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Adjuvant platinum-based chemotherapy for early stage cervical cancer (Review)

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Adjuvant platinum-based chemotherapy for early stage cervical cancer.
Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD005342.
DOI: 10.1002/14651858.CD005342.pub4.

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[Intervention Review]

Adjuvant platinum-based chemotherapy for early stage cervical cancer

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 1, 2022.

Citation: Falcetta FS, Medeiros LRF, Edelweiss MI, Pohlmann PR, Stein AT, Rosa DD, Platt J. Adjuvant platinum-based chemotherapy for early stage cervical cancer. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD005342. DOI: 10.1002/14651858.CD005342.pub4.

ABSTRACT

Background

This is the second updated version of the original Cochrane review published in the Cochrane Library 2009, Issue 3.
Most women with early cervical cancer (stages I to IIA) are cured with surgery or radiotherapy, or both. We performed this review originally because it was unclear whether cisplatin-based chemotherapy after surgery, radiotherapy or both, in women with early stage disease with risk factors for recurrence, was associated with additional survival benefits or risks.

Objectives

To evaluate the effectiveness and safety of adjuvant platinum-based chemotherapy after radical hysterectomy, radiotherapy, or both in the treatment of early stage cervical cancer.

Search methods

For the original 2009 review, we searched the Cochrane Gynaecological Cancer Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library 2009, Issue 1), MEDLINE, Embase, LILACS, BIOLOGICAL ABSTRACTS and CancerLit, the National Research Register and Clinical Trials register, with no language restriction. We handsearched abstracts of scientific meetings and other relevant publications. We extended the database searches to November 2011 for the first update and to September 2016 for the second update.

Selection criteria

Randomised controlled trials (RCTs) comparing adjuvant cisplatin-based chemotherapy (after radical surgery, radiotherapy or both) with no adjuvant chemotherapy, in women with early stage cervical cancer (stage IA2-IIA) with at least one risk factor for recurrence.

Data collection and analysis

Two review authors extracted data independently. Meta-analysis was performed using a random-effects model, with death and disease progression as outcomes.

Main results

For this second updated version we identified only one small trial reporting grade 4 toxicity results, without disease-free or overall survival data with a median follow-up of 16 months.

From the first updated version, we identified three trials that were ongoing, and remain so in 2016.

Four trials including 401 women with evaluable results with early cervical cancer were included in the meta-analyses. The median follow-up period in these trials ranged from 29 to 42 months. All women had undergone surgery first. Three trials compared chemotherapy combined with radiotherapy versus radiotherapy alone; and one trial compared chemotherapy followed by radiotherapy versus radiotherapy alone. It was not possible to perform subgroup analyses by stage or tumour size.

Compared with adjuvant radiotherapy, chemotherapy combined with radiotherapy significantly reduced the risk of death (two trials, 297 women; hazard ratio (HR) = 0.56, 95% confidence interval (CI): 0.36 to 0.87) and disease progression (two trials, 297 women; HR = 0.47, 95% CI 0.30 to 0.74), with no heterogeneity between trials (I^2 = 0% for both meta-analyses). Acute grade 4 toxicity occurred significantly more frequently in the chemotherapy plus radiotherapy group than in the radiotherapy group (three trials, 321 women; risk ratio (RR) 6.26, 95% CI 2.50 to 15.67). We considered the evidence for all three outcomes to be of a moderate quality, using the GRADE approach due to small numbers and limited follow-up in the included studies. In addition, it was not possible to separate data for bulky early stage disease.

In the one small trial that compared adjuvant chemotherapy followed by radiotherapy with adjuvant radiotherapy alone there was no difference in disease recurrence between the groups (one trial, 71 women; HR = 1.34; 95% CI 0.24 to 7.66) and overall survival was not reported. We considered this evidence to be of a low quality.

No trials compared adjuvant platinum-based chemotherapy with no adjuvant chemotherapy after surgery for early cervical cancer with risk factors for recurrence.

Authors' conclusions

The addition of platinum-based chemotherapy to adjuvant radiotherapy (chemoradiation) may improve survival in women with early stage cervical cancer (IA2-IIA) and risk factors for recurrence. Adjuvant chemoradiation is associated with an increased risk of severe acute toxicity, although it is not clear whether this toxicity is significant in the long term due to a lack of long-term data. This evidence is limited by the small numbers and low to moderate methodological quality of the included studies. We await the results of three ongoing trials, which are likely to have an important impact on our confidence in this evidence.

PLAIN LANGUAGE SUMMARY

Adjuvant (supplementary treatment after initial treatment) platinum-based anti-cancer drugs for early stage cervical cancer

Background

Cervical cancer is the second most common cancer among women. Most women with early stage cervical cancer (stages I to IIA) are cured with surgery or, radiotherapy, or both. Radiotherapy uses high energy x-rays to damage tumour cells. Chemotherapy (anti-cancer) drugs use different ways to stop tumour cells dividing so they stop growing or they die.

Review question

We undertook this review because it was unclear whether chemotherapy with a drug called cisplatin offered additional benefits or risks to women with early stage cancer with risk factors for recurrence, when given after surgery, after radiotherapy, or both. (Risks for recurrence include tumour spread to the lymph nodes, spread into the lymph and blood vessels, tumour depth of more than 10 mm, microscopic invasion of the connective tissues next to the womb, non-squamous type of cancer, and when it is unlikely that surgery has removed all the tumour cells).

Main Findings

In this review, we analysed data from four small trials of unclear quality. It was not possible to separate data of bulky early stage disease (stage IB2 and IIA lesions greater than 4 cm) from the overall results. We found limited evidence to suggest that the addition of cisplatin chemotherapy to radiotherapy prolongs survival (time to death) and delays progression of the cancer when given after surgery to women with cervical cancer stage IA2 to IIA with risk factors for recurrence. The combined therapy was associated with more severe side effects than radiotherapy alone.

Quality of the Evidence

This evidence is limited by the small numbers and moderate quality methodological quality of included studies.

What are the conclusions?

We conclude that it seems appropriate to offer these women chemotherapy plus radiotherapy after surgery, however, more evidence regarding the relative benefits and risks is needed; this will hopefully be provided by the results of three ongoing trials.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

Radiotherapy plus chemotherapy compared with**radiotherapy for early stage cervical cancer**

Patient or population: patients with early stage cervical cancer

Settings: inpatient or outpatient

Intervention: radiotherapy plus chemotherapy

Comparison: radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Radiotherapy	Radiotherapy plus chemotherapy			
Death from all causes Follow-up: 42 months	**310 per 1000**[1]	**188 per 1000** (125 to 276)	**HR 0.56** (0.36 to 0.87)	297 (2 studies)	⊕⊕⊕⊖ **moderate**[2]
Disease progression Follow-up: 42 months	**353 per 1000**[1]	**185 per 1000** (122 to 275)	**HR 0.47** (0.3 to 0.74)	297 (2 studies)	⊕⊕⊕⊖ **moderate**[2]
Grade 4 toxicity[3]	**26 per 1000**	**182 per 1000** (72 to 454)	**RR 6.26** (2.50 to 15.67)	321 (3 studies)	⊕⊕⊕⊖ **moderate**[2]

*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; **HR:** Hazard 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] Due to censoring and differing levels of follow-up combined figures from the two studies were not used. Peters 2000 explicitly reported four-year survival rate and carried substantially more weight in the meta-analysis, therefore we used the numbers from this trial.
[2] Trial of Peters 2000 was reported early because interim analysis showed benefit of radiotherapy plus chemotherapy.

[3] The results from radiotherapy plus chemotherapy and chemotherapy plus radiotherapy followed by consolidation chemotherapy in the Sun 2015 trial were analysed together for the outcome of grade 4 toxicity.

Summary of findings 2. Summary of findings

Chemotherapy followed by radiotherapy compared with**radiotherapy for early stage cervical cancer**

Patient or population: patients with early stage cervical cancer

Settings: inpatient or outpatient

Intervention: chemotherapy followed by radiotherapy

Comparison: radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Radiotherapy	Chemotherapy followed by radiotherapy			
Disease progression Follow-up: median 30 months	**297 per 1000**	**376 per 1000** (81 to 933)	**HR 1.34** (0.24 to 7.66)	71 (1 study)	⊕⊕⊖⊖ **low**[1]

*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; **HR:** Hazard 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] Imprecision in point estimate for Tattersall 1992, indicated by large CI due to low number of women with disease progression. This uncertainty means we are unsure whether to use radiotherapy alone or sequentially in combination with chemotherapy.

BACKGROUND

This is the second update of the original review that was published in the *Cochrane Database of Systematic Reviews,* 2009, Issue 3.

Description of the condition

Despite significant advances in the screening and treatment of cervical dysplasia, cervical cancer is the fourth most common cancer in women (GLOBOCAN 2012). Worldwide, there are more than 500,000 new cases of cervical cancer each year, accounting for around 8% of all cancers diagnosed in women. A woman's risk of developing cervical cancer by the age of 75 ranges from 0.9% in more developed countries to 1.6% in less developed countries; the risk of dying from cervical cancer is 0.3% and 0.9% in more- and less developed countries, respectively. Worldwide, over 260,000 women die from cervical cancer every year; over 230,000 of these deaths being in less developed countries. In Europe, about 60% of women with cervical cancer survive five years after diagnosis (EUROCARE 2014).

The International Federation of Gynecology and Obstetrics (FIGO) staging of cervical cancer, determined at the time of primary diagnosis, is summarised in Table 1 (Benedet 2003).

Description of the intervention

Most women with early lesions (stages I to IIA) are cured with surgery or radiotherapy alone. However, patients who present with metastatic disease or locally advanced lesions are at a significant risk of recurrence and account for most cervical cancer deaths (Im 2002). These deaths occur despite current surgical and radiotherapy protocols, often as a direct result of local or in-field treatment failure (Im 2002).

The treatment of women with stage IA1 or micro-invasive cervical cancer usually consists of local excision (a loop or cone biopsy), or a simple hysterectomy. Women with stage IA2 to IIA lesions require either radical hysterectomy with bilateral pelvic lymph node dissection or radiotherapy, combining whole pelvic teletherapy with brachytherapy. There is a trend to increased use of primary radiotherapy with increased stage of disease (Benedet 2003). These treatments (radical surgery and radiotherapy) are considered equally effective with respect to local control and survival if lesions are small and nodal metastasis are absent (Holtz 2002); however, for bulky early lesions (IB2 and IIA), chemoradiation (as primary treatment or after surgery) is considered to be more effective in improving survival and reducing recurrence than radiotherapy alone (CCCMAC 2010).

Disease control for early lesions with risk factors such as lymph node metastasis, lymphovascular space invasion, depth invasion more than 10 mm, parametrial invasion (Ho 2004; Lai 1999; Park 1997), non-squamous histology (Ikeda 1994) and positive surgical margins (Rushdan 2004) is difficult. Retrospective studies analysing the outcome of high-risk women after adjuvant radiotherapy found that radiotherapy decreased the incidence of local recurrence with little or no effect on overall survival (OS) (Kinney 1989; Monk 1994). These findings are supported by a Cochrane review (Rogers 2012). Furthermore, many women with these risk factors are at increased risk for subclinical dissemination of the disease, which will not be affected by radiotherapy directed to the pelvis. To eradicate micrometastases, Wertheim 1985 added chemotherapy to radiotherapy, with an apparent improvement in survival rates when compared to historical controls. Cisplatin-based regimens, evaluated on the basis of shrinkage of the tumour, are the most effective chemotherapy regimens (Morton 1996; Park 1997).

The complete response rate to primary treatment of early stage disease ranges from 70% to 90%, with an overall five-year survival for stage I disease in excess of 90% (Benedet 2003). Adjuvant therapies may improve survival but are associated with several adverse effects and toxicities. Early morbidity from radiotherapy is most frequently seen in the rectosigmoid (around 60%) with proctitis, tenesmus, diarrhoea, fistula, stenosis and ulceration. In one third of patients, toxicity within the urinary bladder such as cystitis, fistula, ulceration and contracted bladder may occur. Local dermal toxicity (oedema, erythema, pigmentation, fibrosis and ulceration) is reported in 20% of patients and gynaecological toxicity (vaginitis, dryness, narrowing, shortening, dyspareunia, necrosis or ulceration of the cervix, uterus infection, pyometra, hematometra, perforation of the uterus and necrosis of the uterus) in 10%. Furthermore, there is a 5% chance of developing late pelvic complications following intra-cavitary and external beam radiotherapy (EBRT), the most frequent being cystitis and proctitis (Maduro 2003). Reviews of chemoradiation in the treatment of locally advanced cervical cancer have shown greater acute haematological and gastro-intestinal toxicity in the combination arm (CCCMAC 2010; Green 2005).

Why it is important to do this review

There is no consensus about the place of chemotherapy in the adjuvant treatment of early stage (stages I to IIA) cervical cancer (Curtin 1997; Kato 1994; Lin 1998; Lin 2000; Mossa 2003; Nitz 1994; Thomas 1996). Adding therapies also adds potential adverse effects and toxicities. We aimed to help clarify the risks and benefits of adjuvant chemotherapy for early cervical cancer by performing this systematic review. Adjuvant radiotherapy for early cervical cancer is the subject of a separate Cochrane review (Rogers 2012), as is chemoradiation for locally advanced cervical cancer (CCCMAC 2010).

OBJECTIVES

To evaluate the effectiveness and safety of adjuvant platinum-based chemotherapy after radical hysterectomy (RH), radiotherapy, or both in the treatment of early stage cervical cancer (stages IA2 to IIA). The main outcomes of interest are survival and disease recurrence.

METHODS

Criteria for considering studies for this review

Types of studies

The review was restricted to randomised controlled trials (RCTs). We excluded trials with quasi-randomised designs (e.g. participants assigned to treatment arms on the basis of date of birth, clinic id-number or surname).

Types of participants

Women with stage IA2 to IIA cervical cancer defined as follows, according to FIGO staging (Benedet 2003; Pecorelli 2009).

- Stage IA2: invasive cancer identified only microscopically, with stromal invasion more than 3 mm and not more than 5 mm with a horizontal spread of 7 mm or less.
- Stage IB1: preclinical lesions higher than stage IA or clinical lesions 4 cm or less.
- Stage IB2: clinical lesions > 4 cm but confined to the cervix.
- Stage IIA: cervix cancer extends beyond the cervix but not to the parametrium, pelvic wall or lower third of the vagina.

We planned to subgroup women by stage and we excluded studies that only included women with bulky lesions (IB2 and IIA, 4cm or more) as we considered these lesions to be 'locally advanced'.

We included studies where participants with at least one of the following risk factors for recurrence were included:

- lymph node metastasis;
- lymphovascular space invasion;
- depth invasion more than 10 mm;
- microscopic parametrial invasion;
- non-squamous histology;
- positive surgical margins.

Types of interventions

We only included studies that addressed chemotherapy in the adjuvant setting i.e. post-surgery or post-radiotherapy (or in combination with radiotherapy). Chemotherapy regimens without platins were excluded. Comparisons were restricted to those that compared an intervention with a control that was similar in all respects, except that chemotherapy was not included in the treatment regimen.

The following comparisons were included.

- Radical hysterectomy (RH) *with* adjuvant radiotherapy *compared with* RH and adjuvant radiotherapy plus chemotherapy (= adjuvant chemoradiation, where chemotherapy may be given before, after or in combination with radiotherapy).
- RH alone *compared with* RH and adjuvant chemotherapy.
- Primary radiotherapy *compared with* primary radiotherapy and adjuvant chemotherapy.

Types of outcome measures

Primary outcomes

- Overall survival (OS), defined as the time from randomisation until death (from any cause).
- Progression-free survival (PFS), defined as the time from randomisation until disease progression or death (by any cause).

Secondary outcomes

- Local recurrence, defined as the time from randomisation until loco-regional progression or recurrence, or death (by any cause).
- Distant recurrence, defined as the time from randomisation until distant progression or recurrence, or death (by any cause).
- Quality of life (QoL) using a validated scale.

Adverse events: type and severity of acute and late toxicity grades 3 and 4 (according to the ECOG Common Toxicity Criteria) (CTCAE 4.0).

Search methods for identification of studies

Electronic searches

For the first version of this review, we conducted the following searches to identify all published and unpublished RCTs, without language restrictions: Specialised Register (SR) of the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers (CGNOC), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, 2009, Issue 1, MEDLINE (January 1990 to 2009), Embase (January 1990 to 2009), LILACS (January 1990 to 2009), BIOLOGICAL ABSTRACTS (January 1990 to 2009) and Cancerlit (January 1990 to 2009). See Appendix 1 for the MEDLINE and Embase search strategies used. The search strategies were developed and executed by the author team for the original review.

The first updated version of the review searches of the SR, CENTRAL, MEDLINE, Embase and LILACS (Appendix 2) were performed in November 2011 by the CGNOC Information Specialist, who also searched the MetaRegister (http://www.controlled-trials.com/mrct/) for ongoing trials.

For this second updated version, searches of CENTRAL, MEDLINE and Embase were performed in September 2016 by the CGNOC Information Specialist.

Searching other resources

For the first version of the review, we handsearched the abstracts of scientific meetings and the citation lists of included studies and other relevant publications. In addition, we attempted to contact experts in the field to identify further reports of trials. We handsearched conferences reports from January 1990 to January 2009 in the following sources: Gynecologic Oncology, International Journal of Gynecological Cancer, British Journal of Cancer, British Cancer Research Meeting, Annual Meeting of the International Gynecologic Cancer Society, Annual Meeting of the American Society of Gynecologic Oncologist, Annual Meeting of European Society of Medical Oncology (ESMO), and the Annual Meeting of the American Society of Clinical Oncology (ASCO). We did not handsearch conference reports for the first or second update, however, the updated electronic search strategies were designed to include any published abstracts.

Data collection and analysis

Selection of studies

For the orginal version of the review, two review authors (DDR, LRM) undertook study selection and extracted data independently to assess whether the studies met the specified inclusion criteria. Any discrepancies were resolved by a third and a fourth review author (ATS, MCB). The review authors were blind to names of authors, institutions and journals. For this second updated version, two review authors selected the studies (FSF, DDR) as described in the inclusion criteria.

Data extraction and management

For the included studies in the original version of the review, five review authors (DDR, LRM, MCB, MIE, ATS) independently abstracted the following data to specifically designed, data

collection forms: characteristics of patients and interventions, study quality, endpoints and deviations from protocol (Table 2; Table 3; Table 4; Table 5; Table 6). Differences between review authors were resolved by discussion or by appeal to a third review author if necessary. When necessary, we sought additional information from the principal investigator of the trial concerned. For this second updated version of the review, two review authors (FSF, DDR) extracted data from the one new included study.

For time-to-event (survival) data, we extracted the log of the hazard ratio (HR) [log(HR)] and its standard error from trial reports. If these were not reported, we digitised the published Kaplan-Meier survival curves using Adobe Photoshop (Adobe 2007) and noted the minimum and maximum duration of follow-up, in order to estimate the log(HR) and its standard error using the methods of Parmar 1998. We performed these calculations in Stata 9 (StataCorp 2005), using a specially written program, which yielded the reported log(HR) and variance when used on the data presented in Table V of Parmar 1998. If possible, we also extracted the log-rank or Cox P value, and number of observed events by treatment arm, in order to make alternative estimates of the log(HR) and its standard error (Parmar 1998).

For one trial for which unpublished individual patient data were available (Protocol CE3005), we used Cox regression to estimate log(HR) and its standard error for overall and recurrence-free survival, both unadjusted and adjusted for age (McCullagh 1989).

For dichotomous outcomes (adverse events), 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 (RR).

Assessment of risk of bias in included studies

We assessed the risk of bias in included RCTs using Cochrane's tool in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included assessment of the following domains.

1) Random sequence generation

We assessed the randomisation of participants to intervention groups as follows.

- Low risk: e.g. a computer-generated random sequence or a table of random numbers.
- High risk: e.g. date of birth, clinic id-number or surname (quasi-randomised).
- Unclear risk: e.g. not reported.

2) Allocation concealment

We assessed the concealment of allocation sequence from treatment providers and participants as follows.

- Low risk: e.g. where the allocation sequence could not be foretold.
- High risk: e.g. allocation sequence could be foretold by patients, investigators or treatment provider.
- Unclear risk: e.g. not reported.

3) Blinding

We assessed the blinding of outcome assessors as follows.

- Low risk if outcome assessors were adequately blinded.
- High risk if outcome assessors were not blinded to the intervention that the participant received.
- Unclear if this was not reported or unclear.

4) Incomplete outcome data

We recorded the proportion of participants whose outcomes were not reported at the end of the study; we noted if loss to follow-up was not reported.

We assessed loss to follow-up as follows.

- Low risk if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
- High risk if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
- Unclear risk, if loss to follow-up was not reported.

5) Selective reporting of outcomes

We assessed whether studies are free of selective outcome reporting as follows.

- Low risk: e.g. if all outcomes that are specified above and also pre-specified in the study were reported in the study.
- High risk: e.g. if it was suspected that outcomes had been selectively reported.
- Unclear risk: e.g. It is unclear whether outcomes had been selectively reported.

6) 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 using the following categories.

- Low risk.
- High risk.
- Unclear risk.

Measures of treatment effect

We used the following measures of the effect of treatment.

- For time-to-event (survival and disease progression) data, we used the log of the HR and its standard error, if possible.
- For dichotomous outcomes (adverse events), we used the RR.

Dealing with missing data

We attempted to extract data on the outcomes only among participants who were assessed at endpoint. We did not impute missing outcome data. Where possible, all data extracted on effectiveness were those relevant to an intention-to-treat (ITT) analysis and data on adverse events were those relevant to the treatments which patients actually received.

Assessment of heterogeneity

Heterogeneity between studies was assessed by visual inspection of forest plots, by the I^2 statistic which estimates of the percentage heterogeneity between trials which cannot be ascribed to sampling

variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001).

Assessment of reporting biases

We were unable to assess reporting bias as only four studies were included.

Data synthesis

The outcomes were pooled statistically using random-effects methods (DerSimonian 1986). For time-to-event data, we pooled the log(HRs) using the generic inverse variance facility of RevMan 5.1 (RevMan 2011).

Subgroup analysis and investigation of heterogeneity

We planned to subgroup analyses by tumour stage and size as follows:

- early stages: IA2, IB1 and IIA less than 4 cm;
- bulky early stages: IB2 and IIA more than 4 cm.

In addition, where possible, we planned to stratify cervical cancer by histology:

- epidermoid or squamous carcinoma;
- adenocarcinoma;
- adenosquamous carcinoma;
- other types.

Sensitivity analysis

We performed sensitivity analysis, using estimates of HRs (i) calculated using alternative methods proposed by Parmar 1998 for one study (Peters 2000) and (ii) adjusted for age for another study (Protocol CE3005). If sufficient trials had been available, we also planned to perform sensitivity analyses, excluding studies which did not report adequate (i) concealment of allocation, (ii) blinding of the outcome assessor.

RESULTS

Description of studies

Results of the search

For the original review, the search strategy identified 716 unique records. The title and abstract screening of these references identified 50 studies as potentially eligible for this review. The full text screening of these 50 studies excluded 47 for the reasons described in the table Characteristics of excluded studies. The remaining three RCTs met our inclusion criteria and are described in the table Characteristics of included studies.

The first updated search identified 1034 records (excluding 166 duplicates) including three ongoing trials identified in the online register of controlled trials (MetaRegister). Of the 12 records that we screened for relevance, we found no new trials to include. However, we added the three ongoing trials to the Ongoing studies section (GOG 0263; Hong 2013; NCT 00806117) and requested the full text of one record (an abstract; Zola 2003), which we subsequently excluded. A summary of the ongoing studies may be found in Characteristics of ongoing studies.

In this second updated search, we identified 1095 records (excluding 195 duplicates). Of the 22 records that we screened for relevance we found two trials that met the inclusion criteria (Sun 2015 and Liu 2014). The trial by Liu 2014 was reported as an abstract with insufficient information and the principal investigator did not respond to our attempt to obtain the correct data for this meta-analysis. we excluded this study. All of the three ongoing trials added in the first update are still recruiting patients (GOG 0263; Hong 2013; NCT 00806117).

Included studies

We included four RCTs, which included a total of 435 women but only 268 women with evaluable results.

1) Peters 2000: 268 women with clinical stage IA2, IB or IIA carcinoma of the cervix treated by surgery were randomised to receive either adjuvant pelvic radiotherapy or pelvic radiotherapy plus four cycles of chemotherapy with cisplatin and 5-fluorouracil. After randomisation, 25 (9%) women were deemed ineligible and so 243 women were assessed: 116 in the radiotherapy-only arm and 127 in the radiotherapy and chemotherapy arm. In the radiotherapy-only arm, three women refused radiotherapy and one was not treated because of physician discretion; in the radiotherapy plus chemotherapy arm, one woman was not treated due to a surgical complication, five women refused chemotherapy and four women refused both chemotherapy and radiotherapy. Accrual took place between 1991 and 1996 in the US. Women were followed up for a median of 42 months.

2) Tattersall 1992: 71 women with clinical stage IB or IIA treated by radical hysterectomy were randomised to receive either pelvic radiotherapy (n = 37) or three cycles of chemotherapy with cisplatin, vinblastine and bleomycin followed by pelvic radiotherapy (n = 34). One woman randomised to receive radiotherapy alone refused all treatment and two women randomised to receive chemotherapy plus radiotherapy refused chemotherapy. Accrual of women took place between May 1985 and November 1990 in Australia. Women were followed up for a median of 30 months.

3) Protocol CE3005: Women with clinical stage IB or IIA were randomised to receive either adjuvant radiotherapy and chemotherapy (n = 27) or adjuvant radiotherapy only (n = 30).Three women were not followed up after randomisation: one in the radiotherapy plus chemotherapy arm and two in the radiotherapy-only arm. Hence 26 and 28 women were evaluated in the radiotherapy plus chemotherapy and radiotherapy-only arms, respectively. Accrual of women took place between September 1988 and October 1995 in the UK. Patients were followed up for a median of 29.5 months.

4) Sun 2015: 39 women with clinical stage IB1 or IIA2 were randomised to receive adjuvant radiotherapy and chemotherapy (n = 15), chemoradiotherapy plus consolidation chemotherapy (n = 5) or adjuvant radiotherapy only (n = 13). Six of all the included patients did not complete the allocated therapy (15%). Thirty-three patients completed the protocol and were evaluated: 13 in the radiotherapy and chemotherapy, 15 in the concomitant radiotherapy and chemotherapy arm and five in the chemoradiotherapy plus consolidation chemotherapy arm. Accrual of women took place between September 2011 and August 2013 in China. Patients were followed up for a median of 16 months.

All the included studies enrolled women with stage IB2 and IIA lesions (potentially larger than 4 cm). Although we intended to perform subgroup analyses by stage and tumour size, it was not possible to separate the data accordingly.

Outcomes

Peters 2000 reported overall survival (OS) but Tattersall 1992 did not. Peters 2000 reported progression-free survival (PFS); Tattersall 1992 reported disease-free survival (DFS). Sun 2015 only reported toxicity results due to a median follow-up of 16 months.

Peters 2000 reported the hazard ratios (HRs) for both OS and DFS, but not their variance. However, the reported HRs compared radiotherapy alone with radiotherapy plus chemotherapy, whereas, we required the converse comparison (with radiotherapy alone as the reference group) and this could not be estimated. Tattersall 1992 did not report HRs.

Both Peters 2000 and Tattersall 1992 presented Kaplan-Meier plots (and therefore the maximum duration of follow-up) for the endpoints which they considered, based on analysis of women in the groups to which they were randomised. We estimated the minimum duration of follow-up for both studies, digitised the survival plots and used Parmar's methods (Parmar 1998) to estimate the log(HR) and its variance for both trials. Peters 2000 reported the number of events in each treatment group and a P value from Cox regression, so we additionally used these data to provide another estimate of the log(HR) and its variance for this trial.

For Protocol CE3005, individual patient data were available, giving: date of birth, date of randomisation, date of death and whether death was due to the primary tumour, date of disease recurrence and toxicities.

Details on the type and severity of acute toxicity grades 3 and 4 were reported in three studies (Peters 2000; Protocol CE3005; Sun 2015).

Excluded studies

In total, we excluded 65 studies for the reasons described in the Characteristics of excluded studies table.

Eight papers found were reviews on the proposed subject (Hansgen 2001; Koh 2000; Lai 1999; Lu 2000; Morton 1996; Park 1997; Roth 1994; Shimizu 1995). Twenty-three studies were retrospective (Buxton 1990; Frigerio 1994; Harrand 2013; Ikeda 1994; Killackey 1993; Kim 2007; Lin 1998; Lin 2000; Mossa 2003; Nakamura 2014; Ng 1995; Park 2001; Park 2012; Ryu 2005; Sivanesaratnam 1987; Sivanesaratnam 1989; Sivanesaratnam 1998; Wada 1995; Wen 2013; Wertheim 1985; Yessaian 2004; Yoon 2014; Zhang 2012); seven were non-randomised clinical trials (Argenta 2006; Dimpfl 1996; Lahousen 1990; Lai 1989; Linghu 2003; Russel 1995; Zanetta 1995); six were phase II studies (Hansgen 2002; Rushdan 2004; Lee 2013; McCaffrey 2011; Strauss 2002; Wang 2015) and three were phase I studies (Schwarz 2011; Shu 2015; Watanabe 2006).

The chemotherapeutic regimen of the intervention group did not include cisplatin in five studies (Blohmer 2001; Kato 1994; Lahousen 1999; Richter 1982; Yamamoto 2004). Two studies evaluated chemotherapy (and not radiotherapy) in the control arm (Curtin 1996; Lahousen 1999). Seven trials were excluded because they included women with stage IIB or more in the analyses (Chatterjee 2013; Iwasaka 1998; Kemnitz 1991; Kim 2007; Lahousen 1999; Morris 1999; Yamamoto 2004) and these data could not be separated.

A multicentre Italian RCT (abstract only) of 204 women compared adjuvant chemotherapy with adjuvant radiotherapy (Zola 2003) in early invasive cervical cancer. Three-year follow-up showed no significant differences in survival and recurrence between the two interventions.

In one study, more than 70% of participants were lost after randomisation (Lai 1998). The protocol MRC CE04/EORTC55954 was excluded since it closed due to lack of accrual and the investigators did not reply our e-mails. On the clinicaltrials.gov web-site the trial is listed as completed since July 2012.

In the second update one randomised trial (Liu 2014) was excluded because it did not report the number of patients allocated to each one of the three groups or their outcomes (DFS, OS) or toxicity). The first author did not respond to our attempt to obtain the correct data from this study. A second RCT (Pu 2013) was excluded because both the intervention group and the control group received cisplatin, since the trial was comparing the inclusion of docetaxel in the adjuvant setting; as was another RCT (Sehouli 2012) that compared single-agent cisplatin and radiotherapy with paclitaxel, carboplatin and radiotherapy. One study (Rogers 2012) was a meta-analysis of adjuvant radiotherapy and chemoradiation therapy after surgery.

Risk of bias in included studies

The risk of bias in included studies is summarised in Figure 1 and Figure 2: most of the methodological quality criteria were unclear.

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

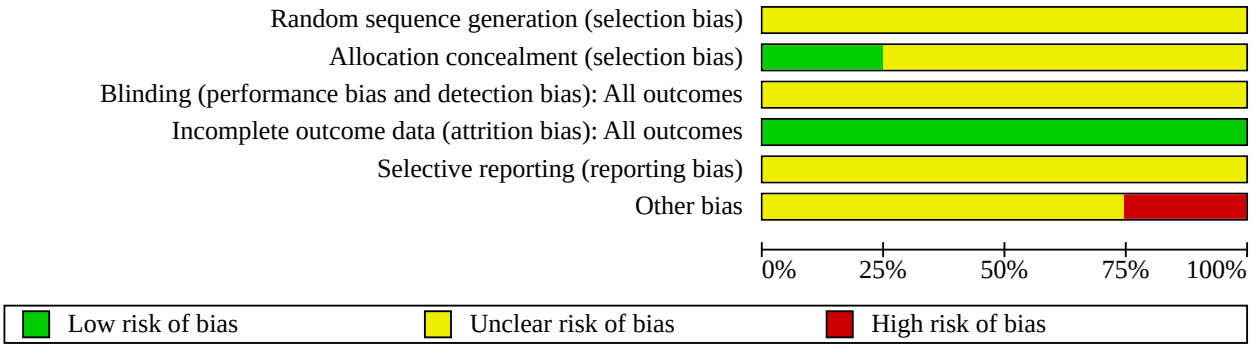
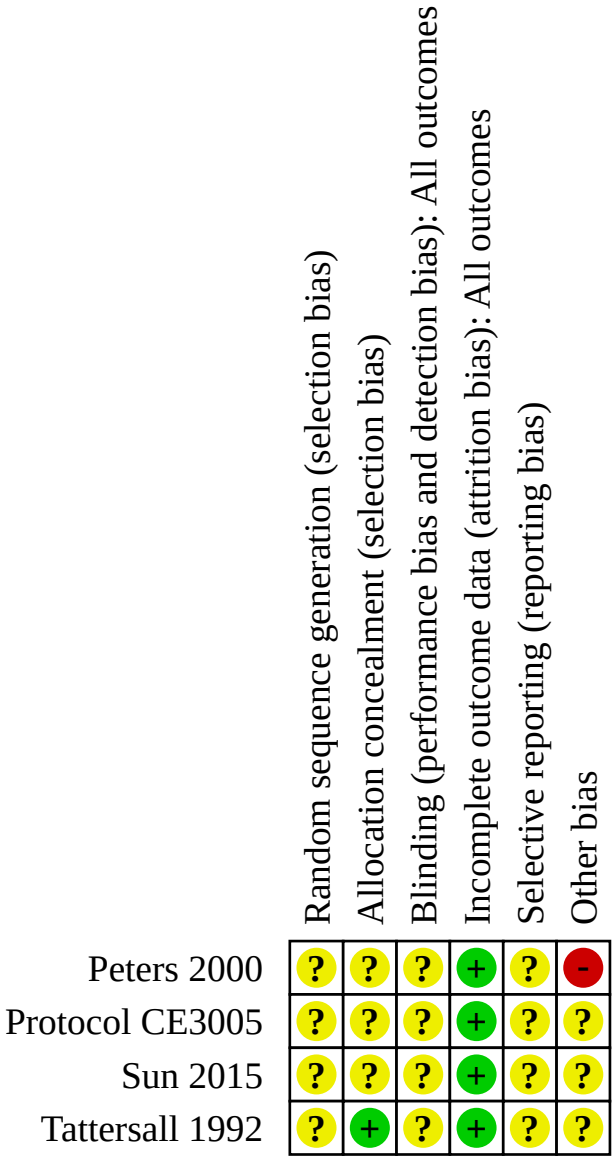


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

None of the four trials described randomisation adequately. Concealment of allocation was adequate in one study (Tattersall 1992), but was not described in the other three studies (Peters 2000; Protocol CE3005; Sun 2015).

Blinding

Blinding of the outcome assessors was not described in any of the four included studies.

Incomplete outcome data

Tattersall 1992 did not report loss to follow-up. Peters 2000 did not assess 25 (9%) of the 268 randomised patients as they were deemed ineligible after randomisation, but the numbers of ineligible patients were not reported by treatment arm. This study did not report any further loss to follow-up. Protocol CE3005 did not follow up 1/27 (4%) women in the radiotherapy plus chemotherapy arm and 2/30 (7%) women in the radiotherapy-only arm; reasons for loss to follow-up were not available. Sun 2015 did not report

recurrence-free survival and OS because of a median follow-up of only 1 months.

Selective reporting

It was unclear whether the studies reported all the outcomes that they assessed.

Other potential sources of bias

Early reporting of findings

The report of Peters 2000 was based on an interim analysis of the data which rejected the null hypothesis of no benefit of chemotherapy. Another study was closed early due to lack of accrual (Protocol CE3005).

Effects of interventions

See: **Summary of findings 1** Summary of findings; **Summary of findings 2** Summary of findings

Adjuvant radiotherapy and chemotherapy versus adjuvant radiotherapy (comparison 1)

Death

Peters 2000 reported the Cox hazard ratio (HR) comparing overall survival (OS) in the radiotherapy group with that in the radiotherapy plus chemotherapy group to be 1.96 (P = 0.007). We estimated the log (HR) comparing OS in the radiotherapy plus chemotherapy group with that in the radiotherapy group and its variance using two of Parmar's methods: see Table 7. In the primary meta-analysis, we used the values estimated from the Kaplan-Meier plots, i.e. a HR of 0.57 (95% confidence interval (CI) 0.33 to 0.96). For Protocol CE3005, we estimated the HR comparing the risk of death in the radiotherapy plus chemotherapy group with that in the radiotherapy group using Cox regression, both unadjusted and adjusted for the age of the participants: see Table 7. In the primary meta-analysis, we used the unadjusted value, i.e. a HR of 0.55 (95% CI 0.25 to 0.1.20).

Meta-analysis of these two studies, which assessed a total of 297 participants, found that women who received radiotherapy plus chemotherapy had a significantly lower risk of death than women who received radiotherapy alone: the pooled HR was 0.56 (95% CI 0.36 to 0.87) with no heterogeneity between the trials (I^2 = 0%) - see Analysis 1.1; *moderate-quality evidence*. Sensitivity analyses, using the alternative Parmar estimates of HRs for the trials of Peters 2000 and age-adjusted estimates for the Protocol CE3005 trial, resulted in a similar estimate of the HR: 0.52 (95% CI 0.34 to 0.80).

As only two studies were included in this meta-analysis, we did not construct a funnel plot or perform sensitivity analyses around quality.

Disease progression

Peters 2000 reported the Cox HR comparing disease progression in the radiotherapy group with that in the radiotherapy plus chemotherapy group to be 2.01 (P = 0.003). We estimated the log(HR) comparing disease progression in the radiotherapy plus chemotherapy group with that in the radiotherapy group and its variance using two of Parmar's methods: see Table 7. In the primary meta-analysis, we used the values estimated from the Kaplan-Meier plots, i.e. a HR of 0.48 (95% CI 0.27 to 0.84). For Protocol CE3005, we estimated the HR comparing the risk of disease recurrence in the radiotherapy plus chemotherapy group with that in the radiotherapy group using Cox regression, both unadjusted and adjusted for the age of the participants: see Table 7. In the primary meta-analysis, we used the unadjusted value, i.e. a HR of 0.46 (95% CI 0.21 to 0.99).

Meta-analysis of these two studies found that women who received radiotherapy plus chemotherapy had a significantly lower risk of disease progression than women who received radiotherapy alone: the pooled HR was 0.47 (95% CI 0.30 to 0.74), with no heterogeneity between the trials (I^2 = 0%) - see Analysis 1.2; *moderate-quality evidence*. Sensitivity analyses, using the alternative Parmar estimates of HRs for the trials of Peters and age-adjusted estimates for the Protocol CE3005 trial, resulted in a similar estimate of the HR: 0.48 (95% CI 0.32 to 0.72).

Adverse events

In the study of Peters 2000, toxicity was only assessed in women who received the treatment to which they were randomised: thus 122 and 112 women were assessed for toxicity in the combination (chemotherapy plus radiotherapy) and radiotherapy-only arms, respectively. There were 27 episodes of grade 4 toxicity in 21 patients in the combination arm, most of which were haematological, and four episodes of grade 4 toxicity in four patients in the radiotherapy-only arm. There was one late death in a patient treated with radiotherapy alone that may have been treatment-related. The numbers of women in each arm who experienced grade 3 toxicities were not reported.

In the Protocol CE3005, there were 37 episodes of grade 3 toxicities in 15 women in the combination arm (23 of alopecia, 13 of nausea and vomiting and one of mild somnolence or agitation) and 13 episodes of grade 4 toxicities in eight women in the combination arm (10 of alopecia, two of nausea and vomiting and one of infection). No episodes of toxicity of grade 3 or higher were reported in the radiotherapy-only arm.

In the study of Sun 2015 there were seven episodes of grade 3 toxicities in 13 women in the radiotherapy arm (most of which were haematological, one of diarrhoea, one nausea/vomiting, one genitourinary), and no grade 4 toxicity. There were 13 grade 3 toxicities episodes in 15 women in the chemoradiotherapy arm (mostly haematological) and seven episodes of grade 4 toxicities (five of neutropenia, one of thrombocytopenia, and one of diarrhoea). There were nine grade 3 toxicities episodes in five women in the chemoradiotherapy plus consolidation chemotherapy arm (most of which were haematological) and three episodes of grade 4 toxicities (all haematological), five of neutropenia, one of thrombocytopenia, and one of diarrhoea).

The pooled risk ratio (RR) comparing grade 4 toxicities in the combination and radiotherapy arms was 6.26 (95% CI 2.50 to 15.67) (three studies, 321 women, with no heterogeneity between the trials (I^2 = 0%), indicating a significantly higher risk of a severe adverse event among women receiving chemotherapy plus radiotherapy than among those receiving radiotherapy alone - see Analysis 1.3; *moderate-quality evidence*.

Adjuvant chemotherapy followed by radiotherapy versus adjuvant radiotherapy (comparison 2)

Disease recurrence

From the Kaplan-Meier plots presented by Tattersall 1992, we estimated the HR comparing the risk of disease recurrence in the chemotherapy followed by radiotherapy group with that in the radiotherapy group to be 1.34 (95% CI 0.24 to 7.66), indicating no significant difference between the treatment groups - see Analysis 2.1; *low-quality evidence*.

Long-term toxicities and quality of life

None of the included studies (for comparison 1 and 2) reported data on long-term toxicities or quality of life (QoL).

DISCUSSION

Summary of main results

We found four randomised controlled trials (RCTs) of the following comparisons: adjuvant chemotherapy plus radiotherapy versus adjuvant radiotherapy (three trials enrolling 364 women of whom 321 (88%) were assessed) and adjuvant chemotherapy followed by radiotherapy versus adjuvant radiotherapy (one trial assessing 71 women). All included trials used chemotherapy regimens consisting of cisplatin alone or in combination with other agents and all included women who had undergone surgery. No trials compared adjuvant chemotherapy after surgery with no adjuvant chemotherapy.

Heterogeneous evidence from two small trials showed that the addition of chemotherapy to the radiotherapy regimen reduced the risk of death by between 13% and 64% and reduced the risk of disease progression by between 26% and 70% (Summary of findings 1). This corresponds to an absolute benefit in overall survival (OS) of 12% and in progression-free survival (PFS) of 16%.

Overall, the risk of severe adverse events was significantly higher among women who received radiotherapy and chemotherapy than among those who received radiotherapy alone.

The trial comparing adjuvant chemotherapy followed by radiotherapy versus radiotherapy alone (Tattersall 1992) found little difference in outcomes between the two treatment groups (Summary of findings 2); it should be noted that in this trial chemotherapy was given sequentially and not in combination with radiotherapy.

Overall completeness and applicability of evidence

One important observation is that the studies analysed in this systematic review included women with bulkier disease (stage IB2 and IIA). Nowadays, it is widely accepted that these women should not be treated primarily with surgery as concurrent chemoradiation improves OS and PFS of women with locally advanced cervical cancer (CCCMAC 2010; Green 2005). It is possible that the exclusion of women with bulky early lesions from the trials could alter these results.

Chemotherapy toxicity may delay radiotherapy, which may be harmful, since local disease control has been shown to fall by up to 1% per day if treatment is prolonged beyond seven weeks (Perez 1995). We were unable to analyse late toxicity as this was not reported by the included trials. While acute side effects are generally of short duration and resolve with medical management (Morris 1999), the late complications of radiotherapy can lead to damage which can be difficult to reverse, and may permanently impair quality of life (QoL). As data on late morbidity are sparse, there is insufficient evidence to say whether it increases with combined therapy (CCCMAC 2010; Green 2005).

We were unable to obtain data about QoL. Increasing interest in the systematic assessment of QoL in cancer patients using standardised, self-administered instruments has emerged over the past two decades, and has become an important focus in the evaluation of the benefit of newer therapies (Ganz 1994; Sloan 2002).

We found no trials comparing platinum-based chemotherapy with no platinum-based chemotherapy after surgery, or after primary radiotherapy, for early cervical cancer. Such trials would not be ethical in high-risk patients as, even although adjuvant radiotherapy has not been shown to improve survival in these women (Rogers 2012), chemoradiation has been shown to improve survival compared with radiotherapy in locally advanced disease (CCCMAC 2010). Ongoing studies in this field, comparing chemoradiation with primary radiotherapy for early cervical cancer without high-risk factors (Hong 2013), and comparing chemoradiation with radiotherapy after surgery in women with intermediate- and high-risk factors (GOG 0263; NCT 00806117), should further elucidate the role of platinum-based chemotherapy in this disease.

Quality of the evidence

It is unclear whether the PFS reported by Peters 2000 is the same as the disease-free survival (DFS) reported by Curtin 1996 and Tattersall 1992 and disease recurrence reported by Protocol CE3005 (Altman 1995). It should be noted that neither trial comparing radiotherapy plus chemotherapy with radiotherapy alone reported allocation concealment, which could have introduced bias. None of the included trials reported blinding of outcome assessors, which could have introduced bias in the assessment of disease progression; hence the meta-analysis of deaths is likely to have greater validity than that of disease progression. Inadequate concealment of allocation and lack of blinding are often associated with an exaggeration of the effects of treatment (Moher 1998; Schulz 1995). None of the trials provided information about QoL.

The trials of Peters 2000 and Protocol CE3005 provide consistent evidence about overall and PFS, however, we downgraded this evidence due to the small size of the trials and the limited period of follow-up. Further research is likely to have an important impact on our confidence in the estimates of effect and may change the estimates. In particular, the trial of Tattersall 1992 may have yielded an inconclusive result because it was so small that it did not have adequate statistical power. It is possible that the limited number of patients enrolled in these studies could be due to the low incidence of cervical cancer in the countries (Australia, UK, USA) in which these trials were conducted. In Australia (SACR 2003), the incidence of cervical cancer is declining. Only 43 new cases of invasive cervical cancer were diagnosed in 2001. The incidence of cervical cancer was reduced by 38% between the years of 1997 to 1999, in comparison with the period of 1977 to1981 (SACR 2001). In addition, the incidence in 2001 showed a 25% reduction when compared with the incidence seen in 1998 to

2000. This downward trend is attributed mostly to the screening and detection of precursor lesions, and their early treatment. The same has occurred in the USA, where the incidence of cervical cancer declined from 13 cases/100,000 women per year in 1975 to 1979 to eight cases/100,000 women in the year 2000 (NCI 2004). In developing countries, on the other hand, the numbers are markedly different, with incidences of cervix cancer as high as 58 cases/100,000 women per year and 31 cases/100,000 women per year in Bolivia and Brazil, respectively (PAHO 2003). Therefore, large multicentre RCTs should include centres in developing countries, where there is a higher prevalence of this disease.

Potential biases in the review process

A comprehensive search was performed, including searches of conference abstracts and clinical trial registers for unpublished results; and all studies were sifted and data extracted by at least two review authors independently for the first version of this review. We restricted the included studies to RCTs as they provide the best evidence available. Hence, we have attempted to reduce bias in the review process.

The greatest potential bias in this review was that the report of Peters 2000 was based on an interim analysis of the data which rejected the null hypothesis of no benefit of chemotherapy and so may over-estimate the benefit of the combination of radiotherapy and chemotherapy. We know of no other potential biases in the review process.

Agreements and disagreements with other studies or reviews

Our findings regarding both the benefits and harms of chemotherapy are consistent with those of other reviews. Similar results were found in a systematic review of concurrent chemoradiation for locally advanced cancer of the uterine cervix (stage IB to IVA), giving an absolute benefit of 10% in OS and of 13% in PFS (Green 2005). In the meta-analysis of Green 2005, acute toxicity, predominantly haematological and gastro-intestinal, was increased in the combined arms (concomitant chemoradiation) of all trials evaluating locally advanced cervical cancer. The CCCMAC 2010 review of individual patient data found an absolute OS benefit of chemoradiation versus radiotherapy of 6% ($P < 0.001$) in locally advanced cervical cancer. Furthermore, they found that the earlier stage lesions may be associated with a greater benefit (10% for stage IA to IIA).

AUTHORS' CONCLUSIONS

Implications for practice

Women with operable early stage cervical cancer (IA2 to IIA) may benefit from the addition of cisplatin-based chemotherapy to adjuvant radiotherapy. However, since subgroup analyses according to stage and size were not possible, it is not clear that the survival benefits apply equally to all early stage lesions. Severe acute toxicities are more likely to occur with chemoradiation than with radiotherapy alone. There is insufficient evidence on late toxicity.

Implications for research

There are very few trials in this area due to difficulties in accrual. We identified three ongoing trials: one trial comparing primary radiotherapy with primary chemoradiation in stage IB to IIB cervical cancer with no high-risk factors (Hong 2013) and two multicentre trials comparing adjuvant chemoradiation with adjuvant radiotherapy in stages I to IIA with intermediate- and high-risk factors (GOG 0263; NCT 00806117). In addition to these ongoing trials, RCTs comparing adjuvant platinum-based chemotherapy with adjuvant radiotherapy and/or chemoradiation for early invasive cervical cancer would be helpful to our understanding of the treatment options for this condition. Such trials should be stratified by FIGO stage and should include evaluation of QoL and toxicity. Since cervical cancer is much more prevalent in developing countries, researchers should collaborate with centres in these regions.

ACKNOWLEDGEMENTS

We thank Sarah Jordan and Caroline Price of the University of Birmingham, UK, for supplying unpublished individual patient data for the CE3005 trial. We thank Chris Williams for his clinical and editorial advice for the first version of the review and Jo Morrison for subsequent updates, Gail Quinn and Clare Jess for their contribution to the editorial process, Andrew Bryant for drafting the 'Summary of findings' and 'Risk of bias' tables and the referees for their many helpful suggestions. We thank Jane Hayes and Jo Platt of the CGNOC for conducting the updated search and Tess Lawrie for assisting us with updating the review. We would also like to thank Heather Dickinson for her contribution to the original review.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Peters 2000 *{published data only}*

Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *Journal of Clinical Oncology* 2000;**18**(8):1606-13. [PMID: 10764420]

Protocol CE3005 *{unpublished data only}*

Cancer Research UK. A prospective randomised trial of adjuvant chemotherapy in node positive early stage carcinoma of the cervix - Protocol CE3005. UK Clinical Trials Register 2001.

Sun 2015 *{published data only}*

Sun W, Wang T, Shi F, Wang J, Hui B, Zhang Y, et al. Randomized phase III trial of radiotherapy or chemoradiotherapy with topotecan and cisplatin in intermediate-risk cervical cancer patients after radical hysterectomy. *BMC Cancer* 2015;**15**:353.

Tattersall 1992 *{published data only}*

Tattersall MH, Ramirez C, Coppleson M. A randomized trial of adjuvant chemotherapy after radical hysterectomy in stage Ib-IIa cervical cancer patients with pelvic lymph node metastases. *Gynecologic Oncology* 1992;**46**(2):176-81. [PMID: 1500019]

References to studies excluded from this review

Argenta 2006 *{published data only}*

Argenta PA, Ghebre R, Dusenbery KE, Chen MD, Judson PL, Downs LS, et al. Radiation therapy with concomitant and adjuvant cisplatin and paclitaxel in high-risk cervical cancer: long-term follow-up. *European Journal of Gynaecological Oncology* 2006;**27**(3):231-5. [PMID: 16800247]

Blohmer 2001 *{published data only}*

Blohmer JU, Paepke S, Bohmer D, Ernhardt B, Sehouli J, Elling D, et al. Adjuvant chemotherapy of cervix carcinoma--results of a phase II study. *Zentralblatt fur Gynakologie* 2001;**123**(5):286-91.

Buxton 1990 *{published data only}*

Buxton EJ, Saunders N, Blackledge GR, Kelly K, Redman CW, Monaghan J, et al. The potential for adjuvant therapy in early-stage cervical cancer. *Cancer Chemotherapy and Pharmacology* 1990;**26**(Suppl 26):S17-21. [PMID: 1693315]

Chatterjee 2013 *{published data only}*

Chatterjee K, Mondal SK, Sarkar P. Adjuvant chemotherapy in the management of cervical cancers - A prospective randomized study. In: European Journal of Cancer. Conference: European Cancer Congress 2013, ECC 2013 Amsterdam Netherlands edition. Vol. 49. 2013:S721-S722.

Curtin 1996 *{published data only}*

Curtin JP, Hoskins WJ, Venkatraman ES, Almadrones L, Podratz KC, Long H, et al. Adjuvant chemotherapy versus chemotherapy plus pelvic irradiation for high-risk cervical cancer patients after radical hysterectomy and pelvic lymphadenectomy (RH-PLND): a randomized phase III trial. *Gynecologic Oncology* 1996;**61**:3-10. [PMID: 8626113]

Dimpfl 1996 *{published data only}*

Dimpfl T, Stumpfe M, Baltzer J, Genz T. Results of adjuvant chemotherapy of operated high risk cervix carcinoma. *Geburtshilfe Frauenheilkd* 1996;**56**(10):517-9. [PMID: 9036063]

Frigerio 1994 *{published data only}*

Frigerio L, Busci L, Rabaiotti E, Mariani A. Adjunctive radiotherapy after radical hysterectomy in high risk early stage cervical carcinoma. Assessment of morbidity and recurrences. *European Journal of Gynaecological Oncology* 1994;**15**(2):132-7. [PMID: 8005143]

Hansgen 2001 *{published data only}*

Hansgen G, Dunst J. Adjuvant radio- and chemotherapy in cervix carcinoma. *Zentralblatt fur Gynakologie* 2001;**123**(5):280-5. [PMID: 11449621]

Hansgen 2002 *{published data only}*

Hansgen G, Kuhnt T, Pigorsch S, Strauss H, Dunst J. Adjuvant simultaneous radiochemotherapy after operated uterine cervix carcinoma in high risk situation. Results of a pilot study. *Strahlentherapie und Onkologie* 2002;**178**(2):71-7. [PMID: 11942040]

Harrand 2013 *{published data only}*

Harrand R, Sadozye AH, Siddiqui N, Burton K, Shanbhag S, Davis J, et al. Audit of adjuvant cisplatin +/-vaginal brachytherapy following radical hysterectomy and nodal dissection for cervical cancer. In: International Journal of Gynecological Cancer. 18th International Meeting of the European Society of Gynaecological Oncology, ESGO 2013 Liverpool United Kingdom edition. Vol. 23. 2013:231.

Ikeda 1994 *{published data only}*

Ikeda M, Teshima K, Noda K, Yamagata S, Sugawa T, Okamura S, et al. Long-term administration of carmofur as a post-operative adjuvant chemotherapy for cervical adenocarcinoma. Cervical Adenocarcinoma Cooperative Research Association. *Gan To Kagaku Ryoho* 1994;**21**(12):1967-74.

Iwasaka 1998 *{published data only}*

Iwasaka T, Kamura T, Yokoyama M, Matsuo N, Nakano H, Sugimori H. Adjuvant chemotherapy after radical hysterectomy for cervical carcinoma: a comparison with effects of adjuvant radiotherapy. *Obstetrics and Gynecology* 1998;**91**(6):977-81. [PMID: 9611008]

Kato 1994 *{published data only}*

Kato T, Yakushiji M, Yamabe T, Sugimori H, Hidaki T, Tsukamoto N, et al. A multicenter cooperative study on supplementary chemotherapy of uterocervical cancer. The Kyushu UFT Study Group of Uterocervical Cancer. *Gan To Kagaku Ryoho* 1994;**21**(8):1221-7.

Kemnitz 1991 *{published data only}*

Kemnitz T, Krafft W, Glaser F, Schirmer A. Efficacy of adjuvant chemotherapy in metastasizing cervix carcinoma. A pilot study. *Zentralblatt fur Gynakologie* 1991;**113**(13):777-81. [PMID: 1927129]

Killackey 1993 *{published data only}*

Killackey MA, Boardman L, Carroll DS. Adjuvant chemotherapy and radiation in patients with poor prognostic stage Ib/IIa cervical cancer. *Gynecologic Oncology* 1993;**49**(3):377-9. [PMID: 8314541]

Kim 2007 *{published data only}*

Kim YB, Cho JH, Keum KC, Lee CG, Seong J, Suh CO, et al. on current chemoradiotherapy followed by adjuvant chemotherapy in uterine cervical cancer patients with high-risk factors. *Gynecologic Oncology* 2007;**104**(1):58-63. [PMID: 16919718]

Koh 2000 *{published data only}*

Koh WJ, Panwala K, Greer B. Adjuvant therapy for high-risk, early stage cervical cancer. *Seminars in Radiation Oncology* 2000;**10**(1):51-60. [PMID: 10671659]

Lahousen 1990 *{published data only}*

Lahousen M, Haas J. Adjuvant chemotherapy in radical surgery of cervix cancer. *Zentralblatt fur Gynakologie* 1990;**112**(11):707-13. [PMID: 2399774]

Lahousen 1999 *{published data only}*

Lahousen M, Haas J, Pickel H, Hackl A, Kurz C, Ogris H, et al. Chemotherapy versus radiotherapy versus observation for high-risk cervical carcinoma after radical hysterectomy: A randomized, prospective, multicenter trial. *Gynecologic Oncology* 1999;**73**(2):196-201. [PMID: 10329034]

Lai 1989 *{published data only}*

Lai CH, Lin TS, Soong YK, Chen HF. Adjuvant chemotherapy after radical hysterectomy for cervical carcinoma. *Gynecologic Oncology* 1989;**35**(2):193-8. [PMID: 2478428]

Lai 1998 *{published data only}*

Lai CH, Tang SG, Chang TC, Tseng CJ, Chou HH, Huang KG, et al. Implications of a failed prospective trial of adjuvant therapy after radical hysterectomy for stage Ib-IIa cervical carcinoma with pelvic node metastases. *Changgeng Yi Xue Za Zhi* 1998;**21**(3):291-9. [PMID: 9849010]

Lai 1999 *{published data only}*

Lai CH, Hong JH, Hsueh S, Ng KK, Chang TC, Tseng CJ, et al. Preoperative prognostic variables and the impact of postoperative adjuvant therapy on the outcomes of Stage IB or II cervical carcinoma patients with or without pelvic lymph node metastases: an analysis of 891 cases. *Cancer* 1999;**85**(7):1537-46.

Lee 2013 *{published data only}*

Lee TS, Kang SB, Kim YT, Park BJ, Kim YM, Lee JM, et al. Chemoradiation with paclitaxel and carboplatin in high-risk cervical cancer patients after radical hysterectomy: a Korean Gynecologic Oncology Group study. *International Journal of Radiation Oncology, Biology, Physics* 2013;**86**(2):304-10.

Lin 1998 *{published data only}*

Lin H, ChangChien CC, Chang SY, Leung SW. Survival advantages and complications of adjuvant therapy in early-stage cervical cancer with pelvic node metastasis. *Changgeng Yi Xue Za Zhi* 1998;**21**(4):383-90.

Lin 2000 *{published data only}*

Lin H, ChangChien CC, Huang EY, Eng HL, Huang CC. The role of radical surgery followed by adjuvant therapy for high-risk early-stage cervical carcinoma patients with pelvic lymph node metastasis. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 2000;**93**(1):85-90. [MEDLINE: PMID: 11000510]

Linghu 2003 *{published data only}*

Linghu H, Xu XR, Mei YY, Tang JY, Tang LD, Sun T. Short-time analysis for adjuvant chemotherapy in patients with early- stage bulky cervical carcinoma. *Chinese Journal for Cancer Research* 2003;**15**(2):144-8. [Embase]

Liu 2014 *{published data only}*

Liu J, Huang H, Li JD, Li YF, Huang X, Zhang YN, et al. Comparison of different adjuvant therapy after radical surgery in early stage cervical carcinoma-interim analysis of a 3-arm randomized control study. In: International Journal of Gynecological Cancer. Conference: 15th Biennial Meeting of the International Gynecologic Cancer Society Melbourne, VIC Australia edition. Vol. 24 (Supplement 4). 2014:7-8.

Lu 2000 *{published data only}*

Lu KH, Burke TW. Early cervical cancer. *Current Treatment Options in Oncology* 2000;**1**(2):147-55. [PMID: 12057052]

McCaffrey 2011 *{published data only}*

McCaffrey R, Bahtiyar M, Kohorn EI, Chambers JT, Schwartz PE, Chambers SK. Neoadjuvant and adjuvant chemotherapy of cervical cancer: Mature results of the phase 2 PBM-PFU protocol. *International Journal of Gynecological Cancer* 2011;**21**:535-44.

Morris 1999 *{published data only}*

Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *New England Journal of Medicine* 1999;**340**(15):1137-43. [PMID: 10202164]

Morton 1996 *{published data only}*

Morton GC, Thomas GM. Does adjuvant chemotherapy change the prognosis of cervical cancer? *Current Opinions in Obstetrics and Gynecology* 1996;**8**(1):17-20. [MEDLINE: PMID: 8777252]

Mossa 2003 *{published data only}*

Mossa B, Framarino ML, Napolitano C, Marziani R, Imperato F, Marzetti L. Does adjuvant chemotherapy improve the prognosis of cervical carcinoma with lymph-node metastasis? A long-term follow-up. *European Journal of Gynaecologic Oncology* 2003;**24**(1):33-40. [MEDLINE: PMID: 12691314]

MRC CE04/EORTC55954 *{unpublished data only}*

EORTC-55954, COSA, EU-98061, NSGO-CC-9502, MRC-CE04. A randomised phase III study of chemotherapy and radiotherapy vs. radiotherapy alone as adjuvant treatment to patients with node positive stages IB or IIA cervix cancer. http://www.controlled-trials.com/mrct/trial/391321/MRC-CE04.

Nakamura 2014 *{published data only}*

Nakamura K, Satoh T, Takei Y, Nagao S, Sekiguchi I, Suzuki M. Analysis of the effect of adjuvant radiotherapy on outcome and complications after radical hysterectomy in FIGO stage IB1 cervical cancer patients with intermediate risk factors. In: Gynecologic Oncology. 45th Annual Meeting on Women's Cancer of the Society of Gynecologic Oncology, SGO 2014 Tampa, FL United States edition. Vol. 133 (Supplement 1). 2014:61-2.

Ng 1995 *{published data only}*

Ng HT, Yuan CC, Kan YY, Ho ES, Yen MS, Chao KC. An evaluation of chemotherapy in patients with cancer of the cervix and lymph node metastases. *Archives of Gynecology and Obstetrics* 1995;**256**(1):1-4. [PMID: 7726648]

Park 1997 *{published data only}*

Park TK. Adjuvant therapy in cervical cancer patients with high risk factors. *Yonsei Medical Journal* 1997;**38**(5):255-60. [MEDLINE: 9409188]

Park 2001 *{published data only}*

Park TK, Kim SN, Kwon JY, Mo HJ. Postoperative adjuvant therapy in early invasive cervical cancer patients with histopathologic high-risk factors. *International Journal of Gynecological Cancer* 2001;**11**(6):475-82. [PMID: 11906552]

Park 2012 *{published data only}*

Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Kim YS, ET AL. Comparison of outcomes between radical hysterectomy followed by tailored adjuvant therapy versus primary chemoradiation therapy in IB2 and IIA2 cervical cancer. *Journal of Gynecologic Oncology* 2012;**23**(4):226-34.

Pu 2013 *{published data only}*

Pu J, Qin SS, Ding JX, Zhang Y, Yu CH, Li T, et al. A randomized controlled study of single-agent cisplatin and radiotherapy versus docetaxel/cisplatin and radiotherapy in high-risk early-stage cervical cancer after radical surgery. *Journal of Cancer Research and Clinical Oncology* 2013;**139**(4):703-8.

Richter 1982 *{published data only}*

Richter P. About the value of adjuvant chemotherapy in advanced cervical cancer. First results of a prospective randomised study (author's transl). *Archiv für Geschwulstforschung* 1982;**52**(2):117-22. [PMID: 7049112]

Rogers 2012 *{published data only}*

Rogers L, Siu SS, Luesley D, Bryant A, Dickinson HO. Radiotherapy and chemoradiation after surgery for early cervical cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No: CD007583. [DOI: 10.1002/14651858.CD007583.pub3]

Roth 1994 *{published data only}*

Roth SL, Nitz U, Mosny D. The value of adjuvant radio- or chemotherapy after primary surgical therapy of cervix cancer. 1. Adjuvant radiotherapy of cervix cancer. *Gynakologe* 1994;**27**(2):89-95. [PMID: 8039748]

Rushdan 2004 *{published data only}*

Rushdan MN, Tay EH, Khoo-Tan HS, Lee KM, Low JH, Ho TH, et al. Tailoring the field and indication of adjuvant pelvic radiation for patients with FIGO stage Ib lymph nodes-negative cervical carcinoma following radical surgery based on the GOG score - A pilot study. *Annals of the Academy of Medicine, Singapore* 2004;**33**(4):467-72. [15329758]

Russel 1995 *{published data only}*

Russell AH. Adjuvant postoperative radiation: what size target? *Gynecologic Oncology* 1995;**58**(1):1-3. [PMID: 7789872]

Ryu 2005 *{published data only}*

Ryu HS, Chun M, Chang KH, Chang HJ, Lee JP. Postoperative adjuvant concurrent chemoradiotherapy improves survival rates for high-risk, early stage cervical cancer patients. *Gynecologic Oncology* 2005;**96**(2):490-5. [PMID: 15661240]

Schwarz 2011 *{published data only}*

Schwarz JK, Wahab S, Grigsby PW. Prospective phase I-II trial of helical tomotherapy with or without chemotherapy for postoperative cervical cancer patients. *International Journal of Radiation Oncology, Biology, Physics* 2011;**81**(5):1258-63.

Sehouli 2012 *{published data only}*

Sehouli J, Runnebaum IB, Fotopoulou C, Blohmer U, Belau A, Leber H, et al. A randomized phase III adjuvant study in high-risk cervical cancer: simultaneous radiochemotherapy with cisplatin (S-RC) versus systemic paclitaxel and carboplatin followed by percutaneous radiation (PC-R): a NOGGO-AGO Intergroup Study. *Annals of Oncology* 2012;**23**(9):2259-64.

Shimizu 1995 *{published data only}*

Shimizu Y. Chemotherapy in the management of advanced or high risk cervical cancer. *Gan To Kagaku Ryoho* 1995;**22**(9):1152-62. [MEDLINE: PMID: 7661566]

Shu 2015 *{published data only}*

Shu P, Shen Y, Zhao Y, Xu F, Qiu M, Li Q, et al. A phase I study of adjuvant intensity-modulated radiotherapy with concurrent paclitaxel and cisplatin for cervical cancer patients with high risk factors. *Medical Oncology* 2015;**32**(11):247.

Sivanesaratnam 1987 *{published data only}*

Sivanesaratnam V, Sen DK, Jayalakshmi P. Adjuvant cytotoxic chemotherapy following Wertheim radical hysterectomy for cervical cancer. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1987;**27**(3):231-3. [PMID: 2449159]

Sivanesaratnam 1989 *{published data only}*

Sivanesaratnam V, Jayalakshmi P. Mitomycin C adjuvant chemotherapy after Wertheim's hysterectomy for stage IB cervical cancer. *Cancer* 1989;**64**(4):798-800. [PMID: 2501019]

Sivanesaratnam 1998 *{published data only}*

Sivanesaratnam V. Adjuvant chemotherapy in "high risk" patients after Wertheim hysterectomy -10-year survivals. *Annals Academy of Medicine Singapore* 1998;**27**(5):622-6. [PMID: 9919328]

Strauss 2002 *{published data only}*

Strauss HG, Kuhnt T, Laban C, Puschmann D, Pigorsch S, Dunst J, et al. Chemoradiation in cervical cancer with cisplatin and high-dose rate brachytherapy combined with external beam radiotherapy. Results of a phase-II study. *Strahlentherapie und OnkologieStrahlenther Onkol* 2002;**178**(7):378-85. [PMID: 12163992]

Wada 1995 *{published data only}*

Wada K, Koyama M, Iijima Y, Inagaki M, Hirota Y, Hongo J, et al. Usefulness of adjuvant chemotherapy with antimetabolites for cervical invasive cancer. *Nippon Sanka Fujinka Gakkai Zasshi* 1995;**47**(3):244-8.

Wang 2015 *{published data only}*

Wang X, Shen Y, Zhao Y, Li Z, Gou H, Cao D, et al. Adjuvant intensity-modulated radiotherapy (IMRT) with concurrent paclitaxel and cisplatin in cervical cancer patients with high risk factors: A phase II trial. *European Journal of Surgical Oncology* 2015;**41**(8):1082-8.

Watanabe 2006 *{published data only}*

Watanabe Y, Nakai H, Shimaoka M, Tobiume T, Tsuji I, Hoshiai H. Feasibility of concurrent cisplatin use during primary and adjuvant chemoradiation therapy: a phase I study in Japanese patients with cancer of the uterine cervix. *International Journal of Clinical Oncology* 2006;**11**(4):309-13. [PMID: 16937305]

Wen 2013 *{published data only}*

Wen H, Liu T. Treatment results of adjuvant chemotherapy for patients with intermediate-risk cervical cancer. In: International Journal of Gynecological Cancer. 18th International Meeting of the European Society of Gynaecological Oncology, ESGO 2013 Liverpool United Kingdom edition. Vol. 23. 2013:806.

Wertheim 1985 *{published data only}*

Wertheim MS, Hakes TB, Doghestani AN, Nori D, Smith DH, Lewis JL Jnr. A pilot study of adjuvant therapy in patients with cervical cancer at high risk of recurrence after radical hysterectomy and pelvic lymphadenectomy. *Journal of Clinical Oncology* 1985;**3**(7):912-6.

Wolfson 2012 *{published data only}*

Wolfson AH, Varia MA, Moore D, Rao GG, Gaffney DK, Erickson-Wittmann BA, et al. ACR Appropriateness Criteria role of adjuvant therapy in the management of early stage cervical cancer. *Gynecologic Oncology* 2012;**125**(1):256-62.

Yamamoto 2004 *{published and unpublished data}*

Yamamoto K, Izumi R, Hasegawa K, Nakajima H, Ohashi K, Kudo R et, al. Adjuvant oral 5-fluorouracil for cervical cancer: Japanese Gynecologic Oncology Group report. *International Journal of Oncology* 2004;**24**(5):1175-9. [PMID: 15067339]

Yessaian 2004 *{published data only}*

Yessaian A, Magistris A, Burger RA, Monk BJ. Radical hysterectomy followed by tailored postoperative therapy in the treatment of stage IB2 cervical cancer: feasibility and indications for adjuvant therapy. *Gynecologic Oncology* 2004;**94**(1):61-6. [PMID: 15262120]

Yoon 2014 *{published data only}*

Yoon H, Cha J, Kim G, Chung Y, Kim Y. The long-term follow-up result of extended field radiation therapy for uterine cervical cancer with positive para-aortic lymph nodes: Does the addition of chemotherapy have survival benefit? In: International Journal of Radiation Oncology, Biology, Physics. 56th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2014 San Francisco, CA United States edition. Vol. 90. 2014:S479.

Zanetta 1995 *{published data only}*

Zanetta G, Colombo A, Milani R, Placa F, Mangioni C. Long-term results of sequential postoperative treatment with vincristine, bleomycin, mitomycin c, cis-platin and radiotherapy after surgery for high-risk patients with cervical carcinoma stage IB-IIA. *International Journal of Gynecological Cancer* 1995;**5**(1):40-4. [PMID: 11578451]

Zhang 2012 *{published data only}*

Zhang N, Zheng H, Gao Y. The effectiveness and safety of adjuvant chemotherapy in patients with intermediate-risk early stage cervical cancer after radical hysterectomy. In: International Journal of Gynecological Cancer. 14th Biennial Meeting of the International Gynecologic Cancer Society, IGCS 2012 Vancouver, BC Canada edition. Vol. 22. 2012:E800.

Zola 2003 *{published data only}*

Zola P, Landoni F, Torri W, Buda A, Mazzola S. Randomised controlled trial of adjuvant treatment in early invasive cervical cancer [abstract]. *International Journal of Gynecological Cancer* 2003;**13 Suppl 1**:5-6.

References to ongoing studies

GOG 0263 *{published data only}*

Ryu SY, Koh W. Radiation therapy with or without chemotherapy in patients with stage I or stage II cervical cancer who previously underwent surgery. www.ClinicalTrials.gov; NCT01101451.

Hong 2013 *{published data only}*

Hong J-H. Cisplatin based chemoradiation v.s radiotherapy for cervical cancer and with clinically defined good prognosis. www.ClinicalTrials.gov;:NCT00846508.

NCT 00806117 *{published data only}*

Liu J, Huang H. A multicenter trial of benefits of adding post-surgery chemotherapy for cervical cancer. www.ClinicalTrials.gov; NCT00806117.

Additional references

Adobe 2007 [Computer program]

Adobe Photoshop CS3 extended (2007). Adobe. Adobe Systems Incorporated, 2007.

Altman 1995

Altman DG, De Stavola BL, Love SB, Stepniewska KA. Review of survival analyses published in cancer journals. *British Journal of Cancer* 1995;**72**:511-8.

Benedet 2003

Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, Heintz AP, et al. Carcinoma of the cervix uteri. *International Journal of Gynaecology and Obstetrics* 2003;**83**(Suppl 1):41-78.

CCCMAC 2010

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No: CD008285. [DOI: 10.1002/14651858.CD008285]

CTCAE 4.0

National Cancer Institute. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Curtin 1997

Curtin JP, Shapiro F. Adjuvant therapy in gynecologic malignancies. Ovarian, cervical, and endometrial cancer. *Surgical Oncology Clinics of North America* 1997;**6**(4):813-30. [MEDLINE: PMID: 9309095]

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, editors(s). Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd edition. BMJ Publication Group, 2001.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

EUROCARE 2014

De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al, EUROCARE-5 Working Group. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5 - a population-based study. *Lancet Oncology* 2014;**15**(1):23-34.

Ganz 1994

Ganz PA. Quality of life and the patient with cancer: Individual and policy implications. *Cancer* 1994;**74**:1445.

GLOBOCAN 2012

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, 2013.

Green 2005

Green JA, Kirwan JJ, Tierney J, Vale CL, Symonds PR, Fresco LL, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No: CD002225. [DOI: 10.1002/14651858.CD002225.pub2]

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration 2011;(Version 5.1):www.cochrane-handbook.org.

Ho 2004

Ho CM, Chien TY, Huang SH, Wu CJ, Shih BY, Chang SC. Multivariate analysis of the prognostic factors and outcomes in early cervical cancer patients undergoing radical hysterectomy. *Gynecologic Oncology* 2004;**93**(2):458-64. [MEDLINE: PMID: 15099962]

Holtz 2002

Holtz DO, Dunton C. Traditional management of invasive cervical cancer. *Obstetrics and Gynecology Clinics of North America* 2002;**29**:645-87.

Im 2002

Im SS, Monk BJ. New developments in the treatment of invasive cervical cancer. *Obstetrics and Gynecology Clinics of North America* 2002;**29**(4):659-72..

Kinney 1989

Kinney WK, Alvarez RD, Reid GC, Schray MF, Soong SJ, Morley GW, et al. Value of adjuvant whole-pelvis irradiation after Wertheim hysterectomy for early-stage squamous carcinoma of the cervix with pelvic nodal metastasis: a matched-control study. *Gynecologic Oncology* 1989;**34**:258-62.

Maduro 2003

Maduro JH, Pras E, Willemse PH, de Vries EG. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. *Cancer Treatment Reviews* 2003;**29**:471-88.

McCullagh 1989

McCullagh P, Nelder JA. Generalized Linear Models. London: Chapman and Hall, 1989.

Moher 1998

Moher D, Pham D, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**:609-13.

Monk 1994

Monk BJ, Cha DS, Walker JL, Burger RA, Ramsinghani NS, Manetta A, et al. Extent of disease as an indication for pelvic radiation following radical hysterectomy and bilateral pelvic lymph node dissection in the treatment of stage IB and IIA cervical carcinoma. *Gynecologic Oncology* 1994;**54**:4-9.

NCI 2004

Surveillance EaERSP. SEER Public-Use 1973-2001. National Cancer Institute. National Cancer Institute, 2004.

Nitz 1994

Nitz U, Roth SL, Mosny D. The value of adjuvant radio- or chemotherapy after primary surgical therapy of cervix cancer. 2. Adjuvant chemotherapy of cervix cancer. *Der Gynäkologe* 1994;**27**(2):95-8. [MEDLINE: PMID: 8039749]

PAHO 2003

Pan American Health Organisation. Regional Core Health Data Initiative. *Epidemiological Bulletin* 2003;**24**:14-5.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**:2815-34.

Pecorelli 2009

Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *International Journal of Gynaecology and Obstetrics* 2009;**105**(2):107-8.

Perez 1995

Perez CA, Grigsby PW, Castro Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of treatment time and timing of brachytherapy on outcome of radiation therapy. *International Journal of Radiation Oncology, Biology and Physics* 1995;**32**:1275-88.

RevMan 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

SACR 2001

South Australian Cancer Registry. Epidemiology of cancer in South Australia. Incidence, mortalityand survival, 1977-2000. Incidence and mortality, 2000. Adelaide: Openbook Publishers, 2001.

SACR 2003

South Australian Cancer Registry. Epidemiology of cancer in South Australia. Incidence, mortality and survival 1977 to 2001. Incidence and mortality 2001. Analysed by type and geographical location. Twenty-five years of data. Adelaide: South Australian Cancer Registry. Epidemiology Branch, 2001.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408-12.

Sloan 2002

Sloan JA, Cella D, Frost M. Assessing clinical significance in measuring oncology patient quality of life: introduction to the symposium, content overview, and definition of terms. *Mayo Clinic Proceedings* 2002;**77**:367.

StataCorp 2005 [Computer program]

College Station, TX: StataCorp LP StataCorp. Stata Statistical Software: Release 9. College Station, TX: StataCorp LP, 2005.

Thomas 1996

Thomas GM. Adjuvant therapy after primary surgery for stage I-IIA carcinoma of the cervix. *Journal of the National Cancer Institute Monograph* 1996;**21**:77-86.

References to other published versions of this review

Rosa 2005

Rosa DD, Medeiros LRF, Bozzetti MC, Edelweiss MI, Pohlmann PR, Stein AT. Adjuvant chemotherapy for early stage cervix cancer. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No: CD005342. [DOI: 10.1002/14651858.CD005342]

Rosa 2009

Rosa DD, Medeiros LRF, Edelweiss EI, Bozzetti MC, Pohlmann PR, Stein AT. Adjuvant platinum-based chemotherapy for early stage cervical cancer. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD005342. [DOI: 10.1002/14651858.CD005342.pub2]

Rosa 2012

Rosa DD, Medeiros LR, Edelweiss MI, Pohlmann PR, Stein AT. Adjuvant platinum-based chemotherapy for early stage cervical cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 6. Art. No: CD005342. [DOI: 10.1002/14651858.CD005342.pub3]

CHARACTERISTICS OF STUDIES

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

Peters 2000

Study characteristics	
Methods	RCT
Participants	Country: USA Enrolled 268 patients, stage IA2, IB or IIA Underwent radical hysterectomy and pelvic lymphadenectomy.

Peters 2000 *(Continued)*

	Ineligible 15 Assessed 243 (91%)
Interventions	Chemotherapy plus radiotherapy versus radiotherapy Arm 1: chemotherapy began on day 1 of radiotherapy and consisted of cisplatin 70 mg/m^2 by 2-hour intravenous infusion given on day 1 and 5-FU 1000 mg/m^2 per day given as a 96-hour continuous infusion on days 1 to 4. The second cycle of chemotherapy began on day 22, and the third and fourth cycles of chemotherapy were scheduled after completion of radiotherapy, to begin on days 43 and 64. Arm 2: consisted of 1.7 Gy per day on days 1 to 5 each week, for a total of 29 fractions (49.3 Gy); pelvic radiotherapy was given to a standard four-field box. Patients with positive high common iliac lymph nodes also received treatment to a para-aortic field with a dose of 1.5 Gy per day on days 1 to 5 of each week, for a total of 30 fractions. The radiation source of treatment was 4MeV or more. Brachytherapy was not permitted.
Outcomes	Overall survival Progression-free survival Grade 3/4 toxicity
Notes	Statistics on survival: Cox HR and P value. Kaplan-Meier survival plots; minimum follow-up estimated from dates of accrual and date of interim analysis. No. of deaths and disease recurrences by treatment arm. The estimated 4-year survival was 81% for chemotherapy plus radiotherapy and 71% for radiotherapy only. The estimated 4-year progression-free survival for patients receiving chemotherapy plus radiotherapy was 80%, versus 63% for patients receiving radiotherapy alone. Median follow-up: 42 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported, "Patients were randomised to either pelvic radiotherapy or pelvic radiotherapy with four cycles of chemotherapy".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For all survival outcomes: % analysed: 243/243 (100%) For toxicity: % analysed: 234/243 (96%) Chemotherapy + radiotherapy group: 122/127 (96%) Radiotherapy group: 112/116 (97%) "122 patients assessable for toxicity in the chemotherapy+ radiotherapy arm ... 112 patients randomised to RT alone and assessable for toxicity".

Peters 2000 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	High risk	Based on an interim analysis of the data which rejected the null hypothesis of no benefit of chemotherapy.

Protocol CE3005

Study characteristics	
Methods	RCT
Participants	Country: UK Enrolled 57 patients, stage IB or IIA Underwent primary surgery Assessed 54 (95%)
Interventions	Arm A: External beam pelvic radiotherapy (EBRT). Arm B: Adjuvant chemotherapy with bleomycin plus ifosfamide plus cisplatin plus external beam radiotherapy.
Outcomes	Survival, recurrence and toxicity.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For all outcomes: % analysed: 54/57 (95%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to permit judgement.

Sun 2015

Study characteristics

Sun 2015 *(Continued)*

Methods	RCT
Participants	Country: China Enrolled 39 patients, stage IA2, IB or IIA Underwent radical hysterectomy and pelvic lymphadenectomy with or without para-aortic lymphadenectomy via laparotomy or laparoscopy Assessed 33 (84%)
Interventions	Radiotherapy versus radiotherapy plus chemoradiotherapy versus chemoradiotherapy plus consolidation chemotherapy Arm 1 (radiotherapy): 3D-CRT pelvic radiation, 95%CTV DT 45Gy/25f. Radiation field includes tumour bed and regional lymph nodes area. Upper border was considered as branching of abdominal aorta; lower border was considered as the inferior margin of obturator foramen. The radiation fields go down along the iliac vessels (including regions of 7 mm out of the iliac vessels) and include the tumour bed region. Arm 2 (chemoradiotherapy): radiotherapy as described for Arm 1 plus topotecan 0.75 mg/m^2 intravenously during 30 minutes on the days 1, 2 and 3 and cisplatin 25 mg/m2^2 intravenously for days 1,2 and 3. Chemotherapy will be carry out in the 2nd and 6th week of radiation therapy. Arm 3 (chemoradiotherapy plus consolidation chemotherapy): radiotherapy as described for Arm 1 plus topotecan 0.75 mg/m^2 intravenously during 30 minutes on the days 1, 2 and 3 and cisplatin 25 mg/m2^2 intravenously for days 1,2 and 3. Chemotherapy will be carry out in the 2nd and 6th week of radiation therapy. The consolidation chemotherapy regimen was delivered in the 4th and 8th week after radiation therapy and consisted of the same regimen already described.
Outcomes	Toxicity.
Notes	Closed ahead of schedule with median follow-up of 16 months because of severe haematologic toxicity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only reported toxicity outcomes, the median follow-up of 16 months did not permit conclusions about recurrence-free survival or overall survival.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Not reported

Tattersall 1992

Study characteristics	
Methods	RCT
Participants	Country: Australia 71 patients, stage IB or IIA Underwent primary surgery
Interventions	Radiotherapy alone versus chemotherapy followed by radiotherapy Arm 1: chemotherapy with cisplatin 50 mg/m^2, vinblastine 4 mg/m^2, and bleomycin 15 mg all given IV on day 1. Bleomycin 15 mg was given intramuscularly on days 8 and 15 and the cycle was repeated on day 22. The chemotherapy was given by a total of 3 cycles. Pelvic radiotherapy began during the eighth week after initiating chemotherapy. Arm 2: each institution entering patients on the trial had their protocol for pelvic radiotherapy, but the study did not describe it. Although there were variations in treatment between institutions, a total of 40 to 55 Gy was given to the whole pelvis over 4 to 5 weeks.
Outcomes	Disease-free survival.
Notes	Statistics on survival. Kaplan-Meier survival plots; minimum follow-up estimated from dates of accrual and date of submission of manuscript. Median follow-up 30 months.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It is unclear how patients were assigned to groups and if minimisation was used, "patients were stratified prior to randomisation according to the clinical stage, and according to the institution".
Allocation concealment (selection bias)	Low risk	Concealment of allocation was satisfactory, "randomisation was accomplished by telephone to the trial centre".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	% analysed: 71/71 (100%).
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

HR: hazard ratio
IV: intravenous
RCT: randomised controlled trial

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

Study	Reason for exclusion
Argenta 2006	Not an RCT. Included 21 women with stage IB-IV.
Blohmer 2001	The chemotherapeutic regimen of the intervention group did not include cisplatin.
Buxton 1990	Retrospective study.
Chatterjee 2013	RCT of 80 patients comparing adjuvant chemotherapy for stage IB to IIIB cervical carcinoma. The chemotherapy regimen of the intervention group consisted of cisplatin and 5-FU.
Curtin 1996	Not an RCT.
Dimpfl 1996	Non-randomised clinical trial.
Frigerio 1994	Retrospective study.
Hansgen 2001	Review.
Hansgen 2002	Phase II study; included stage IIB patients in the analysis.
Harrand 2013	Retrospective study.
Ikeda 1994	Retrospective study.
Iwasaka 1998	Included stage IIB patients in the analysis.
Kato 1994	The chemotherapeutic regimen of the intervention group did not include cisplatin.
Kemnitz 1991	The study included stage IIB patients in the analysis.
Killackey 1993	Retrospective study.
Kim 2007	Retrospective study. Included patients with stage IIB cervical cancer.
Koh 2000	Review.
Lahousen 1990	Non-randomised study.
Lahousen 1999	The control arm had received only chemotherapy as adjuvant treatment; the chemotherapeutic regimen of the intervention group did not include cisplatin; the study included stage IIB patients in the analysis.
Lai 1989	Non-randomised study.
Lai 1998	More than 70% of patients were lost after randomisation.
Lai 1999	Review.
Lee 2013	Phase II study.
Lin 1998	Retrospective study.
Lin 2000	Retrospective study.
Linghu 2003	Not an RCT. Study of neoadjuvant chemotherapy.

Study	Reason for exclusion
Liu 2014	RCT of 564 patients with stage IB1 to IIA2 cervical carcinoma with high-risk features comparing three groups: 1. Radiotherapy; 2. Radiotherapy with weekly cisplatin; 3. Paclitaxel and cisplatin every three weeks followed by radiochemotherapy with the same regimen. The authors did not report the number of patients allocated for each one of the three groups, doses of chemotherapy regimens, outcomes (DFS, OS or toxicity) for each group. No difference for DFS was found.
Lu 2000	Review.
McCaffrey 2011	Phase II study.
Morris 1999	The study included stage IIB patients in the analysis.
Morton 1996	Review.
Mossa 2003	Retrospective study. Included patients with stage IIB cervical cancer.
MRC CE04/EORTC55954	Study closed due to lack of accrual. Investigators did not reply our e-mails.
Nakamura 2014	Retrospective study.
Ng 1995	Retrospective study.
Park 1997	Review.
Park 2001	Retrospective study.
Park 2012	Retrospective study
Pu 2013	RCT of 320 patients comparing two adjuvant chemotherapy regimens for stage IB to IIA cervical carcinoma. Included patients with high-risk features. Control group consisted of single-agent cisplatin and radiotherapy and the intervention group consisted of docetaxel, cisplatin and radiotherapy.
Richter 1982	The chemotherapeutic regimen of the intervention group did not include cisplatin.
Rogers 2012	A meta-analysis of adjuvant radiotherapy and chemoradiation therapy after surgery for early cervical cancer that found only two trials that did not adressed the subject of chemotherapy.
Roth 1994	Review.
Rushdan 2004	Phase II study.
Russel 1995	Non-randomised study.
Ryu 2005	Retrospective study.
Schwarz 2011	Phase I-II study.
Sehouli 2012	An open-label RCT of 271 patients comparing two adjuvant chemotherapy regimens for stage IB to IIB cervical carcinoma. Included patients with high-risk features. Control group consisted of single-agent cisplatin and radiotherapy and the intervention group consisted of paclitaxel, carboplatin and radiotherapy.
Shimizu 1995	Review.

Study	Reason for exclusion
Shu 2015	Phase I study of one cycle of cisplatin and paclitaxel before, two cycles concurrent with intensity-modulated radiotherapy (IMRT) and one cycle after IMRT as adjuvant treatment to stage IB-IIA cervical cancer with high-risk factors in women that underwent radical hysterectomy and pelvic lymphadenectomy.
Sivanesaratnam 1987	Retrospective study.
Sivanesaratnam 1989	Retrospective study.
Sivanesaratnam 1998	Retrospective study.
Strauss 2002	Phase II study.
Wada 1995	Retrospective study.
Wang 2015	Phase II study.
Watanabe 2006	Phase I study.
Wen 2013	Retrospective study. Included patients with stage IIB cervical cancer.
Wertheim 1985	Retrospective study.
Wolfson 2012	Description of an appropriateness criteria to adjuvant radiotherapy in stage I and II cervical carcinoma.
Yamamoto 2004	The study included stage IIB patients in the analysis; the chemotherapeutic regimen of the intervention group did not include cisplatin.
Yessaian 2004	Retrospective study.
Yoon 2014	Retrospective study. Included patients with advanced stage disease.
Zanetta 1995	Non-randomised study.
Zhang 2012	Retrospective study. Included patients with stage IIB cervical cancer.
Zola 2003	RCT that randomised 199 women after radical hysterectomy and pelvic lymphadenectomy to receive EBRT or platinum-based chemotherapy. After 3 years there was no difference in survival between the two treatment groups.

DFS: disease-free survival
EBRT: External beam pelvic radiotherapy
OS: overall survival
RCT: randomised controlled trial

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

GOG 0263

Study name	GOG 0263 and NCT01101451 Radiation therapy with or without chemotherapy in patients with stage I or stage II cervical cancer who previously underwent surgery

GOG 0263 *(Continued)*

Methods	Multicentre RCT.
Participants	Women with intermediate-risk factors stage I-IIA cervical cancer after treatment with radical hysterectomy.
Interventions	Arm 1: external beam (EBRT) or intensity-modulated radiotherapy (IMRT) 5 days a week for 5.5 weeks Arm 2: weekly cisplatin plus radiotherapy as per arm 1
Outcomes	Primary: RFS Secondary: OS, adverse effects, toxicity and QoL
Starting date	April 2010
Contact information	Sang Y. Ryu, MD, Principal Investigator, Korea Cancer Center Hospital Wui-jin Koh, MD, Fred Hutchinson Cancer Research Center
Notes	

Hong 2013

Study name	NCT00846508 Cisplatin-based chemoradiation versus radiotherapy for cervical cancer and with a clinically-defined good prognosis.
Methods	Single-blind RCT.
Participants	208 women with stage IB - IIB cervical cancer who have no LN or systemic metastases.
Interventions	Arm 1: Primary radiotherapy Arm 2: radiotherapy plus 6 x weekly cisplatin (40 mg/m^2)
Outcomes	Primary: survival and toxicity. Secondary: molecular markers associated with radiosensitivity and distant metastases.
Starting date	February 2009; recruiting.
Contact information	Ji-Hong Hong, Department of Radiation Oncology, LIN KOU Chang Gung memorial Hospital, Taiwan
Notes	

NCT 00806117

Study name	NCT 00806117 A multicentre trial of benefits of adding post-surgery chemotherapy for cervical cancer.

NCT 00806117 *(Continued)*

Methods	Single-blind phase III multicentre RCT underway in Guangzhou Province, China.
Participants	990 women with stage IB-IIA cervical cancer with risk factors for recurrence, and who have undergone radical surgery.
Interventions	Radiotherapy, cisplatin and cisplatin plus paclitaxel. Three groups will be compared: radiotherapy versus chemoradiation (concurrent) versus chemoradiation (sequential).
Outcomes	Primary: distant metastasis-free survival; disease-free survival Secondary: OS
Starting date	February 2008; recruiting.
Contact information	Jihong Liu, Ph.D. tel: 86-20-8734-3102; Liujih@mail.sysu.edu.cn He Huang, Ph.D. tel: 86-20-8734-3104; huangh@sysucc.org.cn
Notes	

OS: overall survival
QoL: quality of life
RCT: randomised controlled trial

DATA AND ANALYSES

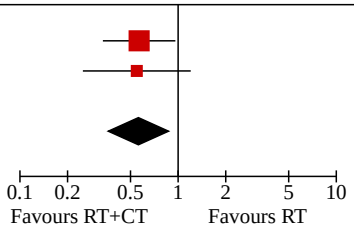
Comparison 1. Radiotherapy plus chemotherapy versus radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death from all causes	2	297	HR (IV, Random, 95% CI)	0.56 [0.36, 0.87]
1.2 Disease progression	2	297	HR (IV, Random, 95% CI)	0.47 [0.30, 0.74]
1.3 Grade 4 toxicity	3	321	Risk Ratio (M-H, Random, 95% CI)	6.26 [2.50, 15.67]

Analysis 1.1. Comparison 1: Radiotherapy plus chemotherapy versus radiotherapy, Outcome 1: Death from all causes

Study or Subgroup	log[HR]	SE	RT+CT Total	RT Total	Weight	HR IV, Random, 95% CI
Peters 2000	-0.5677	0.2692	127	116	68.9%	0.57 [0.33 , 0.96]
Protocol CE3005	-0.6016	0.4005	26	28	31.1%	0.55 [0.25 , 1.20]
Total (95% CI)			**153**	**144**	**100.0%**	**0.56 [0.36 , 0.87]**

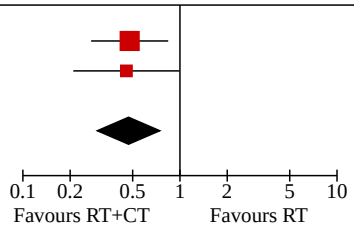
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 2.59 (P = 0.010)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Radiotherapy plus chemotherapy versus radiotherapy, Outcome 2: Disease progression

Study or Subgroup	log[HR]	SE	RT+CT Total	RT alone Total	Weight	HR IV, Random, 95% CI
Peters 2000	-0.7369	0.2883	127	116	65.5%	0.48 [0.27 , 0.84]
Protocol CE3005	-0.7844	0.3975	26	28	34.5%	0.46 [0.21 , 0.99]
Total (95% CI)			**153**	**144**	**100.0%**	**0.47 [0.30 , 0.74]**

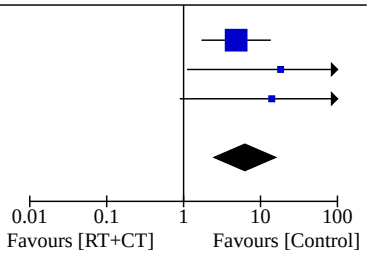
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.23 (P = 0.001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Radiotherapy plus chemotherapy versus radiotherapy, Outcome 3: Grade 4 toxicity

Study or Subgroup	RT+ CT Events	RT+ CT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Peters 2000	21	122	4	112	78.2%	4.82 [1.71 , 13.61]
Protocol CE3005	8	26	0	28	10.7%	18.26 [1.11 , 301.35]
Sun 2015	10	20	0	13	11.1%	14.00 [0.89 , 220.15]
Total (95% CI)		**168**		**153**	**100.0%**	**6.26 [2.50 , 15.67]**
Total events:	39		4			

Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 3.92 (P < 0.0001)
Test for subgroup differences: Not applicable

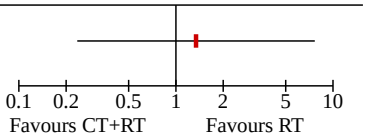


Comparison 2. Chemotherapy followed by radiotherapy versus radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Disease progression	1		HR (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Chemotherapy followed by radiotherapy versus radiotherapy, Outcome 1: Disease progression

Study or Subgroup	log[HR]	SE	CT followed by RT Total	RT Total	HR IV, Random, 95% CI
Tattersall 1992	0.2948	0.8883	34	37	1.34 [0.24 , 7.66]



ADDITIONAL TABLES

Table 1. FIGO staging of cervical cancer

Stage 0	Carcinoma in situ, cervical intraepithelial neoplasia Grade III.
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded). Ia Invasive carcinoma which can be diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are allotted to Stage Ib carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0mm and a horizontal extension of not >7.0 mm. Depth of invasion should not be > 5.0mm taken from the base of the epithelium of the original tissue – superficial or glandular. The involvement of vascular spaces – venous or lymphatic – should not change the stage allotment. Ia1 Measured stromal invasion of not >3.0mm in depth and extension of not >7.0 mm. Ia2 Measured stromal invasion of >3.0mm and not > 5.0 mm with an extension of not >7.0 mm. Ib Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than Stage Ia. Ib1 Clinically visible lesions not > 4.0 cm. Ib2 Clinically visible lesions > 4.0 cm.
Stage II	Cervical carcinoma invades beyond uterus, but not to the pelvic wall or to the lower third of vagina. IIa No obvious parametrial involvement. IIb Obvious parametrial involvement.
Stage III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to other cause. IIIa Tumor involves lower third of the vagina, with no extension to the pelvic wall. IIIb Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV. IVa Spread of the growth to adjacent organs. IVb Spread to distant organs.

FIGO nomenclature (Montreal, 1994) from Benedet 2003.

Table 2. Critical review form: randomised studies

No.	Question	Yes/No

Table 2. Critical review form: randomised studies *(Continued)*

1.	Was the assigned treatment adequately concealed prior to allocation?
2.	Were the outcomes of patients who withdrew or were excluded after allocation described and included in an "intention-to-treat" analysis?
3.	Were the withdrawals < 15% of the study population?
4.	Were the inclusion and exclusion criteria for entry clearly defined?
5.	Were the care programmes, other than the trial options, identical?
6.	Were there any checks to ensure compliance to treatment?
7.	Were the outcome assessors blind to assignment status?
8.	Were the outcome measures used clearly defined?
9.	Were the accuracy, precision, and observer variation of the outcome measure adequate?
10.	Was the timing of the outcome measure appropriate?
11.	Were the outcome measure clearly reported?

Table 3. Were interventions defined adequately?

No.	Question	Answer
1.	Method of randomisation, in order of preference, as follows: (i) third party randomisation (pharmacy, computer or telephone) (ii) true randomisation (opaque numbered envelope or register)	
2.	Study design (i) duration of follow-up (ii) type of follow-up (iii) presence or absence of blinding to allocation	
3.	Size of study (i) number of women recruited (ii) number of women randomised (iii) number of women excluded (iv) number of women withdrawn and lost to follow-up (v) number of women analysed	
4.	Study setting (i) single-centre or multi-centre (ii) location (iii) timing and duration	
5.	Analysis (i) whether 'intention-to-treat' analysis was performed by authors	
6.	Criteria for adjuvant treatment (i) lymph node metastasis (ii) lymphovascular space invasion	

Table 3. Were interventions defined adequately? *(Continued)*

(iii) depth invasion more than 10 mm
(iv) parametrial invasion
(v) non-squamous histology
(vi) positive surgical margins

Table 4. Data extraction: characteristics of the study participants

No.	Question	Answer
1.	Baseline characteristics (i) stage of early cervix cancer by FIGO (ii) age (iii) previous treatments and surgery (iv) how were found participants (v) reason to exclusion participants	

Table 5. Data extraction: intervention

No.	Question	Answer
1.	Number of cycles and type of chemotherapy	
2.	Duration of radiotherapy	

Table 6. Data extraction: outcomes

No.	Question	Answer
1.	Overall survival at 5 years	
2.	Progression-free survival	
3.	Local recurrence (local, distant or local and distant)	
4.	Acute and late toxicity grades 3 and 4 (according to the ECOG Common Toxicity Criteria)	

Table 7. Radiotherapy and chemotherapy versus radiotherapy: hazard ratios in included trials

Outcome	Study	Comparison	ln(HR)	SE[ln(HR)]	HR (95% CI)	Notes
Death						
	Peters 2000	radiotherapy vs. radiotherapy+chemotherapy	0.67	NR	1.96	Cox HR, reported in paper
		radiotherapy+chemotherapy vs. radiotherapy	-0.57	0.27	0.57 (0.33 to 0.96)*	Estimated from Kaplan-Meier plots

Table 7. Radiotherapy and chemotherapy versus radiotherapy: hazard ratios in included trials *(Continued)*

		radiotherapy+chemotherapy vs. radiotherapy	-0.71	0.26	0.49 (0.43 to 0.56)	Estimated from Cox P value and total number of deaths
	Protocol CE3005	radiotherapy+chemotherapy vs. radiotherapy	-0.60	0.25	0.55 (0.25 to 1.20)*	Unadjusted HR from Cox regression
		radiotherapy+chemotherapy vs. radiotherapy	-0.53	0.27	0.59 (0.27 to 1.32)	HR from Cox regression, adjusted for age.
Disease progression	Peters 2000	radiotherapy vs. radiotherapy+chemotherapy	0.70	NR	2.01	Cox HR, reported in paper
		radiotherapy+chemotherapy vs. radiotherapy	-0.74	0.29	0.48 (0.27 to 0.84)	Estimated from Kaplan-Meier plots*
		radiotherapy+chemotherapy vs. radiotherapy	-0.74	0.25		Estimated from Cox P value and total number of deaths
	Protocol CE3005	radiotherapy+chemotherapy vs. radiotherapy	-0.78	0.20	0.46 (0.21 to 0.99)*	Unadjusted HR from Cox regression
		radiotherapy+chemotherapy vs. radiotherapy	-0.76	0.21	0.47 (0.21 to 1.03)	HR from Cox regression, adjusted for age.

* = used in primary meta-analysis; NR = Not reported

APPENDICES

Appendix 1. Original search strategies 2009

MEDLINE

1. Randomized controlled trial.pt.
2. Controlled clinical trial.pt.
3. Randomizes controlled trials/
4. random allocation/
5. double -blind method/
6. single-blind method/
7. or/1-6
8. clinical trial.pt.
9. exp clinical trials/
10. (clin$ adj25 trial$).ti,ab,sh.
11. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or masks$)).ti,ab,sh.
12. placebos/
13. placebo$.ti,ab,sh
14. random$.ti,ab,sh.
15. Research design/
16. or/8-15
17. (animal not human).sh
18. 16 not 17
19. comparative study.sh
20. exp evaluation studies
21. follow up studies.sh
22. prospective studies
23. (prospectiv$ adj5 (stud$ or trial$)).tw

24. or/19-23
25. 24 not 17
26. exp Cervix Neoplasms/
27. (cervi$ adj5 tumo?r).tw
28. (cervi$ adj5 neoplas$).tw
29. (cervi$ adj5 cancer$).tw
30. (cervi$ adj5 carcino$).tw
31.exp Cervix Diseases/
32. early cancer.tw.
33. or/26-32
34. exp chemotherapy/
35. exp radiotherapy/
36. chemotherapy.tw
37. radiotherapy.tw
38. or/ 34-37
39. 33 and 38
40. 18 and 24 and 33 and 39

Embase

1. Controlled study/or Randomized Controlled trial/
2. double blind procedure/
3. single blind procedure/
4. drug comparison/
5. placebo/
6. random$.tw,hw,mf.
7. placebo$.tw,hw,mf.
8. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw,hw,mf.
9. (comparativ$ adj5 trial$).tw,hw,mf.
10. (clinical adj5 trial$).tw,hw,mf.
11. follow up studies.tw,hw,mf.
12. prospective studies
13. (prospectiv$ adj5 (stud$ or trial$)).tw
14. or/ 1-14
15. animal/ not (human/ and animal/)
16. 14 not 15
17. exp Cervix Neoplasms/
18. (cervi$ adj5 tumo?r).tw
19. (cervi$ adj5 neoplas$).tw
20. (cervi$ adj5 cancer$).tw
21. (cervi$ adj5 carcino$).tw
22. exp Cervix Diseases/
23. early cancer.tw.
24. exp chemotherapy/
25. exp radiotherapy/
26. chemotherapy.tw
27. radiotherapy.tw
28. or/ 17-23
29. 24 or 26
30. 25 or 27
31. 16 and 28 and 29 and 30
32. radiation therapy.tw.
33. 30 or 33
34. 16 and 28 and 29 and 33

Appendix 2. Search strategies for updates

MEDLINE Ovid

1 Uterine Cervical Neoplasms/
2 (cervi* adj5 (cancer* or tumor* or tumour* or malignan* or carcinoma* or neoplas*)).mp.
3 1 or 2
4 Chemotherapy, Adjuvant/

5 exp Antineoplastic Agents/
6 Antineoplastic Combined Chemotherapy Protocols/
7 chemotherap*.mp.
8 drug therapy.fs.
9 4 or 5 or 6 or 7 or 8
10 exp Radiotherapy/
11 radiotherap*.mp.
12 radiation.mp.
13 irradiat*.mp.
14 radiotherapy.fs.
15 10 or 11 or 12 or 13 or 14
16 exp Surgical Procedures, Operative/
17 (surg* or hysterectom*).mp.
18 surgery.fs.
19 16 or 17 or 18
20 15 or 19
21 3 and 9 and 20
22 randomized controlled trial.pt.
23 controlled clinical trial.pt.
24 randomized.ab.
25 placebo.ab.
26 clinical trials as topic.sh.
27 randomly.ab.
28 trial.ti.
29 22 or 23 or 24 or 25 or 26 or 27 or 28
30 21 and 29

key:
mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier

Embase OVID

1 exp uterine cervix tumor/
2 (cervi* adj5 (cancer* or tumor* or tumour* or malignan* or carcinoma* or neoplas*)).mp.
3 1 or 2
4 exp chemotherapy/
5 dt.fs.
6 chemotherap*.mp.
7 4 or 5 or 6
8 exp radiotherapy/
9 radiotherap*.mp.
10 radiation.mp.
11 irradiat*.mp.
12 rt.fs.
13 8 or 9 or 10 or 11 or 12
14 exp surgery/
15 (surg* or hysterectom*).mp.
16 su.fs.
17 14 or 15 or 16
18 13 or 17
19 3 and 7 and 18
20 crossover procedure/
21 double-blind procedure/
22 randomized controlled trial/
23 single-blind procedure/
24 random*.mp.
25 factorial*.mp.
26 (crossover* or cross over* or cross-over*).mp.
27 placebo*.mp.
28 (double* adj blind*).mp.
29 (singl* adj blind*).mp.

30 assign*.mp.
31 allocat*.mp.
32 volunteer*.mp.
33 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 19 and 33

key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

CENTRAL

#1 MeSH descriptor Uterine Cervical Neoplasms explode all trees
#2 cervi* near/5 (cancer* or tumor* or tumour* or malignan* or carcinoma* or neoplas*)
#3 (#1 OR #2)
#4 MeSH descriptor Chemotherapy, Adjuvant, this term only
#5 MeSH descriptor Antineoplastic Agents explode all trees
#6 MeSH descriptor Antineoplastic Combined Chemotherapy Protocols, this term only
#7 chemotherap*
#8 Any MeSH descriptor with qualifier: DT
#9 (#4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Radiotherapy explode all trees
#11 radiotherap*
#12 radiation
#13 irradiat*
#14 Any MeSH descriptor with qualifier: RT
#15 (#10 OR #11 OR #12 OR #13 OR #14)
#16 MeSH descriptor Surgical Procedures, Operative explode all trees
#17 surg* or hysterectom*
#18 Any MeSH descriptor with qualifier: SU
#19 (#16 OR #17 OR #18)
#20 (#15 OR #19)
#21 (#3 AND #9 AND #20)

LILACS

(MH:"uterine cervical neoplasms" or (cervi$ and (cancer$ or tumor$ or tumour$ or malignan$ or neoplas$ or carcinoma$))) and (MH:"chemotherapy, adjuvant" or (adjuvant and chemotherap$))

WHAT'S NEW

Date	Event	Description
5 January 2022	Review declared as stable	No longer for update as any future update will require the development of a new protocol reflecting current Cochrane methodological criteria.

HISTORY

Protocol first published: Issue 3, 2005
Review first published: Issue 3, 2009

Date	Event	Description
23 November 2016	Amended	Author contact details updated.

Date	Event	Description
19 September 2016	New citation required but conclusions have not changed	One small randomised controlled trial (Sun 2015) included with only toxicity outcomes. An additional 17 trials excluded. Conclusions remain unchanged.
19 September 2016	New search has been performed	Literature searches updated 8 September 2016.
16 May 2012	Amended	Author listing amended
25 April 2012	New citation required but conclusions have not changed	Review updated: Twelve records screened: one study was added to 'excluded studies' (Zola 2003) and three studies added to 'ongoing studies' (Hong 2013; GOG 0263; NCT 00806117). Conclusions unchanged.
8 November 2011	New search has been performed	Search updated (MEDLINE, EMBASE, CENTRAL, LILACS and SR) rendering 1,197 records (1,031 records after de-duplication, plus three ongoing studies).

CONTRIBUTIONS OF AUTHORS

- Daniela Rosa: Took the lead in writing the protocol, developed background, initial objectives, selection criteria, methods and search strategy.
- Frederico Falcetta: Took the lead in writing the updated version of the review.
- Lidia Medeiros: Took the lead in writing the protocol, developed background, initial objectives, selection criteria, methods and search strategy.
- Maria Isabel Edelweiss: Took the lead in writing the protocol, developed background and initial objectives.
- Mary Bozzetti: Took the lead in writing the protocol, developed background, initial objectives, selection criteria, methods and search strategy.
- Paula Pohlmann: Developed background, initial objectives, selection criteria, methods and search strategy.
- Airton Stein: Contributed to background section, selection criteria, initial objectives, methods and search strategy.
- Heather Dickinson (co-author of original review): Performed data extraction and all the statistical analyses, wrote the results section, revised the review for important intellectual content.

DECLARATIONS OF INTEREST

None to declare.

SOURCES OF SUPPORT

Internal sources

- CAPES, Brazil

External sources

- Department of Health, UK

  UKNHS Cochrane Collaboration programme Grant Scheme CPG-506

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following were specified in the protocol but not implemented because of the small number of included studies:

- For continuous outcomes (e.g. quality of life (QoL) measures), we planned to pool the mean differences between the treatment arms at the end of follow-up using the mean difference method if all trials measured the outcome on the same scale, or using the standardised mean difference method otherwise. If standard deviations of final values were not available, we planned to use change scores (the difference between final value and baseline value) if their standard deviations were available.

- If there was evidence of substantial heterogeneity (e.g. $I^2 > 50\%$), we planned to investigate and report the possible reasons for this. If it was inappropriate to pool the data because of clinical or statistic heterogeneity then we planned to exclude outlying studies from the meta-analysis or conduct a systematic review without a meta-analysis.
- If sufficient trials were available, we planned to examine funnel plots corresponding to meta-analysis of the primary outcome in order to assess the potential for publication bias. If these plots suggested that treatment effects might not be sampled from a symmetric distribution, as assumed by the random-effects model, we planned to perform further meta-analyses using fixed-effect models.

The following 'Risk of bias' criteria were not specified in the protocol, but included in the review as they are now recommended for all Cochrane reviews.

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.

- Yes
- No
- Unclear

The other 'Risk of bias' items now follow RevMan5 format, but are equivalent to those specified in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [*therapeutic use]; Chemotherapy, Adjuvant [methods]; Cisplatin [administration & dosage]; Fluorouracil [administration & dosage]; Hysterectomy; Neoplasm Staging; Platinum Compounds [*therapeutic use]; Radiotherapy, Adjuvant; Randomized Controlled Trials as Topic; Survival Analysis; Uterine Cervical Neoplasms [*drug therapy] [pathology] [radiotherapy] [surgery]

MeSH check words

Female; Humans