The role of adjuvant radiotherapy in stage I endometrial cancer following surgery remains unclear. The management for these patients varies widely, particularly in stage I patients with different risk factors. Using the methodology of Cochrane Collaboration, we did a systematic and meta-analysis of all known randomised controlled trials which compared adjuvant radiotherapy versus no radiotherapy following surgery for patients with stage I endometrial cancer. The meta-analysis was carried out on four trials (three published and one unpublished) and a total of 1770 patients. The addition of pelvic external beam radiotherapy to surgery reduced locoregional recurrence, a relative risk (RR) of 0.28 [95% confidence interval (CI) 0.17–0.44, P < 0.00001], which is a 72% reduction in the risk of pelvic relapse (95% CI 56% to 83%) and an absolute risk reduction of 6% (95% CI of 4% to 8%). The reduction in the risk of locoregional recurrence did not translate into a reduction in the risks of death from all causes, endometrial cancer death or distant recurrence. A subgroup analysis showed a trend towards the reduction in the risks of death from all causes and endometrial cancer in patients with multiple high risk factors (including stage 1c and grade 3). External beam pelvic radiotherapy should be considered in patients with multiple high-risk features including stage 1c and grade 3. However, it carries an inherent risk of damage and toxicity and should be avoided in stage 1 endometrial cancer patients with no high risk factors.

Key words: stage I endometrial carcinoma, adjuvant radiotherapy, systematic review and meta-analysis, death from all causes, locoregional recurrence, endometrial cancer-related deaths

introduction

Endometrial carcinoma is one of the commonest gynaecological cancers in the Western world. Seventy-five per cent of women affected are postmenopausal and ninety-five per cent of tumours are endometrioid adenocarcinomas. Most endometrial cancers are diagnosed with stage 1 disease. The initial treatment of stage 1 disease is usually surgery involving total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH & BSO). The definitive management of this group of patients following surgery remains unclear. Pelvic external beam radiotherapy and/or vaginal brachytherapy may be given as adjuvant treatment to reduce the risk of recurrence. The decision to treat depends on whether the patients have high risk factors including the stage of disease, depth of myometrium invasion, grade of the tumour, lymphovascular invasion and the age of the patient as several retrospective series have suggested that these factors are important in determining the recurrence and death rates [1]. There are, however, great variations between cancer centres and different countries in the practice of adjuvant radiotherapy for these patients.

Both pelvic external beam radiotherapy and vaginal intracavitary brachytherapy (to a lesser extent) carries the risks of acute toxic effects and long-term complications [2]. Although the acute side-effects of pelvic radiotherapy (on the irradiated skin, gastrointestinal (GI) tract and genitourinary tract) settle down in the majority of patients following treatment, >20% of patients continue to have persistent mild (grade 1) complications and a minority of patients (~3%) develop severe long-term complications [2]. Uncertainty as to whether adjuvant radiotherapy improves survival sufficiently to warrant the side-effects for all stage I patients [3–5] may be a factor for the difficulty in deciding adjuvant radiotherapy in this group of patients. The main objective of this review is to assess the efficacy of adjuvant radiotherapy when used following surgery for stage I endometrial cancer.

methods

We used Cochrane Collaboration guidelines to carry out this systematic review after written a predefined protocol. We reviewed randomised controlled trials (RCTs) comparing surgery followed by adjuvant
radiotherapy versus surgery alone for stage I endometrial carcinoma. The primary outcome measure was overall survival (OS). Locoregional recurrence, distant recurrence and endometrial cancer deaths were considered as secondary outcome measures where possible. Data on quality of life (QoL), morbidity as well as the acute and late side-effects of pelvic radiation (on skin, genitourinary tract and GI tract) were recorded, were collected and analysed.

**search strategy**

We developed a search strategy on the basis of the highly sensitive search strategy for RCTs as described in the Cochrane Handbook and on the basis of the terms relating to the review topic. The following electronic databases were searched: CENTRAL on the Cochrane Library (2005), Medline (Silver Platter, from 1966 to 2005), EMBASE (from 1980 to 2005), CANCERLIT (from 1966 to 2005), Physician Data Query of National Cancer Institute (open and closed trials), the Specialised Register of the Cochrane Gynaecological Cancer Review Group (COCRPG). The reference lists of the relevant papers found were searched for further studies. Papers in all languages were sought. Meta-register and its links were searched for ongoing trials. The main investigators of the relevant ongoing trials were contacted for further information (e.g. unpublished trials, interim results). The Proceedings of the Annual Meetings of the American Society of Clinical Oncology were hand searched by the Gynaecological Cancer Group’s Trials Search Coordinator, and abstracts relating to the review were identified. The initial search was done in 2001 with frequent update searches of the Specialist Register of the CGCRG. Dr. Nick Johnson and Dr. Paul Cornes (see acknowledgements) did an independent search and review in 2005 and data and critical comment were shared in 2006.

**quality assessment**

Methodological quality of included RCTs was assessed using the following criteria:

1. **Blinding:** blinding of the patients, treatment providers and assessors were assessed as either yes, no or unclear.
2. **Randomisation:** we coded the randomisation of participants to intervention groups as either (i) adequate (e.g. a computer-generated random sequence), (ii) inadequate (e.g. date of birth, or surname) or (iii) unclear (e.g. not reported).
3. **Allocation concealment:** we coded the concealment of allocation sequence from treatment providers and participants as (i) adequate (e.g. where the allocation sequence could not be foretold), (ii) unclear (e.g. not reported), (iii) inadequate (e.g. the computer-generated random sequence was displayed so treatment providers could see which arm of the trial the next participant was assigned to, or kept in a sealed opaque envelope).
4. **Loss to follow-up:** we recorded the number of participants in each intervention arm whose outcomes were not reported at the end of the study and we noted if loss to follow-up was not reported.

Intention-to-treat (ITT) was not used as part of quality assessment but we attempted to abstract data such that an ITT analysis could be carried out.

**data extraction**

The data from the included trials were extracted using pre-specified data collection form by CW, MC and AK independently. Any discrepancies in data extraction were resolved by discussion.

**analysis**

The primary outcome measure of our review and meta-analysis was OS. The most appropriate statistics to use for this time to event outcome (OS) would be hazard ratio (HR) and individual patient data would be the best for this analysis. However, we do not have such information. Therefore, we extracted the number of patients in each treatment arm who experienced deaths from all causes, in order to estimate a relative risk (RR). For any dichotomous outcomes (e.g. numbers of patients who had locoregional recurrence, distant recurrence or who had deaths related to endometrial carcinoma), the RR was calculated for each study. Statistics from all studies were pooled. Meta-analysis was done using the Cochrane Collaboration’s Review Manager Software 4.2.1.² The statistic which summarises the amount of variation between trials which is not due to sampling variation as well as Chi-square test were used to test statistical heterogeneity in all trials (P < 0.05), in addition to critical review of the inclusion criteria of all the included trials to assess clinical heterogeneity. Random effects models were used for all meta-analyses [6]. The absolute risk and number to treat (NNT) were obtained whenever possible.

**subgroup analysis**

Our initial protocol stated that we would carry out subgroup analysis by prognostic factors if possible. However, the definitions and inclusion of patients with high risk factors varied between the studies. In PORTEC 1 study, the definitions of high intermediate risks had the following risk profiles (revised grade): (i) >60, stage 1c, grade 1 or 2; (ii) >60, grade 3, stage 1b. Patients with both 1c and grade 3 were excluded. In GOG-99 a high intermediate risk subgroup of patients were defined after randomisation as those with (i) grade 2 and 3, presence of lymphovascular invasion (LVC), and stage 1c; (ii) age 50 or greater with any two risk factors listed above; and (iii) age of at least 70 with any risk factor listed above.

Since ASTEC adjuvant radiotherapy trial recruited only stage I patients with high-risk pathology, with one or more of the following: grade 3, stage 1c, serous papillary or clear cell type, International Federation of Gynecology and Obstetrics stage IIA, we decided to do a subgroup analysis on patients on the basis of whether they had at least one or both of the risk factors of grade 3 and stage 1c since these two factors are consistently correlated strongly with the prognosis of these patients. Although there were differences between the trials, we thought that the subgroup analysis may generate some useful hypothesis.

**results**

Twenty-nine studies were chosen for further assessment and the copies of the full text of these potentially relevant references were obtained (unless not published or ongoing) and the eligibility of retrieved papers was assessed independently by CW, MC and AK:

1. Twelve studies were excluded because they are not RCTs.
2. Nine RCTs (three of which are duplicate trials, i.e. six RCTs in total) were excluded because the randomisation was not between adjuvant radiotherapy versus placebo (n = 4) [7–10], unacceptable randomisation (n = 1) [11] and the intervention was preoperative radiotherapy which was an exclusion criteria (n = 1) [12].
3. The remaining eight were potentially appropriate RCTs to be included in the meta-analysis.
4. Four RCTs were either ongoing studies or closed studies awaiting assessment (Table 1).
5. Four RCTs included in the meta-analysis (Table 2) [13–16]. The meta-analysis included four trials (Aalders 1980, GOG study, PORTEC 1 and Soderini 2003) [13–16] and a total of 1770 patients, 870 in the treatment group and 900 patients in the control group. The meta-analysis included both published data and the raw data on 10-year outcome data on different
subgroups of patients with stage I endometrial carcinoma of PORTEC 1.

death from all causes

Our primary outcome was OS. However, we were not able to estimate HR and its variances either directly or indirectly for all trials (see method section). Therefore, we extracted the number of patients in each treatment arm who experienced deaths from all causes, in order to estimate a RR. The meta-analysis of the four trials using random effect (Figure 1A) showed no difference in the deaths from all causes with the RR from additional pelvic radiotherapy of 1.01 [95% confidence interval (CI) 0.71–1.43, P = 0.97]. The test of heterogeneity was not significant ($\chi^2 = 5.9, df = 3, P = 0.12$) although $I^2 = 49.1\%$.

locregional recurrence

The meta-analysis of the four trials (Figure 1B) showed that external beam pelvic radiotherapy following surgery reduced local regional recurrence, with a RR of 0.28 (95% CI 0.17–0.44, P < 0.00001), which was a 72% reduction in the risk of locoregional relapse (95% CI 56% to 83%). The absolute risk reduction (risk difference) was 6% (95% CI 4% to 8%). This means that, for example, if 100 women with endometrial cancer were treated with surgery alone, and 100 were treated with external beam radiotherapy (EBRT), we would expect, on average, between six and 11 to have locoregional recurrence in the group treated with surgery alone and six fewer to recur in the group treated with EBRT. The NNT to prevent one locoregional recurrence was 16.7 patients (95% CI 12.5–25). All four trials showed positive effect of pelvic radiotherapy on locoregional recurrence. The test of heterogeneity was not significant ($\chi^2 = 0.96, df = 3, P = 0.81$ and $I^2 = 0\%$).

distant recurrence

The meta-analysis of the four trials (Figure 1C) showed no statistically significant difference in the distant recurrence
Table 2. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aalders 1980</td>
<td>Methods of randomisation not specified. Attrition rate and application of intention-to-treat analysis were not mentioned</td>
<td>Patients with stage 1 endometrial cancer following TAH and BSO. Also included patients with stage 1b and grade 1 tumour</td>
<td>All had intravaginal radium. Intervention group received further pelvic RT but not the control group. Follow-up was 3–10 years</td>
<td>Pelvic RT reduced vaginal and pelvic recurrences (1.9% versus 6.9%, P &lt; 0.001) but not overall survival rate</td>
<td>Only patients with grade 3 and stage 1c tumour might have benefited from pelvic RT</td>
<td>B</td>
</tr>
<tr>
<td>GOG study</td>
<td>A balanced block randomisation scheme was used. Fifty-six women were excluded from the intention-to-treat analysis on the basis that they were ineligible either because of inadequate staging or because of histology or FIGO stage</td>
<td>Patients with stage 1b and 1c, also IIa (occult) and IIb (occult) and had TAH and BSO and selective bilateral pelvic, and paraaortic lymphadenectomy with removal of any enlarged or suspicious nodes</td>
<td>Patients were randomised to either whole pelvic RT or no additional therapy. Median follow-up was 56 months with 9% followed for &lt;2 years</td>
<td>Pelvic RT reduced pelvic and vaginal recurrences but not the overall survival as pelvic recurrences were often effectively treated with second-line therapy</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>PORTEC</td>
<td>Multicentre RCT. Centre-blocked randomisation by telephone was done at the trial office with variable block sizes and was stratified by radiation oncology centre and depth of myometrial invasion. Intention-to-treat analysis was used</td>
<td>Patients with stage 1 endometrial carcinoma (grade 1 with deep myometrial invasion, grade 2 with any invasion or grade 3 with superficial invasion). All had TAH and BSO without lymphadenectomy</td>
<td>Patients were randomised to pelvic RT or no further treatment. Intravaginal brachytherapy was not given. Follow-up was 5–7 years</td>
<td>Pelvic RT reduced locoregional recurrence (4% versus 14%, P &lt; 0.001) but not overall survival or endometrial cancer-related death. Treatment-related complications occurred in 25% of RT patients and in 6% of the control group</td>
<td>Pelvic RT reduced pelvic and vaginal recurrences but not the overall survival as pelvic recurrences were often effectively treated with second-line therapy</td>
<td>A</td>
</tr>
<tr>
<td>Soderini 2003</td>
<td>Only an abstract. Methods of randomisation not specified. Attrition rate and application of intention-to-treat analysis were not mentioned</td>
<td>Patients with intermediate risk (1b grades 2–3 to 1c) endometrioid endometrium carcinoma. All patients had TAH-BSO, pelvic–paraaortic lymphadenectomy and peritoneal washings</td>
<td>Patients were randomised to pelvic RT 50 Gy or no RT</td>
<td>Recurrence rate was lower in RT arm although not statistically significant</td>
<td>Only an abstract is available</td>
<td>B</td>
</tr>
</tbody>
</table>

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; RT, radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; RCT, randomised controlled trials. A = Adequate, B = Unclear, C = Inadequate.
Figure 1. Meta-analysis on all stage I endometrial cancer patients who had adjuvant radiotherapy versus no radiotherapy. (A) Death from all causes. (B) Locoregional recurrence. (C) Distant recurrence. (D) Endometrial carcinoma-related death.
rate between the two arms, with a RR of 1.28 for the treatment group (95% CI 0.89–1.83, \(P = 0.18\)). Test for heterogeneity was not significant (\(\chi^2 = 2.66, df = 3, P = 0.45\) and I\(^2 = 0\%\)).

**endometrial cancer death**

No endometrial cancer death data were available from Soderini 2003. The meta-analysis from the remaining trials (Figure 1D) showed a RR of 1.22 (95% CI 0.88–1.68, \(P = 0.23\)). Test for heterogeneity was not significant (\(\chi^2 = 1.14, df = 2, P = 0.57\) and I\(^2 = 0\%\)).

**subgroup analysis**

The review showed that although external beam radiotherapy reduced locoregional recurrence in stage 1 endometrial cancer, it did not reduce the risks of deaths from all causes, distant recurrences and endometrial cancer. We proceeded to do a subgroup analysis on patients with high risk factors to see whether adjuvant external beam radiotherapy decreased deaths from all causes and endometrial cancer in patients with high-risk features.

**patients with at least one risk factor of grade 3 and stage 1c.** In GOG study, although the definition of high intermediate risk also included risk factors of age and LVC, it was thought that the majority of the patients in this group would have at least grade 3 or stage 1c. Excluding Soderini 2003 (an abstract only with no subgroup data), the subgroup analysis on these patients from the remaining three trials showed no statistically significant difference in both deaths from all causes and endometrial cancer between the treatment group and control group (Figure 2A and B). The RR of death from all causes for treatment group was 1.00 (95% CI 0.89–1.12, \(P = 0.98\)) and that of endometrial carcinoma-related death was 0.88 (95% CI 0.62–1.24, \(P = 0.45\)) for patients with at least two risk factors including grade 3 and stage 1c. PORTEC I study excluded patients with both 1c and grade 3 and recently reported this group of patients separately [17]. The subgroup analysis of the patients with at least two risk factors showed a trend towards a reduction in both deaths from all causes and endometrial carcinoma-related deaths although these were not statistically significant (Figure 3A and B). The RR of death from all causes for patients having radiotherapy compared with control was of 0.76 (95% CI 0.49–1.19, \(P = 0.24\)) and that of endometrial cancer being 0.65 (95% CI 0.38–1.14, \(P = 0.13\)).

**patients without risk factors grade 3 or stage 1c.** It was also intended to see whether external beam radiotherapy would do more harm to patients without any of the high risk factors. We have survival data in this subgroup of patients from two trials, GOG study and Aalders 1980. The meta-analysis of the two trials showed a greater risk of endometrial carcinoma-related deaths which were statistically significant with a RR of 2.65 (95% CI 1.05–6.67, \(P = 0.04\)) (Figure 4B). This is because the endometrial carcinoma-related deaths also included treatment-related deaths. The analysis also showed a greater risk for deaths from all causes for the treatment group, a RR of 1.49 (95% CI 0.56–3.95) although this was not statistically significant (\(P = 0.42\)) (Figure 4A).

---

**Table A**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O-E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td>16/62</td>
<td>22/70</td>
<td>16.92</td>
<td>0.82</td>
<td>[0.49, 1.42]</td>
<td>0.00</td>
<td>0.46</td>
</tr>
<tr>
<td>Aalders 1980</td>
<td>19/123</td>
<td>21/138</td>
<td>15.46</td>
<td>1.02</td>
<td>[0.57, 1.80]</td>
<td>0.00</td>
<td>0.41</td>
</tr>
<tr>
<td>PORTEC</td>
<td>66/192</td>
<td>67/159</td>
<td>67.63</td>
<td>1.85</td>
<td>[0.80, 3.38]</td>
<td>0.00</td>
<td>0.61</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>177</td>
<td>407</td>
<td>100.00</td>
<td>1.00</td>
<td>[0.80, 1.24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events (Treatment, Control)</td>
<td>103 (Treatment), 110 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table B**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O-E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td>8/62</td>
<td>14/70</td>
<td>18.40</td>
<td>0.65</td>
<td>[0.29, 1.43]</td>
<td>0.00</td>
<td>0.17</td>
</tr>
<tr>
<td>PORTEC</td>
<td>23/192</td>
<td>27/199</td>
<td>44.42</td>
<td>0.88</td>
<td>[0.53, 1.48]</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>Aalders 1980</td>
<td>19/123</td>
<td>21/138</td>
<td>36.70</td>
<td>1.02</td>
<td>[0.57, 1.80]</td>
<td>0.00</td>
<td>0.08</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>377</td>
<td>407</td>
<td>100.00</td>
<td>0.88</td>
<td>[0.62, 1.24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 50 (Treatment), 52 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

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**Figure 2.** Subgroup analysis of patients with at least one high risk factor, stage 1c or grade 3. (A) Death from all causes. (B) Endometrial carcinoma-related death.
It can be argued that pelvic and paraaortic lymphadenectomy will detect micrometastasis in the regional lymph nodes and decrease the benefits of adjuvant external beam radiotherapy. Two trials, GOG study and Soderini 2003 included such patients. The meta-analysis on these two trials, however, did not confirm this presumption (Figure 5A and B). Like the overall meta-analysis results, external beam
radiotherapy reduced all recurrences in this group of patients (RR 0.47, 95% CI 0.28–0.77, P = 0.003) although there was no reduction in death from all causes (RR 0.72, 95% CI 0.26–1.97, P = 0.52).

complications and side-effects
A meta-analysis could not be done as not all the included studies report the exact frequency of the acute and late side-effects. In the PORTEC 1, the 5-year actuarial rates of late complications (all grades) were 26% in the pelvic radiotherapy group and 4% in the control group (P < 0.0001). The majority of patients experienced mild symptoms though and ~3% of treated patients had severe complications. In GOG study, the majority of treated patients also experienced mild symptoms (63% experienced grade 1 or 2 GI side-effects and only 5% experienced grade 3 or 4 GI side-effects). Six women in the radiotherapy arm experienced grade 3 or 4 intestinal obstruction versus only one in the control group. Two women in the radiotherapy arm died from complications involving intestinal injury thought to be radiation related. In the Aalders study, of the patients who received intravagina radium brachytherapy alone, one patient developed a rectovaginal fistula and one developed a urethral stricture. Of the patients who received additional pelvic radiotherapy, two women had severe complications related to radiotherapy and one woman developed radiotherapy-related bladder necrosis necessitating a partial bladder resection.

discussion
The meta-analysis comprised a heterogeneous group of patients with different prognostic factors, ranging from stage 1b/1c to occult stage II and tumour grade 1 to grade 3. Despite the heterogeneity, all the trials showed the same trend for adjuvant external beam radiotherapy to reduce locoregional recurrence in stage 1 endometrial cancer. There was, however, no reduction in the risks of death (from all causes), distant recurrence and endometrial cancer death despite the reduction in the risk of locoregional recurrence. Many patients recruited to the studies were at low risk of recurrence and death. In addition, many of the patients were in an older age group and many of the deaths reported in the studies did not appear to be cancer related. We thought that the four RCTs reviewed might lack the power to detect survival benefit even if there was a true difference. We did subgroup analysis on patients with various risk factors to see whether adjuvant radiotherapy had a survival benefit in patients with different risk factors. And we showed that there was a trend for external beam radiotherapy to reduce deaths from all causes and endometrial cancer for patients with at least two risk factors (most with grade 3 and stage 1c) although neither outcome was statistically significant (which maybe due to low number of patients). The subgroup analysis on patients without these risk factors showed that radiotherapy caused additional treatment-related deaths. This subgroup of patients, who have well-differentiated tumours with minimal invasion have a recurrence risk of ~2% and radiotherapy is clearly inappropriate. The PORTEC I study recommended omitting adjuvant pelvic radiotherapy for stage 1 endometrial cancer patients <60 years and patients with grade 2 tumours with superficial invasion because the analysis of prognostic factors in the study showed that these patients have a low absolute risk of locoregional relapse.

Although this review was not designed to answer whether diagnostic lymphadenectomy has a value in stage 1 endometrial...
cancer, two of the above trials included only patients who had pelvic and paraaortic lymphadenectomy. The subgroup analysis on these two trials showed that radiotherapy reduced all recurrences even after pelvic and paraaortic lymphadenectomy although it did not reduce deaths from all causes. Lymphadenectomy increases permanent radiation lymphoedema risks and there is a greater treatment-related death rate with lymphadenectomy in the ASTEC trial. So far, preliminary reports from the UK ASTEC trial show eight treatment-related deaths from 704 women who were randomised to conventional surgery plus lymphadenectomy compared with two from 704 who had conventional surgery alone [18]. The benefit of diagnostic lymphadenectomy will be clearer when ASTEC trial is published.

The majority of the recurrences are due to vaginal vault recurrences which may be salvageable and may be preventable by vaginal intracavity brachytherapy. In a prospective study [11], patients with low-risk endometrial cancer (stage I, grade 1 to 2 and <50% myometrial invasion) were treated with postoperative vaginal radium/caesium alone without external beam pelvic radiotherapy and the 5-year estimated disease-free survival was 99%. In the PORTEC study, 75% of endometrial cancer patients with pelvic recurrence after previous external beam radiotherapy treatment could be treated with curative intent and 85% of which achieved complete remission. Prophylactic adjuvant radiotherapy does reduce local recurrence but selective salvage therapy may be just as effective and vaginal brachytherapy may be adequate prophylaxis for local recurrent disease. This issue is being explored prospectively in the current Dutch PORTEC 2 trial which is a multicentre randomised phase III trial comparing the external beam radiotherapy and vaginal brachytherapy. This study may be able to answer whether postoperative vaginal brachytherapy alone is adequate in preventing vaginal relapse with a reduction of treatment-related morbidity and a better QOL in patients although the trial seems to include patients with one high-risk feature (stage 1c, grade 3, stage 2a and age 60, see ongoing study for inclusion criteria). For patients with several high-risk features, the current evidence available would support external beam radiotherapy since it definitely reduced the risk of locoregional recurrence with a trend towards reduction in the risks of death from all causes and endometrial cancer.

The review showed that adjuvant radiotherapy did not prevent distant recurrence. The next obvious question is whether adjuvant chemotherapy will be more beneficial in high-risk endometrial carcinoma. There is a trial published recently of adjuvant chemotherapy versus external beam radiotherapy in patients with high-risk endometrial carcinoma (stage Ic grade 3, II grade 3 and III) [8]. The trial failed to show the difference between adjuvant chemotherapy and radiotherapy in the impact on OS or progression-free survival. However, the cumulative incidence of distant relapses was lower in patients who had adjuvant chemotherapy. Conversely, the rate of local recurrence was lower in patients who had adjuvant radiotherapy compared with those who had adjuvant chemotherapy. Therefore, there is a rationale for combined adjuvant chemotherapy and radiotherapy in high-risk endometrial carcinoma patients either concurrently or sequentially. The question may be answered by EORTC 55991 trial which is a randomised study of adjuvant radiation therapy with or without chemotherapy in high-risk patients (stage Ic and grade 3 or occult stage II, clear cell, serous papillary, undifferentiated pathology) and the results from this trial have not been published.

For the ongoing adjuvant radiotherapy studies or studies awaiting analysis, the survival advantage estimate will be more precise in 5 years, when the mature data from the NCIC Clinical Trials Group (CAN-NCIC-ENS) and Medical Research Council (UK) ASTEC are available. Long-term outcome data are important as pelvic relapses occur late, and after a relapse, median survival times in excess of 3 years are reported. We hope to obtain mature data from these trials when they are available and to include them in the meta-analysis in future updates.

In conclusion, the data showed that external beam pelvic radiotherapy should be considered in patients with multiple high-risk factors including stage 1c and grade 3 since it reduced locoregional recurrence with a trend towards reduction in deaths from all causes and endometrial cancer. However, it carries an inherent risk of damage and toxicity and should be avoided in stage 1 endometrial cancer patients with no high-risk factors.

Acknowledgements

We would like to thank the following people: (i) Dr. Nick Johnson (Consultant Gynaecologic Oncologist) and Dr. Paul Cornes (Consultant Clinical Oncologist) from the Royal United Hospital in Bath for the critical comments of the reviews and sharing of the raw data from A. Scholten and C. Creutzberg of the PORTEC 1. (ii) V. Garner of the Cochrane Gynaecological Cancer Review Group (CGCGR) for obtaining papers (iii) A. M. Swart, C. Amos, M. Parmar and E. Eisenhauser from the ASTEC study group for contacting GOG-99 on behalf of our group and providing the information on the ASTEC study. (iv) H. Dickinson for her critical comments on the methods of review (with advice on what to include in text) as well as statistical input on the analysis. (v) M. Powell, Consultant Clinical Oncologist at St Bartholomew’s Hospital, London and M. Quigley, Consultant Clinical Oncologist at Oldchurch Hospital, Romford for reviewing the initial draft of this review. (vi) G. Quinn, CGCGR coordinator for her editing the review and coordinating between various reviewers. We are grateful to the Department of Health (UK) for funding the CGCGR and for access to the Cochrane Library and statistical expertise.

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