Adjuvant radiotherapy and chemoradiation after surgery for cervical cancer (Review)

Rogers L, Siu SSN, Luesley D, Bryant A, Dickinson HO

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[Intervention Review]

Adjuvant radiotherapy and chemoradiation after surgery for cervical cancer

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ABSTRACT

Background

There is an ongoing debate about the indications for, and value of, adjuvant pelvic radiotherapy after radical surgery in women with early cervical cancer. Certain combinations of pathologic risk factors are thought to represent sufficient risk for recurrence, that they justify the use of post-operative pelvic radiotherapy, though this has never been shown to improve overall survival, and use of more than one type of treatment (surgery and radiotherapy) increases the risks of side-effects and complications.

Objectives

To evaluate the effectiveness and safety of adjuvant therapies (radiotherapy, chemotherapy followed by radiotherapy, chemoradiation) after radical hysterectomy for early stage cervical cancer (FIGO stages IB1, IB2 or IIA).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Issue 4, 2008. The Cochrane Gynaecological Cancer Group Trials Register, MEDLINE (January 1950 to November 2008), EMBASE (1950 to November 2008). We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.

Selection criteria

Randomised controlled trials (RCTs) that compared adjuvant therapies (radiotherapy, chemotherapy followed by radiotherapy, or chemoradiation) with no radiotherapy or chemoradiation, in women with a confirmed histological diagnosis of early cervical cancer who had undergone radical hysterectomy and dissection of the pelvic lymph nodes.

Data collection and analysis

Two review authors independently abstracted data and assessed risk of bias. Information on grade three and four adverse events was collected from the trials. Results were pooled using random effects meta-analyses.

Main results

Two RCTs, which compared adjuvant radiotherapy with no adjuvant radiotherapy, met the inclusion criteria; they randomised and assessed 397 women. Meta-analysis of these two RCTs indicated no significant difference in survival at five years between women who received radiation and those who received no further treatment (Relative risk (RR) = 0.8, 95% Confidence interval (CI): 0.3 to 2.4). However, women who received radiation had a significantly lower risk of disease progression at five years (RR = 0.6, 95% CI 0.4 to 0.9).

Although the risk of serious adverse events was consistently higher if women received radiotherapy rather than no further treatment, these increased risks were not statistically significant, probably because the rate of adverse events was low.

Authors' conclusions

We found evidence, of moderate quality, that radiation decreases the risk of disease progression compared with no further treatment, but little evidence that it might improve overall survival. The evidence on serious adverse events was equivocal.

PLAIN LANGUAGE SUMMARY

Radiotherapy, or a combination of radiotherapy and chemotherapy, after surgery for early stage cervical cancer

At present, doctors are not sure whether women with early cervical cancer who have had their womb and pelvic lymph nodes removed should be given radiotherapy. If the woman has a combination of certain risk factors which put her at high risk of having a recurrence of her cancer, doctors often think that it would be a good idea to give her radiotherapy. However, radiotherapy has never been shown to improve overall survival for these women and the combination of surgery and radiotherapy increases the risk of side-effects and complications. We searched for all the available RCTs that assessed whether radiotherapy (with or without chemotherapy) could improve survival in these women.

We found only two trials that compared the use of radiotherapy with no radiotherapy in women with early cervical cancer who had their womb and pelvic lymph nodes removed and who were at risk of having a recurrence of their cancer. These two trials enrolled 397 women. When we combined the findings from these two trials, we found that, on average, women who received radiotherapy were between 40% and 90% less likely to have a relapse of their cancer within five years than women who did not. However, because of the low number of deaths in the trials, we could not confirm whether radiotherapy helped to prolong life: our best estimate was that, five years after treatment, women who received radiotherapy were about 20% more likely to be alive than those who did not, but this estimate may not be very accurate and women's actual prospects could be anywhere between being three times more likely to be alive and being 60% more likely to be dead.

Although women who had radiotherapy tended to have more complications than women who did not, we couldn't be sure whether this was due to chance rather than the radiotherapy because few women reported complications.

The main limitations of the review were that we did not find any trials that evaluated a combination of radiotherapy and chemotherapy and that the two trials of radiotherapy gave very little information about side effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Adjuvant radiotherapy after surgery for cervical cancer

Patient or population: patients with early stage cervical cancer (FIGO stages IB1, IB2 or IIA)
Settings: Inpatient or outpatient
Intervention: Adjuvant radiotherapy after surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Adjuvant radiotherapy after surgery				
Death within 5 years	Study population		RR 0.84 (0.3 to 2.36)	397 (2 studies)	⊕⊕⊕○ moderate[1]	
	160 per 1000	134 per 1000 (48 to 378)				
	Medium risk population					
	124 per 1000	104 per 1000 (37 to 293)				
Disease progression within 5 years	Study population		RR 0.58 (0.37 to 0.91)	397 (2 studies)	⊕⊕⊕○ moderate[2,3]	
	210 per 1000	122 per 1000 (78 to 191)				
	Medium risk population					
	164 per 1000	95 per 1000 (61 to 149)				
Haematological adverse events (grade 3-4)	Study population		RR 2.38 (0.63 to 9.05)	388 (2 studies)	⊕⊕⊕○ moderate[4]	

	15 per 1000	**36 per 1000** (9 to 136)			
	Medium risk population				
	20 per 1000	**48 per 1000** (13 to 181)			
Gastrointestinal adverse events (grade 3-4)	**Study population**		**RR 7.32** (0.91 to 58.82)	388 (2 studies)	⊕⊕⊕○ **moderate**[4]
	0 per 1000	**0 per 1000** (0 to 0)			
	Medium risk population				
	0 per 1000	**0 per 1000** (0 to 0)			
Genitourinary adverse events (grade 3-4)	**Study population**		**RR 2.12** (0.54 to 8.37)	388 (2 studies)	⊕⊕⊕○ **moderate**[4]
	15 per 1000	**32 per 1000** (8 to 126)			
	Medium risk population				
	16 per 1000	**34 per 1000** (9 to 134)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Inconsistent evidence about 5-year survival, so the pooled estimate had wide CIs: thus uncertainty whether radiotherapy improves survival or increases the risk of death.

[2] Inconsistent evidence about 5-year progression-free survival, so the pooled estimate had wide CIs: thus uncertainty whether radiotherapy improves time to disease progression or increases the risk of progression.

[3] Imprecision in point estimate for Bilek 1982, indicated by large CI due to low number of women with disease progression, resulting in increased uncertainty in pooled estimate. However the overall precision of the pooled estimate is satisfactory as the larger study of GOG 92 is given substantially more weight.

[4] Large CI in pooled estimate

BACKGROUND

Description of the condition

Cervical cancer is the second most common cancer and the third most common cause of cancer death in women worldwide, and the leading cause of cancer death in women in developing countries (GLOBOCAN 2002). Worldwide it accounts for around 10% of all cancers diagnosed in women. A woman's risk of developing cervical cancer by age 65 years ranges from 0.8% in more developed countries to 1.5% in less developed countries (IARC 2002). The risk of dying from cervical cancer is 0.2% and 0.8% in more and less developed countries respectively. In Europe, about 60% of women with cervical cancer are alive five years after diagnosis (EUROCARE 2003).

FIGO subdivides cervical cancers into four groups or stages, where stage I disease is confined to the cervix, and stage II tumours invade beyond the uterus, but not to the pelvic sidewall or lower third of the vagina. Stage III tumours extend to the pelvic sidewall and/ or involve the lower third of the vagina and/ or cause a swollen or a non-functioning kidney (hydronephrosis), and stage IV tumours invade other pelvic organs or have distant metastases (Benedet 2000).

Description of the intervention

The treatment of cervical cancer is determined by the stage of the disease. Early cervical cancer (FIGO stage IA, IB and IIA) is a curable condition, and doctors aim to use as few types of treatment as possible to achieve cure, because using more than one increases treatment-related side-effects and complications. An adjuvant treatment is a supplementary treatment, which is given to decrease the risk of the cancer recurring.

Microinvasive carcinoma of the cervix (FIGO stage IA1 and IA2) has a low risk of spread beyond the cervix, and is usually cured by non-radical operations such as a cone biopsy, trachelectomy (excision of the cervix) or simple hysterectomy.

FIGO stage IB1, IB2 or IIA cervical cancer have no standard management, as both radical surgery and radiotherapy have been shown to be equally effective, with 5-year survival rates of 87% to 92% (Gray 2008; Peters 2000), though they differ in terms of side-effects and complications. Stage IB1 disease is usually treated surgically, with radical hysterectomy and dissection of the pelvic lymph nodes (PLND). There is conflicting evidence regarding the management of stage IB2 and stage IIA tumours: some are treating these women with primary radical surgery, followed by adjuvant radiotherapy with or without chemotherapy, while others are using chemoradiation as a primary therapy. Neoadjuvant chemotherapy followed by radical surgery is used as an alternative therapy for these bulkier tumours (Kesic 2006).

After radical surgery, certain pathologic factors are thought to influence risk of recurrence and progression-free survival (PFS), and are therefore indications for adjuvant therapy, which usually consists of radiotherapy with concurrent chemotherapy. These risk factors include: positive pelvic lymph nodes, lower uterine segment involvement, involvement of lymphatics and blood vessels (lymphvascular space involvement or LVSI), deep invasion of tumour into the substance or stroma of the cervix, involvement of the tissue next to the cervix (parametria), non-squamous histologic subtype, tumour grade, vaginal margin involvement, and tumour size >4cm. When one or more of these factors is found, the 5-year survival drops to between 50% and 70% (Peters 2000).

It has long been recognised that using more than one treatment modality results in a very substantial increase in the number and severity of treatment complications and side-effects, such as leg swelling due to lymphatic obstruction (lymphoedema), sexual dysfunction, urinary frequency, diarrhoea or constipation, and bowel obstruction. GOG #92 reported that while adjuvant radiotherapy reduced the risk of pelvic recurrence by only 39%, severe and life-threatening toxicity was reported in 6% of irradiated patients compared to 2% in patients randomised to no further treatment (Sedlis 1999). Peters 2000 reported 27 episodes of grade 4 toxicity in 21 of the 122 (17%) patients in their chemoradiation after radical surgery arm, most of which were haematologic; while only 4 of 112 patients (4%) treated with radiation alone after radical surgery had grade 4 toxicity (Peters 2000). It is therefore important to weigh up the risks and benefits of the use of adjuvant radiotherapy and chemotherapy after radical surgery for each individual patient, in order to maximise their PFS while minimising their treatment-related morbidity.

Why it is important to do this review

The aim of this review is to establish the impact of adjuvant radiotherapy and chemoradiation after surgery in early cervical cancer, on overall and disease-free survival, as well as on treatment-related morbidity and mortality, and quality of life (QOL). The role of adjuvant chemotherapy in cervical cancer is the subject of a separate review (Rosa 2005).

Since the publication of Guttmann 1970 on the significance of post-operative irradiation in carcinoma of the cervix, doctors have been debating the indications for, and value of, adjuvant radiotherapy after radical surgery in cervical cancer. After GOG #92 showed that adjuvant radiotherapy reduced the number of recurrences, the debate has changed to whether this benefit is enough to outweigh the attendant risks.

To our knowledge there has been no previous systematic review of this subject.

OBJECTIVES

To evaluate the effectiveness and safety of adjuvant therapies (radiotherapy, chemotherapy followed by radiotherapy, chemoradiation) after radical hysterectomy for early stage cervix cancer (stages IB1, IB2 or IIA). In particular, we sought to evaluate whether these interventions improve survival and to assess any associated morbidity.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs.

Types of participants

Women with a confirmed histological diagnosis of early cervical cancer (FIGO stage stages IB1, IB2 or IIA) who had radical hysterectomy and pelvic lymph node dissection (PLND). The review included (but was not restricted to) women who may have had any of the following risk factors or any combination of them: positive pelvic lymph nodes, parametrial or vaginal margin involvement, lymphvascular space involvement, lower uterine segment involvement, deep stromal invasion, non-squamous histology, high grade tumours, or tumours > 4 cm in size.

Types of interventions

Only studies that addressed radiotherapy or chemoradiation in the adjuvant setting were included. The following intervention and control groups were eligible:

Interventions:

- Radiotherapy alone, or
- Chemotherapy followed by radiotherapy, or
- Chemoradiation (chemotherapy given concurrently with radiotherapy)

Controls:

- No adjuvant chemotherapy or radiotherapy

Comparisons were restricted to those that compared an intervention with a control that is similar in all respects, except that radiotherapy or chemoradiation was not included in the treatment regimen. Chemotherapy was not limited to platinum-based regimens only, as this would have excluded some earlier trials which may have utilised other chemotherapy regimens.

Types of outcome measures

Primary outcomes

1. Overall survival (OS) (time from entry into the trial until death from any cause)

Secondary outcomes

1. Progression-free survival (PFS) (time from entry into the trial until progression of the disease or death)
2. Disease recurrence
3. QOL, measured by a validated scale
4. Adverse events, classified according to CTCAE 2006:
    - haematological or blood (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage)
    - gastrointestinal or bowel (nausea, vomiting, anorexia, diarrhoea, proctitis, bowel obstruction)
    - genitourinary (sexual dysfunction, urinary frequency, haematuria, incontinence, renal failure)
    - skin (stomatitis, mucositis, desquamation, alopecia, allergy)
    - lymphoedema (swelling of the legs due to lymphatic obstruction)
    - infection
    - neurological or nervous system (peripheral and central)
    - pulmonary or lung (dyspnoea)
    - general (weakness, fatigue, lethargy, malaise)

Search methods for identification of studies

Papers in all languages were sought and translations were carried out as necessary.

Electronic searches

Searches were conducted to identify all published and unpublished RCTs addressing the use of adjuvant radiotherapy and chemoradiation for early stage cervix cancer. Trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL) The Cochrane Library Issue 4, 2008, MEDLINE (January 1950 to November 2008), EMBASE (1950 to Novermber 2008), Cochrane Gynaecological Cancer Group Trials Register.
The Medline search strategy for is presented in Appendix 1. EMBASE is presented in Appendix 2 and CENTRAL is presented in Appendix 3.
Databases were searched from 1990 until 2008.
CENTRAL,The National Research Register (NRR) and Clinical Trials Register were searched in all fields using the following words: cervix cancer, cervical cancer, adjuvant radiotherapy, adjuvant chemoradiation, early stage.

Searching other resources

Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and Gynaecologic Oncologists of Canada (http://www.g-o-c.org) were searched for ongoing trials. The main investigators of any relevant ongoing trials were contacted for further information, as were any major co-operative trials groups active in this area.

The citation list of relevant publications, abstracts of scientific meetings and list of included studies were checked through hand searching and experts in the field were contacted to identify further reports of trials. Reports of conferences were hand searched in the following sources:

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncologists)
- International Journal of Gynecological Cancer (Annual Meeting of the International Gynecologic Cancer Society)
- British Journal of Cancer
- British Cancer Research Meeting
- Annual Meeting of European Society of Medical Oncology (ESMO)
- Annual Meeting of the American Society of Clinical Oncology (ASCO)

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to the reference management database Endnote, duplicates were removed and the remaining references were examined by two review authors (LR and SS) independently. Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers was assessed independently by two review authors (LR and SS). Disagreements were resolved by discussion between the two review authors and if necessary by a third review author (DL). Reasons for exclusion were documented.

Data extraction and management

For included studies, data were extracted as recommended in Chapter 7 of the Cochrane Handbook (Higgins 2008). This included data on:

- Author, year of publication (if published) and journal citation (including language)
- Country
- Setting
- Study design, methodology
- Study population
    - Total number enrolled
    - Patient characteristics (inclusion and exclusion criteria, age, FIGO stage, histological cell type, co-morbidity, previous treatment, number enrolled in each arm)
- Intervention/control details
    - Type of chemotherapy, number of cycles and dose
    - Timing and dose of radiotherapy
- Risk of bias in study - see below
- Duration of follow-up
- Deviations from protocol

and

- Outcomes: Data on all primary and secondary outcomes that are reported were extracted as below:

    - For time to event (OS or PFS) data, we extracted the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these were not reported, we estimated them from other reported statistics using the methods of Parmar 1998. We abstracted site of recurrence, where possible.
    - For dichotomous outcomes (e.g. adverse events, deaths and disease recurrences if it was not possible to use a hazard ratio), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio. We abstracted adverse events by grade of toxicity.
    - The time points at which outcomes were collected and reported were noted.

Both unadjusted and adjusted statistics were extracted, if reported. If adjusted statistics were reported, we noted the variables used in adjustment.

Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in groups to which they were assigned.

Data were abstracted independently by two review authors (LR, SS) onto a data abstraction form specially designed for the review (see Appendix 4). Differences between review authors were resolved by discussion or by appeal to a third review author (DL or HD) if necessary.

Assessment of risk of bias in included studies

Risk of bias in included RCTs was assessed using the following criteria:

Sequence generation

We coded the randomisation of participants to intervention groups as:

- Yes: e.g. a computer-generated random sequence or a table of random numbers
- No: e.g. date of birth, clinic id-number or surname
- Unclear: e.g. not reported

Allocation concealment

We coded the concealment of allocation sequence from treatment providers and participants as:

- Yes: e.g. where the allocation sequence could not be foretold
- No: e.g. allocation sequence could be foretold by patients, investigators or treatment provider
- Unclear: e.g. not reported.

Blinding

We coded the blinding of healthcare professionals who assessed disease progression as:

- Yes
- No
- Unclear.

Incomplete reporting of outcome data

We recorded the proportion of participants whose outcomes were analysed.

We coded loss to follow-up for each outcome as:

- Yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
- No, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms
- Unclear if loss to follow-up was not reportedNo, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms

Selective reporting of outcomes

We coded whether studies are free of selective outcome reporting as follows:

- Yes: e.g. if all outcomes that are specified above and also pre-specified in the study were reported in the study
- No
- Unclear

Other potential threats to validity

We assessed whether studies were apparently free of other problems that could have put them at a high risk of bias as:

- Yes
- No
- Unclear

Measures of treatment effect

We used the following measures of the effect of treatment:

- For time to event data, we used the hazard ratio (HR), if possible.
- For dichotomous outcomes, we used the risk ratio (RR).

Dealing with missing data

We did not impute missing outcome data; if only imputed outcome data were reported, we planned to contact trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity

Heterogeneity between studies was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001). .

Assessment of reporting biases

As only two trials met our inclusion criteria, we did not perform the planned assessment of reporting bias (see Differences between protocol and review).

Data synthesis

Results were pooled in meta-analyses using random effects models with inverse variance weighting (DerSimonian 1986). Adjusted summary statistics were used if available; otherwise unadjusted results were used.

- For time-to-event data (OS and PFS), HRs were pooled using the generic inverse variance facility of RevMan 5.
- For dichotomous outcomes (deaths, disease recurrence, adverse events), RRs were pooled.

Subgroup analysis and investigation of heterogeneity

As only two trials met our inclusion criteria, we did not perform the planned sub-group analyses (see Differences between protocol and review).

Sensitivity analysis

As only two studies met our inclusion criteria, we did not perform the planned sensitivity analyses (see Differences between protocol and review).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The search strategy identified 824 unique references. The title and abstract screening of these references identified three studies as potentially eligible for this review. The full text screening of these three studies excluded one study for the reasons described in the table Characteristics of excluded studies. The remaining two RCTs met our inclusion criteria.
Searches of the grey literature did not identify any additional relevant studies.

Included studies

The two included trials, which are described in detail in Characteristics of included studies, randomised 397 women, all of whom were assessed at the end of the trials. Both trials compared adjuvant radiotherapy with no adjuvant radiotherapy.
GOG #92 (Rotman 2006) reported 67 deaths and 79 disease recurrences; Bilek 1982 reported 6 deaths and 6 disease recurrences; GOG #92 (Rotman 2006) reported 14 instances of severe adverse effects in 12 patients; Bilek 1982 reported 23 instances of adverse effects but it was unclear whether these were all in different women.
The proportion of women who died within five years was considerably lower in the trial of Bilek 1982 (6/120 (5%)) than in GOG #92 48/277 (17%). This was largely because women in the Bilek 1982 trial had shorter average follow-up, but probably also because the GOG #92 trial included older women. It could also be due to different pathologic risk factors among patients in the two trials; Bilek 1982 did not report these.

GOG #92 trial

The GOG #92 trial was designed to establish whether post-operative pelvic radiotherapy would reduce recurrence rates and mortality in stage 1B cervical cancer patients with negative lymph nodes, but any combinations of the following risk factors: large tumour diameter, deep stromal invasion, and lymphvascular space invasion. Of the 277 eligible patients, 137 were randomly assigned to radiotherapy (RT), and 140 to no further treatment (NFT). Patients in the RT group received external beam radiotherapy in doses between 46Gy in 23 fractions to 50.4Gy in 28 fractions, and no brachytherapy.
The median age of the included patients was 41 years (range: 20 to 80 years), and most tumours (79%) were squamous . The distribution of individual risk factors was not balanced between the two different treatment regimens, but the overall risk for recurrence was very similar for each regimen when all risk factors were considered as a group.
Women were followed up for a median of 120 months (range: 0 to 192 months).

The Bilek 1982 trial

The trial of Bilek 1982 is a much older study, which aimed to report the treatment results and treatment-related morbidity of 120 women with stage 1B cervical cancer. Sixty women were randomised to no further treatment (NFT) after radical hysterectomy, while another sixty women received 52Gy of whole pelvic external beam radiotherapy (RT), at a rate of 2Gy per day.
The median age was 42 years (range: 23 to 59 years) in the NFT group, and 39 years (range: 23 to 60 years) in the RT group. All tumours in this study were squamous carcinomas. It was reported that there were no significant differences between the groups with regard to prognostic factors, but details of prognostic factors in the two groups were not presented,
Women were followed up for a mean of 44 months (range: 24 to 72 months).

Outcomes reported

Both studies reported OS. The GOG #92 trial reported HRs for OS, disease recurrence (based on time to evidence of disease recurrence or date when patient was last seen) and PFS (survival until disease recurrence or death) and also the number of women who had disease recurrence or died after 5 years and 12 years follow-up. The trial of Bilek 1982 did not report HRs; although it presented a survival plot, so we were unable to estimate a HR using the methods of Parmar 1998 since the plot was based on only six deaths. However, it was possible to deduce from the survival plot and supporting text the number of participants who died within five years; the number of women who had disease recurrence was also reported.
Adverse events (hematologic, gastrointestinal and genitourinary side effects) were reported in both trials. Additionally the GOG #92 trial reported neurologic side effects, and the trial of Bilek 1982 reported lymphoedema, rectal or sigmoid strictures and hydronephrosis. The GOG #92 trial reported only grade 3 and 4 adverse effects but the trial of Bilek 1982 had no such restriction.

Excluded studies

The trial of Lahousen 1999 was a multi-centre RCT which randomised women who had undergone a radical hysterectomy for either chemotherapy, radiation therapy or observation. Radiation therapy consisted of total pelvic external irradiation with 50Gy, where the treatment was given within - 21 days after surgery. This study was excluded as 19 of the 76 women enrolled had stage IIB disease and we were unable to extract the outcomes separately for women without stage IIB disease.

Risk of bias in included studies

Both studies were at high risk of bias: they satisfied only one of the criteria that we used to assess risk of bias - see Figure 1, Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

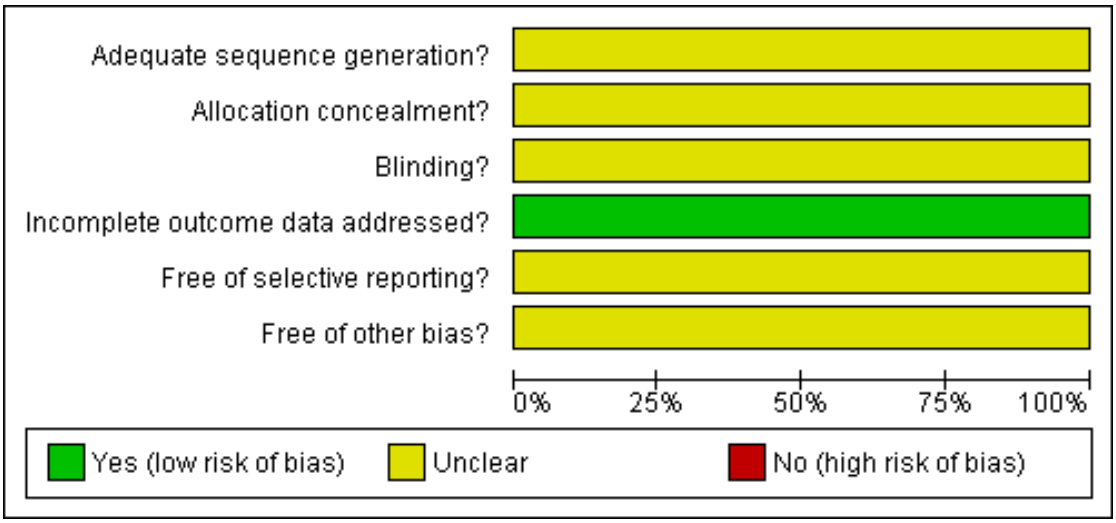
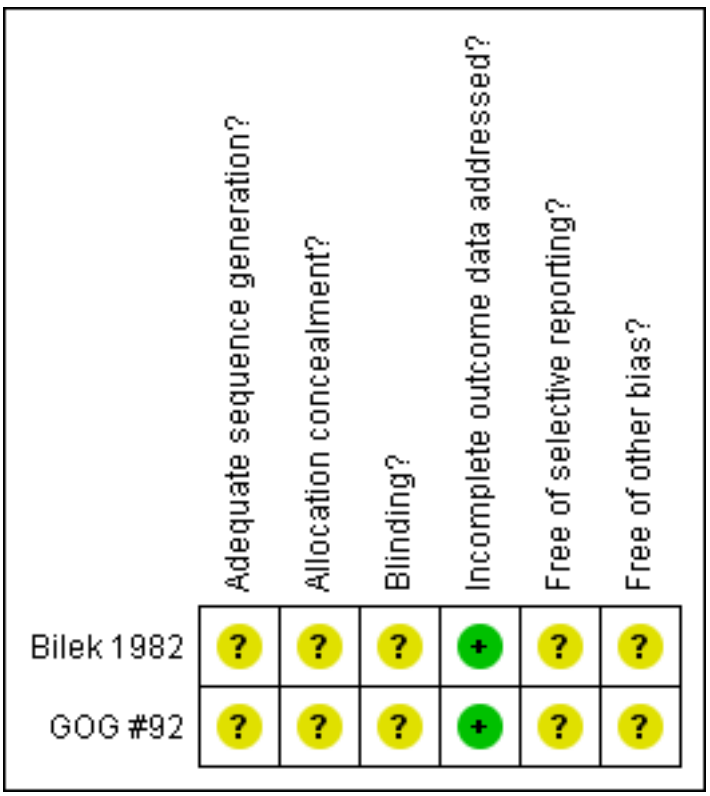


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Neither study reported the method of generation of the sequence of random numbers used to allocate women to treatment arms, or concealment of this allocation sequence from patients and health-care professionals involved in the study, or blinding of the health-care professionals who assessed disease progression. It was unclear whether the studies reported all the outcomes that they assessed or if any additional bias have been present. However, in both studies, all women who were enrolled were assessed at endpoint.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: comparison of radiotherapy with no further treatment

Survival

Overall survival

Analysis 1.1. Using a HR to compare the survival experience of women in the two treatment groups, the GOG #92 trial found no statistically significant difference in OS between the radiation and control groups, after adjustment for capillary lymphatic space status , depth of invasion , and tumour size (HR= 0.7, 95% CI 0.5 to 1.1).

However, in a sub-group analysis of OS by prognostic category, GOG #92 found that patients with a combination of negative capillary lymphatic space, deep stromal invasion and tumour size greater than 4cm had a significantly lower risk of death if they received radiotherapy. Results were inconclusive for other sub-groups.

Deaths within 5 years

Analysis 1.2. Meta-analysis of both trials (Bilek 1982; GOG #92) showed little difference in the risk of death within five years of treatment in women who received radiotherapy and those who received no further treatment (RR= 0.8, 95% CI 0.3 to 2.4). There was moderate heterogeneity between trials (I^2 = 43%).

Progression free survival

Analysis 1.3 Using a HR to compare PFS of women in the two treatment groups the GOG #92 trial found that women who received radiotherapy had a significantly lower risk of disease progression than women who received no further treatment (HR = 0.6, 95% CI 0.4 to 0.9).

Furthermore, only 9% (3 of 34) of the patients with adenocarcinoma or adenosquamous tumours in the radiotherapy arm had disease recurrence, compared with 44% (11 of 25) in the no further treatment arm, suggesting that radiotherapy may be beneficial for patients with non-squamous histology.

Disease recurrence within 5 years

Analysis 1.4. Meta-analysis of both trials (Bilek 1982; GOG #92) showed that women who received radiotherapy had a significantly lower risk of disease progression within five years of treatment than women who received no further treatment (RR = 0.6, 95% CI 0.4 to 0.9). There was no heterogeneity between trials (I^2 = 0%).

Recurrence-free survival

Analysis 1.5. Sensitivity analysis combining the unadjusted relative risk of recurrence in the trial of Bilek 1982 with HRs adjusted for prognostic factors for GOG #92 yielded similar results (HR = 0.6, 95% CI 0.4 to 1.0), with no heterogeneity between trials (I^2 = 0%).

Grade 3-4 adverse events

Hematologic

Analysis 1.6. Meta-analysis of both trials (Bilek 1982; GOG #92) showed no statistically significant difference in the risk of hematologic side effects (abnormalities of the blood) in women who received radiation therapy and those who received no further treatment (RR = 2.4, 95% CI 0.6 to 9.0). There was no heterogeneity between trials (I^2 = 0%).

Gastrointestinal

Analysis 1.7. Meta-analysis of both trials (Bilek 1982; GOG #92) showed no statistically significant difference in the risk of gastrointestinal (bowel) side effects in women who received radiation therapy and those who received no further treatment (RR = 7.3, 95% CI 0.9 to 58.8). There was no heterogeneity between trials (I^2 = 0%).

Rectal/sigmoid strictures

Analysis 1.8. The trial of Bilek 1982 showed no statistically significant difference in the risk of rectal or sigmoid strictures (scarring caused by radiotherapy, that can lead to bowel obstruction) in women who received radiation therapy and those who received no further treatment (RR= 7.0, 95% CI 0.4 to 132.7).

Genitourinary

Analysis 1.9. Meta-analysis of both trials (Bilek 1982; GOG #92) showed no statistically significant difference in the risk of genitourinary side effects in women who received radiation therapy

and those who received no further treatment (RR = 2.1, 95% CI 0.5 to 8.4). There was no heterogeneity between trials (I^2 = 0%).

Lymphoedema

Analysis 1.10 The trial of Bilek 1982 showed no statistically significant difference in the risk of lymphoedema in women who received radiation therapy and those who received no further treatment (RR= 2.4, 95% CI 0.9 to 6.4).

Hydronephrosis

Analysis 1.11. The trial of Bilek 1982 showed no statistically significant difference in the risk of hydronephrosis (swelling of the kidney due to obstruction of the ureters) in women who received radiation therapy and those who received no further treatment (RR = 2.0, 95% CI 0.2 to 21.5).

Neurologic

Analysis 1.12. The GOG #92 trial showed no statistically significant difference in the risk of neurologic (nervous system) side effects in women who received radiation therapy and those who received no further treatment (RR = 3.3, 95% CI 0.1 to 79.8).

DISCUSSION

Summary of main results

We found only two trials, enrolling 397 women, that met our inclusion criteria. These trials compared the use of radiotherapy with no radiotherapy in women with early cervical cancer who had radical hysterectomy and PLND and who were at high risk of disease recurrence.

These trials showed that adjuvant radiotherapy after radical surgery significantly decreases local recurrence rates, but provides only weak evidence that it might improve OS. When we combined the findings from these two trials, we found that, on average, the risk of relapse within five years among women who received radiotherapy was between 40% and 90% of the risk among women who did not (RR = 0.6, 95% CI 0.4 to 0.9). However, because of the low number of deaths in the trials, we could not confirm whether this apparently beneficial effect translated into better survival: five years after treatment the risk of death among women who received radiotherapy was, on average, 80% of the risk among women who did not, but the 95% confidence interval was wide, ranging from a much lower risk of death to over twice the risk (RR = 0.8, 95% CI: 0.3 to 2.4) - see Summary of findings for the main comparison. .

The trials had two major limitations. Firstly, they gave very little information about adverse events. Although we found no statistically significant difference in risk of grade 3 and grade 4 adverse events in women who did and did not receive radiotherapy, this was largely because the trials reported very few side effects and so lacked the statistical power to detect any difference in risk that might be present. Overall the risk of adverse events was consistently higher among women who received radiotherapy. Secondly, the evidence from these trials does not assist us in determining which pathological risk factors, or combinations of risk factors, indicate that women should be treated with adjuvant radiotherapy.

Overall completeness and applicability of evidence

We did not find any studies that assessed either chemoradiation or chemotherapy followed by radiotherapy. Hence the available evidence addresses radiotherapy alone.

Although we specified QOL as an outcome of interest, neither trial reported this. QOL after treatment for cancer is an extremely important outcome, as treatment-related morbidity very often degrades the quality of the time that patients live in the future.

Current practice definitely differs from centre to centre, and from population group to population group, and depends on such varied factors as local interpretation of evidence and complication rates, availability of resources, and incidence of human immunodeficiency virus (HIV) infection. The two studies identified, with similar interventions, small numbers of patients, limited information about treatment-related morbidity and QOL outcomes, and little information about patients' risk factors in one study (Bilek 1982), provide limited evidence that is relevant to the range of clinical practice.

Quality of the evidence

The amount of available evidence does not allow robust conclusions, especially as one of the included studies (Bilek 1982) had an extremely small number of patients and a dearth of information about those patients.

Both included studies had a high risk of bias, since they did not report the method of generation of the sequence of random numbers used to allocate women to treatment arms, or concealment of this allocation sequence from healthcare providers and patients, or blinding of outcome assessors. Inadequate concealment of allocation and lack of blinding are often associated with an exaggeration of the effects of treatment (Moher 1998; Schulz 1995). The evidence on OS is more robust than that for PFS, since blinding of outcome assessors is of less relevance for death than for disease progression.

Only one study reported a HR which is the best statistic to summarise the difference in risk in two treatment groups over the duration of a trial, when there is "censoring" i.e. the time to death (or disease progression) is unknown for some women as they were still alive (or disease free) at the end of the trial. The analyses of death (and disease recurrence) that are based on RRs are less reliable than those based on HRs because different women had different lengths of follow-up and the RRs did not allow for this.

The two studies gave inconsistent evidence about five-year survival, so the pooled estimate of five-year survival had wide confidence intervals: therefore we cannot be sure whether radiotherapy improves survival or increases the risk of death. Few women experienced disease progression, adverse events or death. Consequently the quality of the evidence is moderate and the findings of the review should be interpreted cautiously.

Furthermore, the available evidence does not assist us in deciding which women with high-risk early cervical cancer are likely to benefit from adjuvant radiotherapy, apart from the subgroup in GOG #92 which had the combination of negative capillary lymphatic space, deep stromal invasion and tumour size greater than 4cm; these women had a significantly lower risk of death if they received radiotherapy. GOG #92 also suggests that women with non-squamous histology derive benefit from radiotherapy. This is not strong evidence, as it is not confirmed by other studies, and several sub-group combinations of risk factors were examined, so it could be a chance finding.

Potential biases in the review process

A comprehensive search was performed, including a thorough search of the grey literature and all studies were sifted and data extracted by two review authors independently. We restricted the included studies to RCTs as they provide the strongest level of evidence available. Hence we have attempted to reduce bias in the review process.

The greatest threat to the validity of the review is likely to be the possibility of publication bias i.e. studies that did not find the treatment to have been effective may not have been published. We were unable to assess this possibility as we found only two included studies.

Agreements and disagreements with other studies or reviews

The excluded study of Lahousen 1999 concluded that adjuvant chemotherapy or radiotherapy do not improve survival or recurrence rates in high-risk cervical cancer patients after radical hysterectomy. However, comparing this with the included studies is difficult, as Lahousen 1999 randomised patients with high-risk cervical cancers, including those with stage IIB cancers - by definition a far more heterogenous and higher risk group of patients than those in the included studies.

AUTHORS' CONCLUSIONS

Implications for practice

1) The available evidence is not of high quality. The best available evidence suggests that women with stage IB cervical cancer who have pathologic risk factors after undergoing treatment with radical hysterectomy, should be carefully counselled about the risks and benefits of adjuvant radiotherapy, before a decision regarding adjuvant treatment is made. The counselling should emphasise not only the benefit of decreased local recurrence rates, but also the risks of increased treatment-related side-effects and the lack of evidence that radiotherapy improves survival.

2)The available evidence does not provide clear guidance in determining which patients should be offered adjuvant radiotherapy after radical hysterectomy. Unconfirmed evidence from one study suggests that women with a combination of negative capillary lymphatic space, deep stromal invasion and tumour size greater than 4cm and women with non-squamous histology might benefit from radiotherapy.

Implications for research

Ideally, a large RCT with long-term follow-up is needed to assess the risks and benefits of adjuvant radiotherapy, compared to no radiotherapy, after radical hysterectomy for women with early stage cervical cancer. Ideally, trials should be large enough to have power to detect any benefit of radiotherapy in prognostic sub-groups defined by capillary lymphatic space status, depth of invasion, tumour size and tumour type. Outcomes should include not only OS and PFS and adverse events, but also QOL. However, due to the decreasing incidence of cervical cancer in developed countries, which have the resources to run such a trial, this is unfortunately unlikely to occur.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bilek 1982

Methods	Multicenter RCT
Participants	Country: German Democratic Republic n=120. Women with squamous cell carcinomas of the cervix uteri stage $pT_{1b}N_0M_0$ previously treated by radical hysterectomy The mean age at study entry was 40.6 years (range: 23 to 60) All women presented with FIGO stage I. Tumor cell type was squamous in all 120 (100%) women Tumor grade: 1: 36 (30%), 2: 60 (50%), 3: 24 (20%)
Interventions	Women were randomised into two groups: • Group A: women without further treatment (n = 60) • Group B: women received an additional radiotherapy with 52 gy tumour dose to the whole pelvis by external radiation with a Co^{60} unit. This was delivered at a rate or 2 gy per day beginning 6 weeks after surgery (n = 60).
Outcomes	• Number of deaths within 5 years (and time to death) were reported: HR was not reported and insufficient data were presented to allow estimation using Parmar's methods • Time to disease recurrence • Adverse events: ○ gastrointestinal ○ genitourinary ○ lymphoedema ○ rectal/ sigmoid strictures ○ hydronephrosis
Notes	Mean length of follow up was 44 months (24-72 months)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	For all outcomes: % analysed: 120/120 (100%) "All patients (n = 120) entered into the study were evaluable for survival rate, date and anatomical location of recurrences, results

Bilek 1982 (*Continued*)

		of autopsy and morbidity of therapy"
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

GOG #92

Methods	Multicenter RCT
Participants	Country: US n=277. Patients were eligible for the study if they had primary Stage IB squamous, adenosquamous carcinoma, or adenocarcinoma of cervix initially treated with a standard radical hysterectomy and who had negative lymph nodes but one of a specified combination of risk factors The median age at study entry was 41 years (range: 20 to 80) All patients had primary Stage IB The tumour cell type was squamous in 218 (79%) women, adenosquamous in 32 (12%) , and adenocarcinoma in 27 (10%) GOG Performance Grade: 0: 185 (67%), 1: 86 (31%), 2: 6 (2%)
Interventions	• Radiation Therapy Radiation therapy was started within 4 to 6 weeks postoperatively. Patients received external beam irradiation and no brachytherapy. The pelvic irradiation was given with a fourfield technique with a megavoltage beam, although cobalt-60 was allowed if the SSD was greater than 80 cm. Radiation dose was from 46 Gy in 23 fractions to 50.4 Gy in 28 fractions, 5 fractions per week. Each patient was to be given daily fractions of 1. 80 -2.00 Gy over 41/2 to 6 weeks. Treatment breaks for clinical problems (vomiting or diarrhoea) were allowed to total no more than 1 week • No adjuvant chemotherapy or radiotherapy Additional details: *Follow-up Observation* Patients were to be evaluated by physical examination, blood counts, blood chemistries, and chest x-rays, every 3 months during the first 2 years of follow-up, and every 6 months during the subsequent years. Intravenous pyelogram, renal sonogram, or computed tomography (CT) scan with contrast was to be done at 6 months and then yearly. Results of these tests as well as changes of therapy, adverse effects, progression, or death were reported
Outcomes	• OS: HR adjusted for prognostic categories = 0.74 (90% C.I: 0.49 to 1.12) (See Rotman 2006). • PFS • Adverse events: ○ Haematological ○ Gastrointestinal ○ Genitourinary ○ Neurological

GOG #92 (*Continued*)

Notes	Of the 137 patients randomised to radiotherapy, 9 (6.6%) refused all radiotherapy and 6 (4.4%) refused to continue therapy after receiving less than 85% of the prescribed dose of 50.4 Gy (3.6, 3.6, 10.4, 14.4, 16.2, and 36.0 Gy). One patient discontinued radiotherapy due to an adverse reaction after receiving 21.6 Gy. In addition, 9 (6.6%) noncompliant patients had acceptable radiation doses (85% of 50.4 Gy) but in excess of 20% protraction of overall treatment time. Two other patients exceeded 20% protraction of treatment time due to an adverse reaction to the radiation requiring interruption of therapy Median length of follow up: 10.0 years (range, 0.003-16 years)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported, "After the eligibility criteria were verified, patients were randomly assigned to one of the two regimens: pelvic radiation or no further therapy"
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	For grade 3-4 adverse events: % analysed: 268/277 (97%) Radiation Therapy: 128/137 (93%) Control: 140/140 (100%) Analysis of overall and PFS used survival methods that allowed for loss to follow up "There is a small but noteworthy imbalance in the follow-up between the two treatment regimens. Of those who are alive, six patients are lost-to-follow-up within the first year in the RT group while one is lost in the NFT group. Within 2 years on study, there are eight and three patients in the RT group and NFT group, respectively"
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Lahousen 1999	Study includes women with stage IIB disease -19/76 (25%).