the other risk factors. All other women were considered at low–intermediate risk (15). We were unable to obtain the data from the ASTEC/EN.5 study (6) grouped by the GOG 99 risk factors, for the high–intermediate risk subgroup analysis.

As standard radiotherapy protocols for stage I endometrial cancer may include VBT, we anticipated heterogeneity and grouped the trials by control group for the purposes of investigation and clarification as follows: EBRT vs no additional treatment, EBRT vs no additional treatment (with similar numbers of women in each group also receiving VBT), and EBRT vs VBT.

We performed sensitivity analyses when there was a risk of bias associated with the quality of some of the included trials or when the risk of bias was unclear. In addition, we performed sensitivity analyses when potential clinical heterogeneity existed without statistical heterogeneity. We assessed statistical heterogeneity in each meta-analysis by using a χ² test and the I² statistic of inconsistency, which describes the percentage of variation across studies that is because of heterogeneity rather than chance (Cochrane handbook Version 5.1.0, http://www.cochrane-handbook.org/). Statistically significant heterogeneity was defined as a P value of less than .10 in the χ² test for heterogeneity or if I² was greater than 30%. All statistical tests were two-sided.

Results

Included Studies and Critical Appraisal

For the original review (1), four studies (13 records) were selected for inclusion and 20 were excluded. The updated search (February
1, 2006 to January 16, 2012) identified 2165 records; of these, we selected 20 records as potentially relevant to the review (Figure 1). After independent assessment of the full text of these records, four additional studies (11 records) were included and nine studies were excluded. Therefore, we included eight studies (24 reports) in this review (Aalders 1980, ASTEC/EN.5, GOG 99, PORTEC-1, PORTEC-2, Soderini 2003, Sorbe 2009, and Sorbe 2011) (6,15–21) and excluded 29 studies/reports. One included study (6) consisted of combined data from two trials (ASTEC/EN.5). We considered six of eight studies to be of a high quality. The Soderini (21) and Aalders (16) trials were assessed as having a high and moderate risk of bias, respectively, and did not report time-to-event data, and so they were excluded from the time-to-event meta-analyses. The characteristics of studies included in our analysis are listed in Table 1.

Effects of Interventions

**EBRT (with or without VBT) vs no EBRT (or VBT alone).** There was no statistically significant difference in OS between the EBRT treatment group and the no EBRT group (time-to-event data: five trials, 2965 women; HR = 0.99, 95% CI = 0.82 to 1.20; F = 0%; P = .95) (Figure 2) or endometrial cancer–specific survival (CSS) (time-to-event data: five trials, 2965 women; HR = 0.96, 95% CI = 0.72 to 1.28; F = 12%; P = .80) (10). External beam pelvic radiotherapy statistically significantly reduced locoregional recurrence (LRR) (time-to-event data: five trials, 2965 women; HR = 0.36, 95% CI = 0.25 to 0.52; F = 0%; P < .001) (Figure 3). Dichotomous data for these outcomes (including data from seven trials) produced similar results and may be found in the full review in the Cochrane Library (10). There was no statistically significant difference in distant recurrence rates (dichotomous data; seven trials, 3628 women; RR = 1.04, 95% CI = 0.80 to 1.35; P = .77) (10).

**Low-risk women.** Among low-risk women, who were defined as having grade 1 or 2 disease and less than 50% invasion, EBRT increased the risk of endometrial carcinoma–related death (two trials, 517 women; RR = 2.64, 95% CI = 1.05 to 6.66; F = 0%; P = .04) in a meta-analysis (10) that included only two trials (Aalders 1980, GOG 99) (15,16). We included data from GOG 99 (15) that had been defined by investigators as “low–intermediate risk.” In this trial, endometrial cancer deaths included treatment-related deaths and deaths from unknown causes. There were insufficient data for a meta-analysis of other outcomes.

**Intermediate-risk women.** There was no statistically significant difference in OS (five studies, 2560 women; HR = 1.05, 95% CI = 0.85 to 1.31; F = 0%; P = .63) (Figure 4) or CSS (five trials, 2560 women; HR = 1.03, 95% CI = 0.70 to 1.51; F = 25%; P = .90) (10) among intermediate-risk women (intermediate risk was defined by the investigators or was defined as stage IC or grade 3). The data from the PORTEC-2 study (18) were reported as “true high–intermediate risk” data (366 women) and included some...
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<th>Study</th>
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<td>Aalders 1980</td>
<td>RCT—methods were not clearly specified; ITT analysis was not specified</td>
<td>540 women; stage I endometrial cancer including stage IB (grade 1); total abdominal hysterectomy and bilateral salpingo-oophorectomy; pelvic and para-aortic lymphadenectomy were not routine</td>
<td>EBRT vs no EBRT; all women also received vaginal brachytherapy</td>
<td>OS, CSS, locoregional recurrence, distant recurrence (dichotomous data only)</td>
<td>Range = 3–10 y</td>
<td>No loss to follow-up; the baseline characteristics were comparable among the study participants; moderate risk of bias</td>
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<td>ASTEC/EN.5</td>
<td>Combined data from two multicenter RCTs; central computer-generated randomization; allocation by telephone; analysis by ITT; outcome assessor blinding in ASTEC only</td>
<td>905 intermediate risk and high-risk women; total abdominal hysterectomy and bilateral salpingo-oophorectomy; pelvic and para-aortic lymphadenectomy were not routine (29.4%); intermediate risk was defined as stage IA/IB (grade 3), stage IC, and stage IIA (grade 1/2); high risk was defined as stage IC, stage IIA (grade 3), and stage IIB</td>
<td>EBRT vs no EBRT; approximately half of the women received vaginal brachytherapy, balanced between the two groups</td>
<td>OS, CSS, locoregional recurrence, disease-specific recurrence-free survival, toxicity</td>
<td>58 mos</td>
<td>Low attrition; baseline characteristics were comparable except for a small difference in the proportion of high-risk women (20% in the EBRT group vs 25% of control subjects); low risk of bias</td>
<td>UK Medical Research Council, National Cancer Research Network, National Cancer Institute of Canada</td>
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<td>GOG 99</td>
<td>RCT—balanced block randomization; allocation concealment not described; analysis by ITT</td>
<td>392 women; stage IB/C and stage IIA/B (occult) patients were included; routine total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic and para-aortic lymphadenectomy; high-intermediate risk was defined as stage IC (grade 2/3) and presence of lymphovascular space invasion, or age ≥ 50 y with any two risk factors listed above; or age ≥ 70 y with any risk factor listed above</td>
<td>EBRT vs no EBRT</td>
<td>OS, CSS, locoregional recurrence, distant recurrence, toxicity</td>
<td>69 mos</td>
<td>Low attrition; 9.5% of women were stage IIA/B and were balanced across the treatment groups; low risk of bias</td>
<td>National Cancer Institute</td>
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<td>PORTEC-1</td>
<td>Multicenter RCT, block randomization done centrally, allocation by telephone</td>
<td>714 women; total abdominal hysterectomy and bilateral salpingo-oophorectomy; pelvic and para-aortic lymphadenectomy were not routine; intermediate risk was defined as stage IB (grade 2); high-intermediate risk was defined as age &gt; 60 y, stage IC (grade 1/2), or age &gt; 60 y, stage IB (grade 3)</td>
<td>EBRT vs no EBRT</td>
<td>OS, CSS, locoregional recurrence, distant recurrence, QOL</td>
<td>52 mos; 8, 10 and 15 y</td>
<td>Low attrition; 31% immediate-risk women (and some low-risk women) were balanced across the treatment groups; low risk of bias</td>
<td>Dutch Cancer Society</td>
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<td>PORTEC-2</td>
<td>Multicenter open label, noninferiority RCT; analysis by ITT; outcome assessors blind to group allocation</td>
<td>427 high-risk women; total abdominal hysterectomy and bilateral salpingo-oophorectomy; pelvic and para-aortic lymphadenectomy were not routine; included high-intermediate risk only; defined as age &gt; 60, stage IC (grade 1/2), or stage IB (grade 3), or stage IIA (excluding grade 3)</td>
<td>EBRT vs vaginal LRR, OS, CSS, toxicity, QOL</td>
<td></td>
<td>45 mos</td>
<td>No loss to follow-up; women with stage II disease (11.5%) were balanced across the treatment groups; baseline characteristics were comparable; results were reported as vaginal brachytherapy vs EBRT; analyses were repeated after central pathology reviewed “true” high-intermediate risk (366 women); some unpublished data were obtained; low risk of bias</td>
<td>Dutch Cancer Society</td>
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<td>Soderini 2003</td>
<td>RCT; randomization by computer-generated table after complete surgical staging; allocation concealment not described</td>
<td>123 intermediate-risk women; routine total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic and para-aortic lymphadenectomy; intermediate risk was defined as stage IB/C (grade 2/3)</td>
<td>EBRT vs no EBRT</td>
<td>OS, PFS, locoregional recurrence, distant recurrence</td>
<td>48 mos</td>
<td>No loss to follow-up; only published as an abstract; some unpublished data were obtained; high risk of bias</td>
<td>Not stated</td>
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<td>Sorbe 2009</td>
<td>Multicenter RCT, central randomization with stratification by center; allocation concealment by sealed envelopes; analysis by ITT; outcome assessors blind to group allocation</td>
<td>645 low-risk women (stage I/AVB, grade 1/2), total abdominal hysterectomy, bilateral salpingo-oophorectomy; pelvic and para-aortic lymphadenectomy was not routine</td>
<td>Vaginal brachytherapy vs no vaginal brachytherapy</td>
<td>OS, locoregional recurrence, toxicity</td>
<td>Mean = 68 mos</td>
<td>Low attrition; some unpublished data were obtained; low risk of bias</td>
<td>Not stated</td>
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<td>Sorbe 2011</td>
<td>Multicenter RCT; randomization and allocation concealment not described</td>
<td>527 medium-risk women; medium risk was defined as FIGO stage I endometrioid type; grade 3 or deep myometrial infiltration or DNA aneuploidy; nuclear grade i–2; negative lymph nodes (optional); and negative cytology (optional); primary surgery included total abdominal hysterectomy, bilateral salpingo-oophorectomy, appendectomy, node sampling and cytology; pelvic and para-aortic lymphadenectomy were not routine.</td>
<td>EBRT vs no EBRT; all women also received vaginal brachytherapy</td>
<td>OS, locoregional recurrence, RFS, CSS, toxicity, QOL</td>
<td>62 mos</td>
<td>Low attrition; baseline characteristics were comparable; QOL was not yet reported; unclear risk of bias</td>
<td>Not stated</td>
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* CSS = endometrial cancer-specific survival; EBRT = external beam radiotherapy; FIGO = International Federation of Gynecology and Obstetrics; ITT = intention-to-treat analysis; LRR = locoregional recurrence; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; RFS = recurrence-free survival.
unpublished data. We included low–intermediate risk data from GOG 99 (15) in these subgroup analyses. If we excluded GOG 99 (15) from the meta-analyses, the hazard ratios for OS (HR = 1.06, 95% CI = 0.84 to 1.32; I² = 0%; P = .64) and CSS (HR = 0.97, 95% CI = 0.66 to 1.41; F = 21%; P = .86) were similar to those above (10).

**High-risk women.** There was no statistically significant difference in OS (two trials, 334 women; HR = 0.91, 95% CI = 0.60 to 1.39; F = 0%; P = .67) (Figure 5) or CSS (two trials, 334 women; HR = 0.84, 95% CI = 0.51 to 1.40; F = 0%; P = .51) among women at high risk, which was defined by the investigators or as stage IC and grade 3 (10). We included high–intermediate risk women from GOG 99 (15) in these meta-analyses. Three trials contributed data to the dichotomous meta-analyses that produced similar results for this subgroup, which can be found in the full review in the Cochrane Library (10). When we excluded GOG 99 data (15) from the dichotomous meta-analyses, the results were similar to those with GOG 99 data included (10).

**Long-term follow-up data.** Only two studies reported long-term data: PORTEC-1 (17) and Aalders 1980 (16). PORTEC-1 reported follow-up at 8, 10, and 15 years (17,22–24). When the 10-year follow-up data from PORTEC-1 and 9-year follow-up data from Aalders 1980 were combined, the relative risk for OS was 1.26 (95% CI = 1.03 to 1.54; F = 0%; P = .02) in favor of no EBRT (10).

**Toxicity and quality of life.** Severe acute grade 3 or 4 toxicity was more frequent in the EBRT group than in the no EBRT group and was statistically significant (two trials, 1328 women; RR = 4.68, 95% CI = 1.35 to 16.16; F = 0%; P = .01), as was severe late grade 3/4 toxicity (six trials, 3501 women; RR = 2.58, 95% CI = 1.61 to 4.11; F = 0%; P < .001) (10). Two women in the EBRT group of GOG 99 (15) and two in Aalders 1980 (16) died from radiotherapy-related complications involving intestinal injury. One study (PORTEC-1) reported long-term adverse effects and quality of life at a median follow-up of 13.3 years (24). These investigators found that PORTEC-1 women who had received EBRT had statistically significantly higher rates (P < .01) of urinary incontinence, diarrhea, and fecal leakage that limited their daily activities (17,23,24). EBRT was also associated with statistically significantly worse “physical functioning” (P = .004) and “bodily pain” (P = .009) scores than no EBRT (17,23,24).
no meta-analyses could be performed to compare OS for VBT vs no additional treatment. In this trial, there was no statistically significant difference in survival between the women who received VBT compared with the control group (645 women, RR = 1.09, 95% CI = 0.56 to 2.11; \( P = .81 \)) or CSS (RR = 1.43, 95% CI = 0.46 to 4.46; \( P = .54 \)) (19). However, the vaginal recurrence rate in the VBT group and the control group was similar (1.2% vs 3.1%, RR = 0.39, 95% CI = 0.14 to 1.09; \( P = .07 \)) (19).

**Discussion**

Since our original review (1), findings from several major EBRT studies in endometrial carcinoma, including ASTEC/EN.5 (15), PORTEC-2 (18), Sorbe 2009 (19), and Sorbe 2011 (20), have been published. We were therefore able to update our initial review and drew more definitive conclusions about adjuvant radiotherapy in stage I endometrial carcinoma. Our updated review included eight trials and showed that adjuvant EBRT statistically significantly reduced locoregional recurrence but not OS, endometrial CSS, or distant metastases. There were no survival benefits from EBRT for women in any of the risk subgroups either. These findings appear to hold true over time (22–24). Furthermore, EBRT was associated with statistically significantly more severe acute toxic effects and late complications (grade 3 and 4) compared with no EBRT.

It is important to note that the original Cochrane review described a nonstatistically significant trend toward a survival benefit for EBRT in high-risk women (1C G3) (1,2). The ASTEC/EN.5 data (6) now dominate these high-risk meta-analyses (weighting of 45%–65%) and have shifted the survival hazard ratios in the direction of no difference. However, the number of high-risk women participating in the reported trials of adjuvant EBRT is relatively small. We cannot exclude the possibility that our analyses may lack power to detect a small advantage.

There is insufficient evidence to draw conclusions about VBT. We could find only one trial that compared VBT to no additional treatment in women with low-risk disease (19). This study found that postoperative VBT resulted in a nonstatistically significant reduction in locoregional recurrence. Compared with EBRT, VBT was effective in ensuring vaginal control in high–intermediate risk women in PORTEC-2, although the locoregional relapse rate was slightly higher (2.1% vs 5.1%, \( P = .17 \)) in the VBT group (18). Sorbe 2011 reported that EBRT plus VBT reduced locoregional relapse slightly more than VBT alone in intermediate-risk women (1.5% vs 5%, \( P = .01 \)) but not endometrial CSS or OS (20). VBT has been recommended as the adjuvant treatment of choice for women with endometrial carcinoma of intermediate (20) and high–intermediate risk (PORTEC-2) (18), respectively.

![Forest plot of hazard ratios (HRs) comparing the locoregional recurrence for stage I endometrial carcinoma patients who received external beam radiotherapy (EBRT) treatment vs those who received no EBRT treatment. HRs for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis random effect of all trials. Inverse variance (IV) and random effects methods were used to calculate HRs, 95% CIs, \( P \) values, and the test for overall effect; these calculations were two-sided. The \( \chi^2 \) test and the \( F \) statistic were used to calculate heterogeneity. Random = random effects method; SE = standard error; VBT = vaginal brachytherapy.](https://academic.oup.com/jnci/article-abstract/104/21/1625/952113/figure-3)
Figure 4. Forest plot of hazard ratios (HRs) comparing the overall survival (OS) for the intermediate-risk women who received external beam radiotherapy (EBRT) treatment vs those who received no EBRT treatment. HRs for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis random effect of all trials. Inverse variance (IV) and random effects methods were used to calculate HRs, 95% CIs, \( P \) values, and the test for overall effect; these calculations were two-sided. The \( \chi^2 \) test and the \( I^2 \) statistic were used to calculate heterogeneity. Random = random effects method; SE = standard error; VBT = vaginal brachytherapy.

Figure 5. Forest plot of hazard ratios (HRs) comparing the overall survival (OS) for the high-risk women who received external beam radiotherapy (EBRT) treatment vs those who received no EBRT treatment. HRs for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis random effect of all trials. Inverse variance (IV) and random effects methods were used to calculate HRs, 95% CIs, \( P \) values, and the test for overall effect; these calculations were two-sided. The \( \chi^2 \) test and the \( I^2 \) statistic were used to calculate heterogeneity. Random = random effects method; SE = standard error; VBT = vaginal brachytherapy.
The definitions and inclusions of low risk, intermediate risk, and high risk differed between the trials included in our analyses. To carry out subgroup analyses, we grouped women by the investigators’ definitions of risk. However, when this was not possible, we defined women as intermediate risk if they had stage IC or grade 3 and as high risk if they had stage IC and grade 3. In GOG 99, the low–intermediate risk could not be separated from the low-risk group, and their high–intermediate risk data were included in the high-risk subgroup (15). Sensitivity analyses were performed to analyze the results with and without these included data. To assess the effect of EBRT vs no EBRT, we included PORTEC-2 (18), although this trial directly compared EBRT with VBT and therefore VBT was not balanced between the two groups. We grouped VBT with “no treatment” or the “control” group for this trial and compared EBRT vs no EBRT. However, sensitivity and subgroup analyses showed that the results remained largely similar when PORTEC-2 data (18) were excluded, even for locoregional recurrence. Although Aalders 1980 (16) was undertaken before the introduction of FIGO staging, and Soderini 2003 (21) was only published as an abstract and a poster, we included these lower quality trials in the dichotomous data analyses, which may be found in the full review (10). These two trials did not report time-to-event data. We performed sensitivity analyses to assess the impact of including their data on the review and found that their inclusion had little impact on the overall risk ratios (10).

Another potential limitation of this review is that we relied on the initial histologic classification provided by the original published studies. As is the case in most pragmatic randomized trials, real-time central pathology review was not performed in the trials in this meta-analysis, with the exception of GOG 99 (15). Grading of endometrial cancer is subjective. The expert review of the pathology in the PORTEC-1 trial reclassified many grade 2 tumors as grade 1 (23). However, there was no reclassification of most grade 3 tumors, and the regrading exercise made no difference to the summary statistic in the PORTEC-1 trial (17,23). Some low-risk women who would not be considered for radiotherapy by today’s standard were recruited to trials, but this would not affect the analysis of the data from women with high-grade tumors. The Aalders study (16) was conducted before the implementation of surgical staging, but there is no suggestion that the authors inadvertently recruited women with advanced disease. The ASTEC/EN.5 trial (6) has not yet analyzed data that are based on a single expert pathology review, but patients recruited in the UK to the ASTEC study (6) would have been reviewed by a multidisciplinary team including pathologists who had a special interest in gynecological pathology. Despite the differing profiles of risk, the rates of death from disease were similar in both women participating in the PORTEC-1 (17), PORTEC-2 (18), and ASTEC/EN.5 (6) studies. Subjective tumor grade assessments have important implications for interpretation of the data from these trials but should not affect the results of our meta-analyses. Women who were diagnosed with intermediate-risk cancer are not likely to benefit from EBRT, so their adjuvant options should be unaffected by a central review downgrading some of the histological diagnoses. Uncertainties in the histological classification provided by the original publications will weaken the conclusions from the subgroup analyses from our review. We cannot make definitive conclusions about the cost–benefit ratio for high- or high-intermediate-risk disease as classified by specialist pathologists, but we can say that the accumulated randomized trial data do not support the use of EBRT to improve survival in any stage I endometrial cancer when graded by local pathologists.

Our updated review confirms the main findings of the original review that adjuvant EBRT reduces locoregional recurrence but does not improve CSS or OS in stage I endometrial carcinoma. EBRT is associated with statistically significantly increased morbidity and a reduction in quality of life. In women who are at low risk, EBRT may have an adverse effect on endometrial CSS. Because the locoregional recurrence rate in this subgroup is low and not statistically significantly improved by VBT, VBT is probably not required in treatment of low-risk women. There is no demonstrable survival advantage from adjuvant EBRT for high-risk stage I endometrial cancer, but the meta-analyses of this subgroup were underpowered and also included high–intermediate risk women. This was further complicated by the lack of specialist pathologist review and errors in histological classifications found in several major trials. Therefore, although there appears to be no survival benefits in the routine use of EBRT in women with stage I endometrial cancer, we cannot exclude a benefit in high-risk women. This study supports the recommendations of ASTEC/EN.5 (6) investigators that routine EBRT cannot be recommended to improve survival in women with stage I endometrial carcinoma. However, further evidence may be needed to guide practice for women who are at truly high risk or high–intermediate risk as classified by expert pathologists. We did not find any studies that assessed the benefits and risks of adjuvant VBT vs no additional treatment in women with intermediate- or high-risk stage I endometrial cancer. We are therefore unable to draw definitive conclusions about VBT in these women. However, VBT appears to be useful in preventing vaginal tumor recurrence in high-intermediate subgroups compared with EBRT.

References


**Funding**

This work was funded by The Cochrane Gynaecological Cancer Review Group through the NHS Research and Development Programme, Bath, UK.

**Notes**

This systematic review is based on a Cochrane Review published in The Cochrane Library Issue 3 2012 (10). This review would not have been possible without the editorial support of Clare Jess, Gail Quinn, and Jane Hayes of the Cochrane Gynaecological Cancer Review Group. For a complete list of acknowledgments, please refer to the Cochrane Review (10). The authors take full responsibility for the design of the study; the data collection, analysis, and interpretation; the writing of the systematic review; and the decision to submit it for publication.

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