Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer (Review)

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[Intervention Review]

Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer

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ABSTRACT

Background

Cervical cancer is the second commonest cancer among women up to 65 years of age and is the most frequent cause of death from gynaecological cancers worldwide. Sources suggest that a very high proportion of new cervical cancer cases in developing countries are at an advanced stage (IB2 or more) and more than a half of these may be stage III or IV. Cervical cancer staging is based on findings from clinical examination (FIGO) staging). Standard care in Europe and US for stage IB2 to III is non-surgical treatment (chemoradiation). However in developing countries, where there is limited access to radiotherapy, locally advanced cervical cancer may be treated with a combination of chemotherapy and hysterectomy (surgery to remove the womb and the neck of the womb, with or without the surrounding tissues). It is not certain if this improves survival. Therefore, it is important to systematically assess the value of hysterectomy in addition to radiotherapy or chemotherapy, or both, as an alternative intervention in the treatment of locally advanced cervical cancer (stage IB2 to III).

Objectives

To determine whether hysterectomy, in addition to standard treatment with radiation or chemotherapy, or both, in women with locally advanced cervical cancer (stage IB2 to III) is safe and effective compared with standard treatment alone.

Search methods

We searched the Cochrane Gynaecological Cancer Group Trials Register, CENTRAL, MEDLINE, EMBASE and LILACS up to February 2014. We also searched registers of clinical trials, abstracts of scientific meetings and reference lists of included studies.

Selection criteria

We searched for randomised controlled trials (RCTs) that compared treatment protocols involving hysterectomy versus radiotherapy or chemotherapy, or both, in women with advanced stage (IB2 to III) cervical cancer presenting for the first time.

Data collection and analysis

We assessed study eligibility independently, extracted data and assessed risk of bias. Where possible, overall and progression or disease-free survival outcomes were synthesised in a meta-analysis using the random-effects model. Adverse events were incompletely reported so results of single trials were described in narrative form.

Main results

We included seven RCTs (1217 women) of varying methodological quality in the review; most trials were at moderate or high risk of bias.

Three were multi-centre trials, two were single-centre trials, and in two trials it was unclear if they were single or multi-centre. These trials compared the following interventions for women with locally advanced cervical cancer (stages IB2 to III):

hysterectomy (simple or radical) with radiotherapy (N = 194) versus radiotherapy alone (N = 180); hysterectomy (simple or radical) with chemoradiotherapy (N = 31) versus chemoradiotherapy alone (N = 30); hysterectomy (radical) with chemoradiotherapy (N = 111) versus internal radiotherapy with chemoradiotherapy (N = 100); hysterectomy (simple or radical) with upfront (neoadjuvant) chemotherapy (N = 298) versus radiotherapy alone (N = 273).

One trial (N = 256) found no difference in the risk of death or disease progression between women who received attenuated radiotherapy followed by hysterectomy and those who received radiotherapy (external and internal) alone (hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.61 to 1.29). This trial also reported no difference between the two groups in terms of adverse effects (18/129 grade 3 or 4 adverse effects in the hysterectomy and radiation group and 19 cases in 18/121 women in the radiotherapy alone group). There was no difference in 5-year tumour-free actuarial survival (representation of the probable years of survivorship of a defined population of participants) or severe complications (grade 3) in another trial (N = 118) which reported the same comparison (6/62 versus 6/56 in the radiation with surgery group versus the radiotherapy alone group, respectively). The quality of the evidence was low for all these outcomes.

One trial (N = 61) reported no difference (P value > 0.10) in overall and recurrence-free survival at 3 years between chemoradiotherapy and hysterectomy versus chemoradiotherapy alone (low quality evidence). Adverse events and morbidity data were not reported.

Similarly, another trial (N = 211) found no difference in the risk of death (HR 0.65, 95% CI 0.35 to 1.21, P value = 0.19, low quality evidence), disease progression (HR 0.70, 95% CI 0.31 to 1.34, P value = 0.24, low quality evidence) or severe late complications (P value = 0.53, low quality evidence) between women who received internal radiotherapy versus hysterectomy after both groups had received external-beam chemoradiotherapy.

Meta analysis of three trials of neoadjuvant chemotherapy and hysterectomy versus radiotherapy alone, assessing 571 participants, found that women who received neoadjuvant chemotherapy plus hysterectomy had less risk of death than those who received radiotherapy alone (HR 0.71, 95% CI 0.55 to 0.93, I^2 = 0%, moderate quality evidence). However, a significant number of the participants that received neoadjuvant chemotherapy plus hysterectomy had radiotherapy as well. There was no difference in the proportion of women with disease progression or recurrence between the two groups (RR 0.75, 95% CI 0.53 to 1.05, I^2 = 20%, moderate quality evidence).

Results of single trials reported no apparent (P value > 0.05) difference in long-term severe complications, grade 3 acute toxicity and severe late toxicity between the two groups (low quality evidence).

Quality of life outcomes were not reported in any of the trials.

Authors' conclusions

From the available RCTs, we found insufficient evidence that hysterectomy with radiotherapy, with or without chemotherapy, improves the survival of women with locally advanced cervical cancer who are treated with radiotherapy or chemoradiotherapy alone. The overall quality of the evidence was variable across the different outcomes and was universally downgraded due to concerns about risk of bias. The quality of the evidence for neoadjuvant chemotherapy and radical hysterectomy versus radiotherapy alone for survival outcomes was moderate, with evidence from other comparisons of low quality. This was mainly based on poor reporting and sparseness of data where results were based on single trials. More trials that assess medical management with and without hysterectomy may test the robustness of the findings of this review as further research is likely to have an important impact on our confidence in the estimate of effect.

PLAIN LANGUAGE SUMMARY

Hysterectomy with medical management for cervical cancer that has spread to nearby tissues only

The issue

Cancer of the neck of the womb (cervical cancer) is the commonest cancer among women up to 65 years of age. A high proportion of women in developing countries are diagnosed with locally advanced disease (spread to nearby tissues, but no obvious distant spread). They are usually treated with radiotherapy, with or without chemotherapy (medical treatment). Hysterectomy (surgery to remove the womb and the cervix) with medical treatment is also used, especially in developing countries where access to radiotherapy is limited.

The aim of the review

Is hysterectomy with medical treatment more beneficial compared to medical treatment alone in locally advanced cervical cancer?

How was the review conducted?

A literature search from 1966 to February 2014 identified seven trials at moderate to high risk of bias. These included 1217 women and compared: hysterectomy with radiotherapy versus radiotherapy alone; hysterectomy with chemoradiotherapy versus chemoradiotherapy alone; hysterectomy with chemoradiotherapy versus internal radiotherapy (brachytherapy) with chemoradiotherapy; and hysterectomy with upfront (neoadjuvant) chemotherapy versus radiotherapy alone.

What are the main findings?

Two studies, including 374 women, compared preoperative radiotherapy and hysterectomy versus radiotherapy alone, but only one trial reported overall survival, with no difference between the groups. These studies found no difference in the risk of disease progression (or death) or five-year tumour-free survival.

One study, including 61 women, reported no difference in overall and recurrence-free survival between chemotherapy and hysterectomy versus chemoradiotherapy alone.

Another study comparing internal radiotherapy (brachytherapy) versus hysterectomy in 211 women who received chemoradiotherapy found no difference in the risk of death or disease progression.

By combining results from three of the independent studies that assessed 571 women, we found that fewer women who received neoadjuvant chemotherapy plus hysterectomy died than those who received radiotherapy alone. However, many women in the first group also had radiotherapy. There was no difference in the number of women who were disease-free after treatment.

Adverse events were incompletely reported. Results of single trials showed no differences in severe adverse events between the two groups in any comparison. Limited data suggested that the interventions appeared to be reasonably well tolerated, although more evidence is needed.

Quality of life measures were not reported.

What are the conclusions?

We found insufficient evidence that hysterectomy added to radiation and chemoradiation improved survival, quality of life or adverse events in locally advanced cervical cancer compared with medical treatment alone. Overall, the quality of the evidence was variable and was universally downgraded due to concerns about risk of bias. The quality of the evidence for neoadjuvant chemotherapy and radical hysterectomy versus radiotherapy alone for survival outcomes was moderate, with evidence from other comparisons being of low quality. Further data from carefully planned trials assessing medical management with and without hysterectomy are likely to impact on how confident we are about these findings.

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

Neoadjuvant chemotherapy and radical hysterectomy compared with radiotherapy alone for women with locally advanced cervical cancer

Patient or population: Women with locally advanced cervical cancer
Settings: Outpatient
Intervention: Neoadjuvant chemotherapy and radical hysterectomy
Comparison: Radiotherapy alone

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Overall survival Median follow-up ranged from 39 to 60 months in the 3 trials	**HR 0.71** (0.55 to 0.93)	571 (3 RCTs)	⊕⊕⊕◯ **moderate**	Downgraded due to concerns regarding the uncertainty of risk of bias in individual trials
Disease or progression-free survival Median follow-up ranged from 39 to 60 months in the 3 trials	**HR 0.75** (0.53 to 1.05)	571 (3 RCTs)	⊕⊕⊕◯ **moderate**	Downgraded due to concerns regarding the uncertainty of risk of bias in individual trials and varying definitions of disease and progression-free survival. Although we did not feel the latter merited a further downgrade to low quality evidence
Severe adverse events and toxicity	Acute severe toxicity: RR 1.32, (0.47 to 3.71) long-term severe complications: RR 0.86 (0.49 to 1.50) Severe late toxicity: RR 0.60 (0.27 to 1.34)	Acute toxicity 118 (1 RCT) Long-term severe complications 409 (1 RCT) Severe late toxicity: 118 (1 RCT)	⊕⊕◯◯ **low**	Downgraded due to incomplete and poor reporting of important adverse events and toxicities and sparseness of data

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.

BACKGROUND

Description of the condition

Cervical cancer is the second most common cancer among women up to 65 years of age and is the most frequent cause of death from gynaecological cancers worldwide (GLOBOCAN 2013). The introduction in 1988 of a national cervical screening programme in the UK led, within a decade, to a halving in the incidence of cervical cancer, from an age-standardised incidence rate (ASIR) of 16.2 per 100,000 to an ASIR of 8.3 per 100,000 in 2008 (NCIN 2010). In addition, the mortality from cervical cancer has declined in many developed countries over the last two decades (GLOBOCAN 2013), particularly in countries with organised cervical screening programs (Laara 1987; Quinn 1999). Despite similar successes in other countries, cervical cancer remains a major international problem.

In many developing countries, access to health services is limited and screening for cervical cancer is either absent or reaches few of the women who need it. In these areas, cervical cancer is the most common cancer in women and the leading cause of cancer death (Mothers 2008). One report from a developing country has shown that over 80% of new cervical cancer cases are found at advanced stages (IB2 or more), and over half of these are stage III to IV (Khuhaprema 2010). In 2012, about 265,000 women died of the disease with over 87.8% of them living in developing countries (GLOBOCAN 2013). In Europe, about 60% of women with cervical cancer are alive five years after diagnosis (EUROCARE 2003). Remaining or recurrent disease frequently occurs after initial treatment in more than 50% of stage III to IVA cervical cancer, leading to mortality (Appendix 1).

Cervical cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO) system (Benedet 2003), which is based on findings from clinical examination (see Appendix 1 for descriptions of the disease at different FIGO stages). In this review, women with FIGO stage IB2 to III (locally advanced) cervical cancer were the population of interest.

Description of the intervention

Treatment decisions for invasive cervical cancer should be individualised and based on factors such as age, medical condition of the women, stage of disease and other tumour-related factors in order to yield the best cure with minimum complications (Kesic 2006). As a general rule, multiple treatment modalities have more potential complications and side effects than one treatment modality.

For stage IA1, local cervical treatments (large loop or needle excision of the transformation zone (LLETZ/NETZ), knife cone biopsy) or total hysterectomy (surgery to remove the womb and the neck of the womb) can be used, depending on women's preferences and fertility aspirations.

For stage IA2 to IB1, radical hysterectomy with pelvic lymphadenectomy or chemoradiotherapy have been the accepted treatment modalities with reported similar efficacies (Eifel 1993). This finding was supported mainly by a randomised control trial (RCT) before the concurrent chemoradiotherapy era (Landoni 1997). In younger women surgery is preferred, partly because of the advantage of preservation of ovarian function.

Radical hysterectomy, and bilateral pelvic lymphadenectomy, involves the removal of the womb, the cervix, the upper part of the vagina and the tissues around the cervix (parametrial tissue), as well as the lymph nodes (glands) in the pelvis to see if they contain cancer (pelvic lymphadenectomy). Although this type of surgery has excellent results, it can result in side effects such as organ injury (bladder, bowel, blood vessel, nerve) and long-term side effects such as sexual or bladder dysfunction, pelvic cyst formation and lymphoedema (swelling) of the legs.

Radical trachelectomy may be an alternative to radical hysterectomy in women who want to preserve their fertility, provided they meet certain criteria. These are tumour size no greater than 2 cm and no metastasis to regional lymph nodes (Shepherd 2012). Radical trachelectomy involves removing the cervix, the upper part of the vagina and the parametrial tissue and the pelvic lymph glands. This treatment is well-established, appears to be safe and effective in preserving fertility, and has a high chance of conception. Late miscarriage and premature labour are the most serious side effects in pregnancies where the women have had a trachelectomy.

For stage IB2 tumours and above, the incidence of lymph node metastasis increases significantly, as well as the incidence of central, regional and distant recurrences (Alvarez 1989; Burghardt 1978; Chung 1980; Delgado 1990; Piver 1975). If a surgical approach is chosen, there may be difficulties in removing all of the tumour with a margin of normal tissue (that is adequate surgery), therefore there is a high probability of requiring additional treatment (radiotherapy with or without chemotherapy) with the increased morbidity of combined treatment. For women with FIGO stage IB2 disease and higher, chemoradiotherapy is now standard care; it has been shown to improve disease-free survival, progression-free survival and overall survival (CCMAC 2010; Keys 1999; NCI 1999). It involves administration of cisplatin-based chemotherapy during the course of radiotherapy, all delivered within seven weeks. The chemotherapy makes the cancer cells more sensitive to the radiotherapy and therefore improves the treatment results. However, surgery in locally advanced cervical cancer (stage IB2 to III) has been considered in the following cases:

- after chemoradiotherapy, for those in whom no complete remission is achieved within two to three months following treatment, the tumour is oncologically operable and the patient is clinically fit to undergo additional surgery;
- after either radiotherapy or chemotherapy are used to shrink the cervical tumour to a size where it can be removed with normal margins;
- following neoadjuvant chemotherapy (chemotherapy given

before other treatments to reduce the size of the tumour), especially in developing countries with limited access to radiotherapy, but it remains unclear whether it offers a benefit over surgery alone or chemoradiotherapy (Rydzewska 2012).

Stage IVA cervical cancer, where the cancer has spread to the adjacent bladder or rectum, is usually treated with chemoradiotherapy (CCMAC 2010). Some authors have suggested that neoadjuvant chemotherapy followed by radical surgery (including removal of the affected bladder or rectum) might be a valid alternative to standard treatment (Benedetti Panicci 2007).
For stage IVB, the aim of treatment is generally palliative radiotherapy and chemotherapy (Kesic 2006; NCI 2014).

How the intervention might work

Although surgical resection of advanced non-metastatic forms of cervical cancer is controversial, it may help improve local control (Houvenaeghel 1998). Many studies report favourable outcomes of hysterectomy for women with advanced cervical cancer after radiotherapy (Classe 2006; Kornovski 2007; Leino 1994; Noterman 2006; Potish 1990; Tsuda 2001; Wang 2002). Whether simple total hysterectomy (Leino 1994; Potish 1990; Wang 2002) or radical hysterectomy (Classe 2006; Kornovski 2007; Noterman 2006; Tsuda 2001; Wang 2002) is needed is unclear (Noterman 2006). Multimodal treatment of hysterectomy combined with chemotherapy or radiotherapy, or both, may improve survival; but it may (Touboul 2010) or may not (Classe 2006; Perez 1987) cause significantly worse adverse events compared with radiotherapy or chemoradiotherapy alone.

Why it is important to do this review

It is important to assess the value of hysterectomy in addition to chemotherapy, radiotherapy or chemoradiotherapy in the treatment of locally advanced cervical cancer.

OBJECTIVES

To determine whether hysterectomy, in addition to standard treatment with radiation or chemotherapy, or both, in women with locally advanced cervical cancer (stage IB2 to III) is safe and effective compared with standard treatment alone.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs)

Types of participants

Adult women (aged 18 years or older) with locally advanced cervical cancers (stage IB2 to III)

Types of interventions

We compared hysterectomy in combination with neoadjuvant, concurrent or adjuvant therapy versus non-surgical interventions.

1. Hysterectomy (simple or radical) with radiotherapy versus radiotherapy alone.
2. Hysterectomy (simple or radical) with chemoradiotherapy versus chemoradiotherapy alone.
3. Hysterectomy (radical) with chemoradiotherapy versus internal radiotherapy (brachytherapy) with chemoradiotherapy.
4. Hysterectomy (simple or radical) with neoadjuvant chemotherapy versus radiotherapy alone.

Types of outcome measures

Primary outcomes

- Overall survival: survival until death from all causes was assessed from the time when women were enrolled in the study, or defined by the trial authors

Secondary outcomes

- Progression-free survival
- If authors reported disease-free survival rather than progression-free survival then this was assessed
- Quality of life measured using a scale that has been validated through reporting of norms against a validated scale in a peer-reviewed publication
- Adverse events

Surgery-related complications

Measured as the proportion of women who developed one of the items below (according to the study definition) within 12 weeks. These were classified as either early (before discharge from hospital or within 7 days of surgery), late (from 7 days to within 12 weeks of surgery), or total complications (early and late):

a) any postoperative infection;
b) surgery-related injuries (blood vessel, nerve, bladder, bowel);
c) excessive blood loss (according to the study definition);
d) thromboembolic events;
e) any anaesthesiological complications;

f) other severe adverse event;
g) fistula formation;
h) voiding or bladder dysfunction;
i) lymphocysts or lymphoedema;
j) psychosexual dysfunction.

Chemotherapy and radiotherapy-related complications

Grades of chemotherapeutic and radiotherapeutic toxicity were extracted and grouped as:

- haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage);
- gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver toxicity, proctitis);
- genitourinary;
- skin (stomatitis, mucositis, alopecia, allergy);
- neurological (peripheral and central); and
- pulmonary.

Search methods for identification of studies

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

Electronic searches

See: Cochrane Gynaecological Cancer Group methods used in reviews.

We searched the following electronic databases: the Cochrane Gynaecological Cancer Review Group Specialised Register, Cochrane Register of Controlled Trials (CENTRAL) (Issue 1, 2014) (Appendix 2), MEDLINE (1948 to week 5 January 2014) (Appendix 3), EMBASE (1980 to 2014 week 6) (Appendix 4) and LILACS (February 2014) (Appendix 5).

All relevant articles that were found were identified on PubMed and using the 'related articles' feature we carried out further searches for newly published articles.

Searching other resources

Unpublished and grey literature

We conducted a Google search for Internet-based resources and open-access publications. We searched Metaregister (http://www.controlled-trials.com/rct), Physicians Data Query (http://www.nci.nih.gov), http://www.clinicaltrials.gov and http://www.cancer.gov/clinicaltrials for ongoing trials. One trial was identified through these searches; this trial closed to recruitment in September 2014. We have contacted the principal investigator for more details and preliminary results, but have not received a reply as yet. Therefore, we have added this trial to the Ongoing studies section.

We searched conference proceedings and abstracts through ZETOC (http://zetoc.mimas.ac.uk) and WorldCat Dissertations.

Handsearching

We handsearched the citation lists of included studies, key textbooks and previous systematic reviews.

We handsearched reports of the following conferences:

- International Gynecological Cancer Society (IGCS);
- European Society of Gynaecological Oncology (ESGO);
- Society of Gynecologic Oncologists (SGO);
- British Gynaecological Cancer Society (BGCS);
- Australian Society of Gynaecologic Oncologists (ASGO);
- American Society of Clinical Oncology (ASCO);
- European Society of Medical Oncology (ESMO);
- Clinical Oncological Society of Australia (COSA).

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database, Endnote. Duplicates were removed and two review authors (AB, FK) independently examined the remaining references. Those studies that clearly did not meet the inclusion criteria were excluded and the full texts of potentially relevant references were obtained. Two review authors (AB, FK) independently assessed the eligibility of the retrieved papers. Disagreements were resolved by discussion between the two review authors with a final review by the other authors (EB, MP, DO). Reasons for exclusion are documented.

Data extraction and management

For included studies, data were abstracted as recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The data included the following:

- author, year of publication and journal citation (including language);
- country;
- setting;
- inclusion and exclusion criteria;
- study design, methodology;
- study population:
  a) total number enrolled,
  b) patient characteristics,
  c) age,
  d) co-morbidities,
  e) type of initial or primary treatment

(chemotherapy, chemoradiation, or radiotherapy), including details on dose, duration and combination.

f) performance status;

- advanced cervical cancer details at diagnosis:
    a) stage,
    b) grade,
    c) histology;
- intervention (hysterectomy) details:
    a) type of hysterectomy (total or subtotal, simple or radical ± pelvic lymphadenectomy),
    b) timing of hysterectomy,
    c) prevention of complications (prophylactic antibiotics or any other measures),
    d) grade or prior training of surgeon;
- comparison details:
    a) details of dose and duration of chemotherapeutic, radiotherapeutic, or a combination treatment used,
    b) method of primary treatment administration,
    c) drug regimen;
- local control e.g. bleeding, pressure symptoms, pain;
- risk of bias in study (assessment of risk of bias in included studies);
- duration of follow-up;
- outcomes, overall survival and progression-free survival, quality of life and severe adverse events:
    a) for each outcome, outcome definition (with diagnostic criteria if relevant),
    b) unit of measurement (if relevant),
    c) for scales, upper and lower limits, and whether high or low score is good,
    d) results, number of participants allocated to each intervention group, and
    e) for each outcome of interest, sample size, missing participants.

We extracted data on outcomes as follows.

- For time to event (overall survival and progression-free 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 attempted to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events), we extracted the number of participants in each treatment arm who experience the outcome of interest and the number of participants.

These were assessed at the endpoint in order to estimate a risk ratio (RR).

Where possible, all the data extracted were those relevant to an intention-to-treat analysis in which the participants were analysed in the groups to which they were assigned. We noted the time points at which outcomes were collected and reported.

Two review authors (AB, FK) abstracted data independently onto a data abstraction form specially designed for the review. We resolved differences between review authors by discussion.

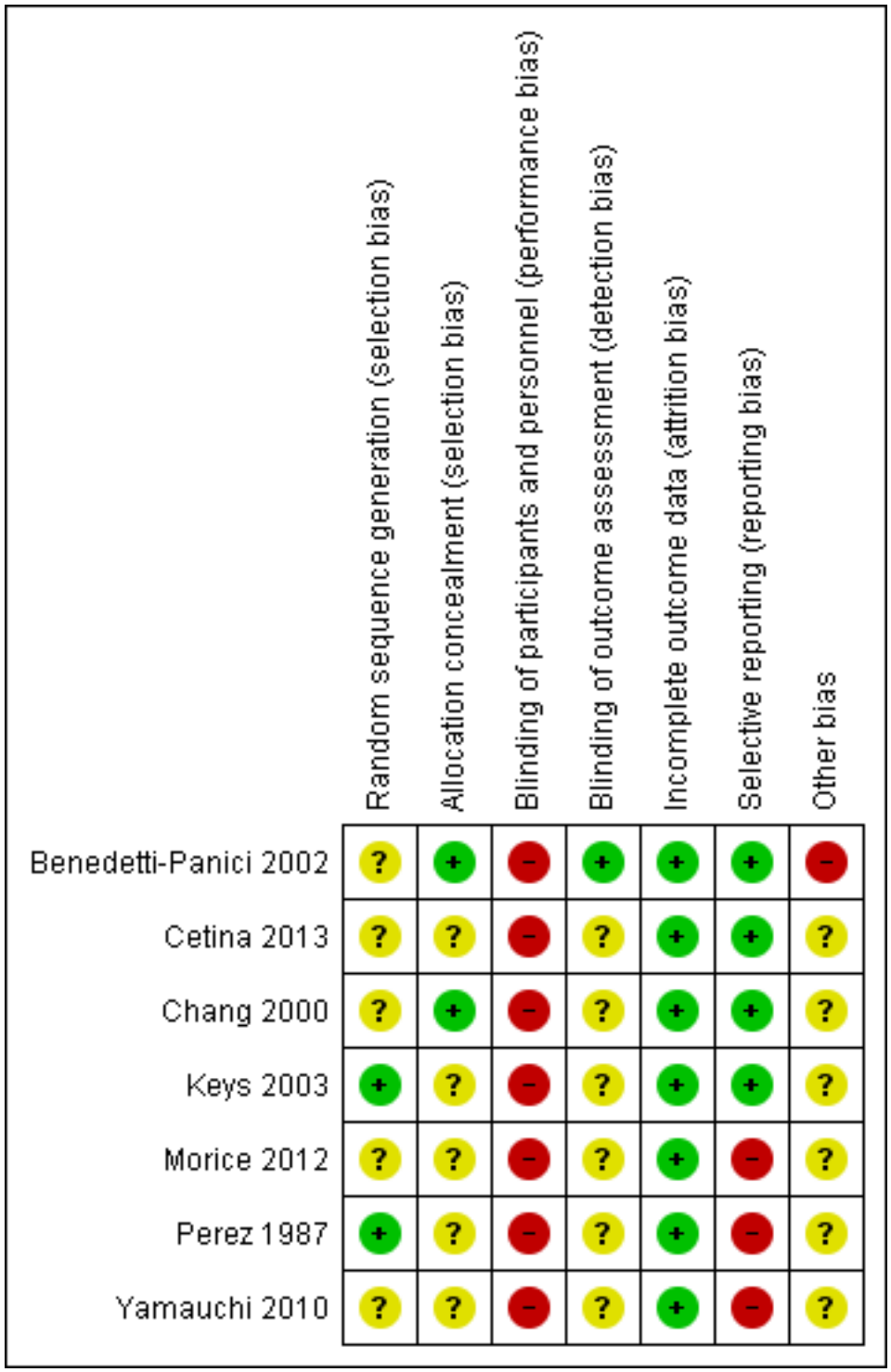
Assessment of risk of bias in included studies

We assessed the risk of bias in the included RCTs in accordance with the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* using the Cochrane Collaboration's tool and the criteria specified in Chapter 8 (Higgins 2011). This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (restricted to blinding of outcome assessors as it was not possible to blind participants or investigators to these treatment modalities);
- incomplete outcome data, we recorded the proportion of participants whose outcomes were not reported at the end of the study. We coded the satisfactory level of losses to follow-up for each outcome as:
    - yes, if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms,
    - no, if more than 20% of participants were lost to follow-up or reasons for loss to follow-up were different between treatment arms,
    - unclear, if loss to follow-up was not reported;
- selective reporting of outcomes;
- other possible sources of bias.

We (FK, AB) applied the risk of bias tool independently and differences were resolved by discussion. Results were summarised in a risk of bias summary (Figure 1). Results of meta-analyses were interpreted in light of the findings with respect to risk of bias.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

We used the following measures of the effect of treatment:

- for time to event data we used the HR, where possible;
- for dichotomous outcomes we used the RR.

Dealing with missing data

We did not impute missing outcome data for any of the outcomes.

Assessment of heterogeneity

Heterogeneity between studies was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, the possible reasons for the heterogeneity were investigated and reported.

Assessment of reporting biases

Funnel plots corresponding to meta-analysis of the primary outcome were not examined to assess the potential for small study effects such as publication bias, as stated in the protocol a priori, due to the fact that meta-analyses of only three trials were possible.

Data synthesis

If sufficient clinically similar trials were available, their results were pooled in meta-analyses.

- For time to event data, HRs were pooled using the generic inverse variance facility of Review Manager 5 (RevMan 2011).
- Random-effects models with inverse variance weighting were used for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

We had intended to conducted subgroup analysis in the meta-analysis of progression and disease-free survival, grouping trials by whether the trial measured progression or disease-free survival. However, this was not possible due to the lack of statistical heterogeneity and sparse data, but it may be considered in any future update of the review (see Differences between protocol and review).

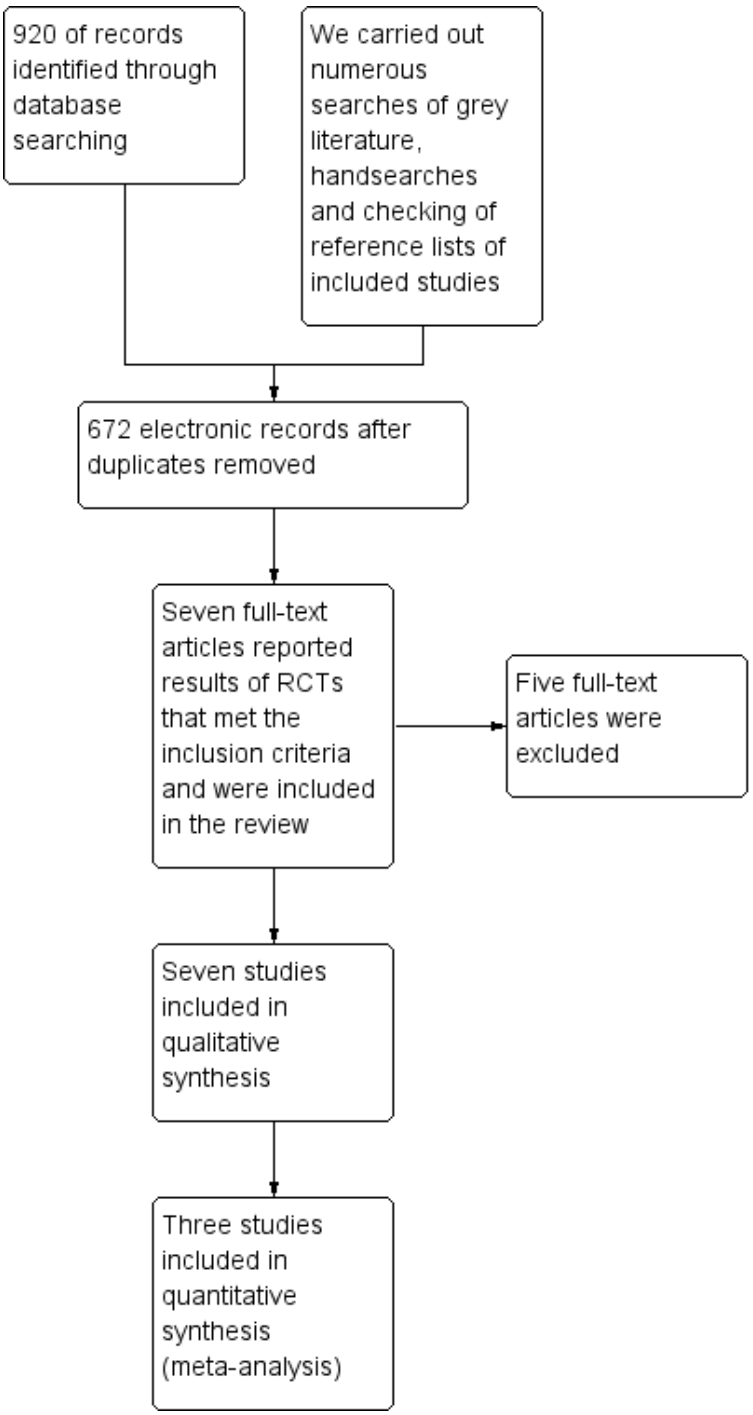
RESULTS

Description of studies

Results of the search

The search strategy identified 672 unique references. Two review authors (FK, AB) read the abstracts independently and those that did not meet the inclusion criteria were excluded at this stage. Ten articles were retrieved in full and full text screening of these references excluded five of them for the reasons described in the table Characteristics of excluded studies. Seven studies (Benedetti-Panici 2002; Cetina 2013; Chang 2000; Keys 2003; Morice 2012; Perez 1987; Yamauchi 2010) were identified as having met our inclusion criteria and are described in the table Characteristics of included studies (see PRISMA flow chart for further details of study selection process (Figure 2)).

Figure 2. Study flow diagram.



Searches of the grey literature did not identify any additional studies.

Included studies

The seven included studies (Benedetti-Panici 2002; Cetina 2013; Chang 2000; Keys 2003; Morice 2012; Perez 1987; Yamauchi 2010) randomised a total of 1217 eligible women, all of whom were assessed for primary survival outcomes at the end of the studies.

The review identified the following treatment comparisons for the seven included studies:

- hysterectomy (simple or radical) with radiotherapy versus radiotherapy alone (Keys 2003; Perez 1987);
- hysterectomy (simple or radical) with chemoradiotherapy versus chemoradiotherapy alone (Morice 2012);
- hysterectomy (radical) with chemoradiotherapy versus internal radiotherapy (brachytherapy) with chemoradiotherapy (Cetina 2013);
- hysterectomy (simple or radical) with neoadjuvant chemotherapy versus radiotherapy alone (Benedetti-Panici 2002; Chang 2000; Yamauchi 2010).

The duration of follow-up of participants varied from 36 months to 72 months, in Keys 2003 study those who were last seen alive had a median follow-up time of 9.6 years (range 0.3 to 16.1).

Trials comparing preoperative radiotherapy and hysterectomy (simple or radical) versus radiotherapy alone

Two studies (Keys 2003; Perez 1987), which included a total of 374 women, compared preoperative radiotherapy and radical hysterectomy versus radiotherapy alone. Keys 2003 included 256 eligible women with stage IB2 disease (tumour size 4 to 8 cm); Perez 1987 included 118 women with stage IIA disease as well as stage IB (but women with a tumour more than 5 cm were excluded). Ths age distribution was comparable in the two groups in both trials, but additional information was not reported in the trial of Perez 1987. In the Keys 2003 trial just over three quarters of the women were 50 years old or under. The majority of women in both trials had squamous cell carcinoma of the cervix. Additional baseline information was not reported in the Perez 1987 trial; but the performance status of women in Keys 2003 was generally good (more than 76% and more than 20% in both arms with performance status of 0 and 1, respectively). Keys 2003 did not mention whether the participants were evaluated clinically or radiologically after radiotherapy in order to assess the tumour response and residual disease.

In the Keys 2003 study, daily fraction size was to be prescribed as 180 Gy and external treatment carried to a total dose of 40 Gy and 45 Gy for the radiation-only and the adjuvant hysterectomy regimens, respectively. Both groups were to have brachytherapy one to two weeks after completing external treatment. The brachytherapy dose prescription was different between the treatment arms; the radiation-only group was to receive a dose of 40 Gy with a total dose of 80 Gy to 'point A', while those who were to have a hysterectomy received only 30 Gy with a total dose of 75 Gy to point A. A minimum dose of 55 Gy was prescribed to point B for both regimens. All irradiation was to be completed within 10 weeks. The surgical group in the Keys 2003 trial was then to undergo simple hysterectomy with removal of tubes and ovaries, if present, two to six weeks after completion of all irradiation.

In the Perez 1987 trial, participants who were treated with preoperative radiotherapy and surgery received 20 Gy whole pelvis irradiation and one brachytherapy for 5000 to 6000 mgh (approximately 5 to 6 Gy low dose rate given over 6 days), followed 2 to 6 weeks later by a radical hysterectomy and bilateral pelvic lymphadenectomy (up to the bifurcation of the common iliac vessels). The dose to the cervix was about 70 Gy and to the pelvic lymph nodes 30 Gy.

Treatment with irradiation alone in the Perez 1987 trial consisted of 10 to 20 Gy delivered to the whole pelvis and an additional parametrial dose to total of 50 Gy to the external iliac lymph nodes combined with two brachytherapy insertions for a total of approximately 7500 mgh (65 to 70 Gy to point A). The dose to the paracervical tissues was about 85 Gy and to the pelvic lymph nodes 60 Gy.

Keys 2003 assessed overall survival, pelvic-free survival and the rate of pelvic recurrence. Perez 1987 assessed the five-year tumour-free actuarial survival, the sites of failure after therapy and treatment complications.

Trial comparing chemoradiotherapy and hysterectomy (simple or radical) versus chemoradiotherapy alone

One RCT (Morice 2012) included 61 women with FIGO stage IB2 or II cervical cancer with a complete clinical and radiological response after chemoradiotherapy, randomly allocated to the treatment arms: hysterectomy or no hysterectomy. The median age and stage distribution was similar in both groups (45 years in the chemoradiotherapy and hysterectomy arm and 44 years in the chemoradiotherapy and no hysterectomy arm). Half of the women had FIGO stage IB2 and half stage II disease. The majority of participants in each group (more than 80%) had squamous cell cancer. The performance status of the included women was not described.

Radiotherapy was delivered to the pelvis for a total dose of 45 to 50 Gy, in five fractions of 1.8 to 2 Gy per week, followed 1 to 2 weeks later by brachytherapy. Most women in both groups had one application of brachytherapy at a dose of 15 Gy. Concomitant

chemoradiotherapy was cisplatin during external radiotherapy. A complete clinical and radiological response (based on magnetic resonance imaging (MRI)) was evaluated six to eight weeks after internal radiotherapy.

Hysterectomy could be performed via laparotomy or a laparoscopy and could be extrafascial or radical (type II according to the Piver classification) according to the preoperative examination. A selective or complete pelvic lymphadenectomy was optional and could be performed if lymphadenopathy was detected during surgery.

The trial gave HRs for overall and recurrence-free survival as well as reporting the site of first recurrence. Morbidity was not reported after confirmation from the study authors. The median duration of follow-up was 3.8 years (range 0.4 to 5.8) when the trial was closed early because of poor accrual.

Trial comparing internal radiotherapy after external-beam radiotherapy with chemotherapy versus radical hysterectomy after external-beam radiotherapy with chemotherapy

One RCT (Cetina 2013) conducted in Mexico included 211 women aged between 18 and 70 years with a histological diagnosis of untreated FIGO stage IB2 to IIB cervical cancer and no evidence of para-aortic lymph node involvement. It was reported that these 211 women were randomly allocated to either brachytherapy after external-beam radiotherapy with chemotherapy or radical hysterectomy after external-beam radiotherapy with chemotherapy. Women were ineligible for the study if they had previously received chemotherapy or radiotherapy. The median age, and stage distribution, was similar in both groups (44 years in the brachytherapy arm and 45 years in the hysterectomy arm). The median performance status (Karnofsky) score was 90 in both arms and the median tumour size was also the same in the two arms (32 mm). Most participants in each treatment arm had FIGO stage IIB disease (70% and 74% of participants in the brachytherapy and hysterectomy arms, respectively). The majority of participants in each group (more than 80%) had squamous cell cancer.

Participants received 50.4 Gy external-beam radiotherapy to the entire pelvic region in 28 sessions of 1.8 Gy/day, 5 days/week, over the 6 weeks of chemotherapy.

Immediately after completion of external-beam radiotherapy with chemotherapy, participants in arm 1 underwent low-dose rate brachytherapy. A brachytherapy dose of 30 to 35 Gy was delivered to point A, to result in a cumulative dose of 80 to 85 Gy combining external-beam radiotherapy and brachytherapy. The cumulative external-beam radiotherapy and brachytherapy dose to point B (the pelvic wall) was 55 to 65 Gy.

Within four to six weeks after the external-beam radiotherapy with chemotherapy, arm 2 participants were submitted to type III radical hysterectomy and bilateral pelvic lymph node dissection and para-aortic lymph node sampling, if the multidisciplinary team judged the disease could be resected obtaining margins free of disease. Postoperative low-dose rate brachytherapy was mandated in the surgical arm participants only if the surgical specimen revealed positive surgical margins and was administered within 4 weeks after surgery at a median dose of 30 Gy to the vaginal mucosa delivered to a depth of 0.5 cm.

The trial gave HRs for overall and progression-free survival. The trial also reported pathological response, operative complications, toxicity to chemoradiation with cisplatin and gemcitabine, long-term complications and late complications including proctitis, cystitis and hydronephrosis. Only the latter was reported in a breakdown by treatment arm. The median duration of follow-up in the trial was 36 months (3 to 80 months).

Trials comparing neoadjuvant chemotherapy and hysterectomy (simple or radical) versus radiotherapy alone

Three RCTs (Benedetti-Panici 2002; Chang 2000; Yamauchi 2010) that randomised a total of 571 participants compared neoadjuvant chemotherapy and hysterectomy (simple or radical) versus radiotherapy alone. Benedetti-Panici 2002 included women with stage IB2 to III cervical cancer, Chang 2000 included women with IB to IIA bulky disease, and Yamauchi 2010 had only women with stage IIIB disease. The median age in each arm was similar in Benedetti-Panici 2002 and Chang 2000 (range 46 to 52), whereas in Yamauchi 2010 women were significantly older in the radiotherapy arm (mean age was 53 in the neoadjuvant chemotherapy and hysterectomy versus 60 years in the radiotherapy arm). All the women in Benedetti-Panici 2002 and Yamauchi 2010 and the majority in Chang 2000 had squamous cell cancer cancers. In Benedetti-Panici 2002 and Chang 2000 the Eastern Cooperative Oncology Group performance status was zero for the majority of the eligible women. The performance status was not reported in Yamauchi 2010.

In Benedetti-Panici 2002 the neoadjuvant chemotherapy regimen was not predetermined; minimal requirements were a cisplatin-containing regimen with a $\geq$ 240 mg/m^2 total cisplatin dose with a maximum of two additional drugs, administered over a period of 6 to 8 weeks. After neoadjuvant chemotherapy, the women were clinically reassessed and classified as suitable or unsuitable for radical surgery. The latter participants were treated with radiotherapy. Surgery consisted of radical hysterectomy (type III to V) plus systematic (at least 20 nodes to be resected) pelvic lymphadenectomy (aortic lymphadenectomy was optional). Postoperative radiotherapy was given in participants with positive surgical resection margins or metastatic nodes, or both. In the case of node metastasis, the choice of adjuvant treatment was based on the institution's policy (for example chemotherapy, external-beam radiotherapy, or no further therapy). Adjuvant treatment was given to 48 participants in the surgical group (29%); 38 (23%) participants in the surgical group underwent adjuvant radiotherapy.

Conventional radiotherapy consisted of external-beam, megavoltage radiotherapy (45 to 50 Gy) to the whole pelvis over five to six

weeks. In the presence of metastatic pelvic nodes an extra dose of 5 to 7 Gy was administered. Low-dose rate brachytherapy (20 to 30 Gy to the tumour volume) was provided two to four weeks after external radiotherapy. Aortic node metastases, when present, were irradiated (45 Gy/5 weeks, followed by a 5 Gy boost if residual disease was eventually detected) with extended fields encompassing pelvic and aortic volume or at the end of pelvic irradiation, in the case of a pelvic complete remission. Salvage treatments were allowed in women who showed progressive disease.

In Chang 2000 the neoadjuvant chemotherapy was cisplatin and vincristine, followed by bleomycin. Two to four weeks after the completion of neoadjuvant chemotherapy participants underwent a type III radical abdominal hysterectomy and pelvic lymphadenectomy. The adnexae were usually left in women $\leq$ 40 years old if they were gross appearance was normal.

The radiotherapy usually included a combination of external radiotherapy and high-dose rate brachytherapy; with 40 to 44 Gy whole pelvic irradiation. The para-aortic lymph nodes were not routinely included in the treatment field. Parametria received up to 50 Gy. If bulky tumour persisted after 44 Gy of irradiation, external-beam doses to the lower pelvis were increased to 50 to 54 Gy without central block followed by brachytherapy, or to 70 Gy without internal radiotherapy. The median cumulative dose to point A in this treatment protocol was 70 Gy. Thirty-seven participants were treated using this method. The postoperative radiotherapy was given by using techniques similar to those described above. The dose to the whole pelvis was 44 to 45 Gy, and that to the true pelvis was 50 to 54 Gy. After external radiotherapy, brachytherapy was given in two to three fractions with a total dose of 4 to 6 Gy/0.5 cm below the vaginal mucosa.

Participants in the neoadjuvant chemotherapy arm had a higher incidence of receiving adjuvant therapy with either radiotherapy or chemotherapy after the scheduled treatment than those in the radiotherapy arm, who received radical hysterectomy as the adjuvant therapy. Of the 68 women in the neoadjuvant chemotherapy arm 62 underwent hysterectomy and 19 of those had adjuvant radiotherapy, six had adjuvant chemotherapy and two had combined chemotherapy and radiotherapy.

In Yamauchi 2010 the neoadjuvant chemotherapy regimen consisted of cisplatin, bleomycin and mitomycin for three courses every four weeks. If the tumour was surgically removable, a radical hysterectomy was performed with bilateral salpingo-oophorectomy and pelvic lymphadenectomy, and then radiotherapy was given at 40 Gy to the whole pelvic region. If the tumour progressed or relapsed, combined chemotherapy of bleomycin, vincristine, mitomycin and cisplatin (BOPM) was given, and then irinotecan with cisplatin as the third line. If the local tumour was inoperable (N = 1), radiotherapy was given at 40 Gy to the whole pelvic region with 20 Gy brachytherapy, followed by BOPM chemotherapy.

The radiotherapy group received radiotherapy to the whole pelvic region in 20 fractions total ling 40 Gy. The total dose delivered to point B as a boost dose with midline shield coverage was 20 Gy. The total dose delivered by brachytherapy was 24 to 30 Gy. The pelvic field extended from the upper margin of L5 to the mid-portion of the obturator foramen or the lowest level of disease, with a 3 cm margin, and laterally 1.5 to 2 cm beyond the lateral margins of the bony pelvic wall. The duration of the radiotherapy was four weeks. In cases with local recurrence or progression of the primary lesion, chemotherapy was added, which included BOMP, irinotecan with cisplatin, and cisplatin or carboplatin alone. When distant metastasis occurred, the researchers added radiotherapy, or the single lesion was surgically removed.

All three studies assessed overall survival, and additionally progression-free survival in Benedetti-Panici 2002 and disease-free survival in the other two studies (Chang 2000; Yamauchi 2010). However, the definition of disease-free survival in Chang 2000 was absence of persistent or recurrent disease, so this appeared to be a combination of progression and disease-free survival. It was possible to include all three studies in a meta-analyses of overall survival and progression or disease-free survival as HR estimates were either explicitly reported, deduced (Parmar 1998) or obtained via personal correspondence (Yamauchi 2010). Benedetti-Panici 2002 reported severe toxicity and complications and Chang 2000 reported tumour response to treatment and toxicity. Yamauchi 2010 did not report adverse events and none of the three studies reported on quality of life outcomes.

Excluded studies

Out of the 12 references that were retrieved in full text, five were excluded for the following reasons.

- Four studies (Katsamuta 2013; Keys 1999; Sardi 1997; Sun 2013) included women who received hysterectomy or surgical staging in both arms.
- Sundfor 1996 compared surgery versus radiotherapy in women with early stage carcinoma of the cervix.

For further details of the excluded studies see the table Characteristics of excluded studies.

Risk of bias in included studies

Five studies (Benedetti-Panici 2002; Cetina 2013; Chang 2000; Keys 2003; Morice 2012; Perez 1987; Yamauchi 2010) were at high risk of bias, and Benedetti-Panici 2002 (which satisfied four of the criteria that we used to assess risk of bias) and Chang 2000 (which satisfied three items) appeared to be at moderate to high risk of bias (see Figure 1).

Allocation

Only Keys 2003 and Perez 1987 reported the method of generation of the sequence of random numbers used to allocate women to the treatment arms, but they did not report concealment of

this allocation sequence from participants and the healthcare professionals involved in the trials. The other five trials did not report on the method of sequence generation, although two trials (Benedetti-Panici 2002; Chang 2000) reported adequate concealment of allocation. Allocation concealment was unclear in five trials (Cetina 2013; Keys 2003; Morice 2012; Perez 1987; Yamauchi 2010).

Blinding

Since it was not possible to blind participants and clinicians to these particular interventions, performance bias may have been an issue in all seven included trials. Blinding of the outcome assessors was not reported in any of the trials with the exemption of Benedetti-Panici 2002, which reported adequate blinding, so the other six trials may have been prone to detection bias.

Incomplete outcome data

At least 80% of eligible women who were randomised were assessed at the endpoint in all seven trials. Intention-to-treat analyses were used in the Benedetti-Panici 2002, Cetina 2013, Keys 2003 and Yamauchi 2010 trials. In the Chang 2000 trial, intention-to-treat analysis was carried out for survival outcomes. Intention-to-treat analyses were not used in the Perez 1987 and Morice 2012 trials.

Selective reporting

The authors of four studies (Benedetti-Panici 2002; Cetina 2013; Chang 2000; Keys 2003) reported pertinent outcomes, although none reported quality of life outcomes. Adverse events or toxicity were not reported in two studies (Morice 2012; Yamauchi 2010) and overall survival was not reported in Perez 1987, despite the fact that the number of women who had died would have been known since disease progression was defined as the number of women whose disease had progressed or died. This raised concern about a significant reporting bias.

Other potential sources of bias

It was unclear whether any additional forms of bias may have been present in six studies so this item was scored as being at unclear risk of bias, although over a quarter of participants in each arm deviated from the protocol in Benedetti-Panici 2002 and so this study was at high risk of bias for this item.

Effects of interventions

See: **Summary of findings for the main comparison**

Preoperative radiotherapy and hysterectomy (simple or radical) versus radiotherapy alone

Keys 2003 and Perez 1987 included a total of 374 women and compared preoperative radiotherapy and radical hysterectomy versus radiotherapy alone. The trialists gave a breakdown by FIGO stage and intervention group in Perez 1987 but did not report overall survival or use appropriate survival techniques to allow the trial to be pooled.

Overall survival

In Keys 2003 there was no difference in the risk of death between women who received radiotherapy followed by extrafascial hysterectomy and those who received radiotherapy alone (HR 0.89, 95% CI 0.61 to 1.29, low quality evidence).

Progression-free survival

In Keys 2003 there was no difference in the risk of disease progression or death between women who received radiotherapy followed by hysterectomy and those who received radiotherapy alone (HR 0.77, 95% CI 0.54 to 1.10, low quality evidence).

Tumour-free actuarial survival at five years

In Perez 1987 5-year, tumour-free actuarial survival for women with stage IB was 80% in the preoperative radiotherapy and surgery group and 89% with radiotherapy alone. It was not reported how many women were stage IB1 and how many stage IB2 (the latter group was the group of interest for this Cochrane review). Women with barrel-shaped cervix (endocervical lesion with cervix diameter larger than 5 cm) were excluded. In stage IIA, the 5-year tumour-free survival was 79% in the preoperative radiotherapy and surgery group and 56% in the radiotherapy alone group. These differences were not statistically significant (low quality evidence).

Severe complications and adverse effects

In the women with stage IB disease in Perez 1987, only 1/48 (2%) of women experienced a severe complication (grade 3) in the radiotherapy and surgery group (ureteral stricture) whereas 5/40 experienced severe complications in the radiotherapy alone group (including rectovaginal fistula, vesicovaginal fistula, ureteral stricture and pelvic infection). This difference was not statistically significant. Similarly in women with stage IIA disease, 5/14 (40%) women experienced a severe complication in the radiotherapy and surgery group (including proctitis, rectal stricture, small bowel stricture and ureteral stricture) whereas only 1/16 experienced a severe complication in the radiotherapy alone group (rectal stricture). This difference was not statistically significant (low quality evidence).

In Keys 2003 it was stated that both treatment programs were well tolerated and there did not appear to be a difference between the two groups in terms of adverse effects. There were 18/129 women with a grade 3 or 4 adverse effect in the hysterectomy and radiotherapy group and 19 cases in 18/121 women of severe adverse effects in the radiotherapy alone group. Two women in each group received no radiotherapy and were not included (low quality evidence).

Chemoradiotherapy and hysterectomy (simple or radical) versus chemoradiotherapy alone

Morice 2012 included 61 women and compared chemoradiotherapy and simple or radical hysterectomy versus chemoradiotherapy alone.

Overall survival at three years

There was no difference in the 3-year event-free (death) survival rate (86% and 97% in the chemoradiotherapy plus hysterectomy and chemoradiotherapy alone groups, respectively; log rank P value = 0.15, low quality evidence).

Recurrence-free survival at three years

There was no difference in the 3-year event-free (recurrence) survival rate (72% and 89% in the chemoradiotherapy plus hysterectomy and chemoradiotherapy alone groups, respectively; log rank P value = 0.17, low quality evidence).
The authors reported that morbidity was studied in a further publication, but when we contacted them they could not provide data on morbidity.

Brachytherapy after external-beam radiotherapy with chemotherapy versus radical hysterectomy after external-beam radiotherapy with chemotherapy

Cetina 2013 included 211 women and compared brachytherapy versus radical hysterectomy in women who had already received external-beam chemoradiotherapy with gemcitabine plus cisplatin.

Overall survival

There was no difference in the risk of death between women in the brachytherapy group and those in the radical hysterectomy group (HR 0.65, 95% CI 0.35 to 1.21, P value = 0.19, low quality evidence).

Progression-free survival

There was no difference in the risk of disease progression or death between women in the brachytherapy group and those in the radical hysterectomy group (HR 0.70, 95% CI 0.31 to 1.34, P value = 0.24, low quality evidence).

Severe late complications

There was no difference in the proportion of women with severe late complications in the brachytherapy and radical hysterectomy groups (P value = 0.53, low quality evidence). There were four cases of grade 3 or 4 proctitis in the brachytherapy group and two cases in the radical hysterectomy group. There were three cases of severe cystitis in the internal radiotherapy group and none in the radical hysterectomy group, and there were no reported cases of grade 3 or 4 hydronephrosis in either group.
Of the 211 participants in the trial chemoradiotherapy with cisplatin and gemcitabine appeared to be reasonably well tolerated, although nearly a third of women experienced severe neutropenia (grade 3 in the majority). Of the 86 women who received a radical hysterectomy, the number of intraoperative and early surgical complications appeared to be reasonably low, with bleeding (9/86) being the most common.

Neoadjuvant chemotherapy and hysterectomy (simple or radical) versus radiotherapy alone

Overall survival

Meta-analysis of three studies (Benedetti-Panici 2002; Chang 2000; Yamauchi 2010), assessing 571 participants, found that women who received neoadjuvant chemotherapy plus hysterectomy had a lower risk of death compared with those women who received radiotherapy alone (HR 0.71, 95% CI 0.55 to 0.93, moderate quality evidence, see Analysis 1.1).The percentage of the variability in effect estimates that was due to heterogeneity rather than sampling error (chance) was not important (I^2= 0%).

Progression and disease-free survival

Meta-analysis of three studies (Benedetti-Panici 2002; Chang 2000; Yamauchi 2010), assessing 571 participants, found no difference in the risk of disease progression between women who received neoadjuvant chemotherapy plus hysterectomy and those who received radiotherapy alone (HR 0.75, 95% CI 0.53 to 1.05, moderate quality evidence, see Analysis 1.2). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance might not have been important (I^2 = 20%).

Severe adverse events and toxicity

Acute toxicity

Benedetti-Panici 2002 reported short-term complications but it was not possible to make comparisons because participants were compared in terms of those who received neoadjuvant chemotherapy, hysterectomy and radiotherapy separately, and participants may have experienced more than one toxicity in each category (low quality evidence).

Chang 2000 reported 9/68 (13%) cases of grade 3 acute toxicity in the neoadjuvant chemotherapy plus hysterectomy group and 7/50 (22%) cases of severe acute toxicity (5/7 were grade 3) in the radiotherapy alone group. This difference was not significant (RR 1.32, 95% CI 0.47 to 3.71, low quality evidence). Acute toxicities reported in the trial included nausea, vomiting, diarrhoea, liver and dermatological adverse effects.

Long-term complications and toxicity

In Benedetti-Panici 2002 long-term severe complications occurred in 32 (19.5%) women in the neoadjuvant chemotherapy arm and late severe morbidity with radiotherapy was observed in 39 (22%) women. There was no difference in long-term severe complications between neoadjuvant chemotherapy plus hysterectomy and radiotherapy alone (RR 0.86, 95% CI 0.49 to 1.50, low quality evidence).

Chang 2000 reported 9/68 (13%) cases of severe late toxicity (8/9 were grade 3) in the neoadjuvant chemotherapy plus hysterectomy group and 11/50 (22%) grade 3 cases in the radiotherapy alone group. This difference was not significant (RR 0.60, 95% CI 0.27 to 1.34, low quality evidence). Late toxicities reported in the trial included intestinal obstruction, radiation cystitis, radiation proctitis and lower leg oedema.

Quality of life outcomes were not reported in any of the trials.

DISCUSSION

Summary of main results

We found seven studies that met our inclusion criteria. These studies assessed the role of hysterectomy (radical or simple) in combination with chemotherapy or radiotherapy, or both, in the treatment of locally advanced cervical cancer. The seven trials included a total of 1217 women.

The randomised controlled trials (RCTs) were of varying methodological quality; most trials were at high risk of bias. These trials compared the following treatments for women with locally advanced cervical cancer (IB2 to III):

- hysterectomy (simple or radical) with radiotherapy versus radiotherapy alone (Keys 2003; Perez 1987);
- hysterectomy (simple or radical) with chemoradiotherapy versus chemoradiotherapy alone (Morice 2012);
- hysterectomy (radical) with chemoradiotherapy versus internal radiotherapy (brachytherapy) with chemoradiotherapy (Cetina 2013);
- hysterectomy (simple or radical) with neoadjuvant chemotherapy versus radiotherapy alone (Benedetti-Panici 2002; Chang 2000; Yamauchi 2010).

Keys 2003 and Perez 1987 included a total of 374 women and compared preoperative radiotherapy and hysterectomy versus radiotherapy alone. These two trials reported no differences in the risk of death or disease progression, 5-year tumour-free actuarial survival and severe complications between women who received radiotherapy followed by hysterectomy and those who received radiotherapy alone.

Morice 2012 included 61 women and reported no difference in overall and recurrence-free survival at three years between chemoradiotherapy and hysterectomy (simple or radical) versus chemoradiotherapy alone. Adverse events and morbidity data were not reported.

Similarly, Cetina 2013 compared brachytherapy versus radical hysterectomy in 211 women who had already received chemoradiotherapy with gemcitabine plus cisplatin. They found no difference in the risk of death, disease progression or severe late complications between women in the brachytherapy group and those in the hysterectomy group.

Meta analysis of three studies (Benedetti-Panici 2002; Chang 2000; Yamauchi 2010), assessing 571 women, found that women who received neoadjuvant chemotherapy plus hysterectomy had less risk of death than those who received radiotherapy alone, but there was no difference in the proportion of women with disease progression or recurrence between the two groups.

Benedetti-Panici 2002 reported no difference in long-term severe complications between neoadjuvant chemotherapy plus hysterectomy and radiotherapy alone. Moreover, it has to be considered that 38 (23%) of the women who were operated on also underwent adjuvant radiotherapy and that 30% of these women were likely to present with severe late complications.

Chang 2000 found no difference in grade 3 acute toxicity and severe late toxicity between the neoadjuvant chemotherapy plus hysterectomy group and the radiotherapy alone group.

In summary these data demonstrate a possible beneficial effect of neoadjuvant chemotherapy plus hysterectomy versus radiotherapy in terms of survival, but no difference in disease-free survival. This difference may be due to the neoadjuvant chemotherapy, the adjuvant treatment, or both, rather than hysterectomy since these also differed between the two groups.

Harms of treatment, especially in terms of quality of life data, were poorly reported on. Studies comparing the more modern standard treatment of chemoradiotherapy did not demonstrate a benefit

with the addition of hysterectomy.

Overall completeness and applicability of evidence

All seven included studies are relevant in terms of the patient population, types of interventions, effectiveness and outcomes. However, in four studies (excluding the Cetina 2013, Morice 2012 and Keys 2003 trials) the role of hysterectomy as adjuvant treatment is more difficult to assess because the women received different types of primary or neoadjuvant treatment compared with the group who had a hysterectomy. Three trials (Benedetti-Panici 2002; Chang 2000; Yamauchi 2010) which compared neoadjuvant chemotherapy and hysterectomy versus radiotherapy alone appeared to have external validity and represented a wide geographic area including Italy, China and Japan. Benedetti-Panici 2002 was a multi-centre trial. The generalisability of other studies is less strong as the comparisons differed across studies and only results of single studies could be reported although some were from multiple centres, which strengthens their representativeness.

Morice 2012 included women who had a complete response after chemoradiotherapy. In the rest of the studies an assessment of the response before surgery was not provided. It is important to note that women with a complete response to treatment before surgery potentially have a better prognosis compared to women with residual disease, therefore the role of adjuvant hysterectomy should be assessed in subgroups with similar prognostic factors (Gadducci 2013; Landoni 2013; Touboul 2010).

Overall, studies reported survival data well, although data on harms were poorly reported. These data are insufficient to recommend, outside of clinical trials, adding hysterectomy to chemoradiotherapy in women with locally advanced cervical cancer.

The evidence appears to be of low or very low quality (GRADE Working Group 2004) for all comparison outcomes other than for neoadjuvant chemotherapy and radical hysterectomy versus radiotherapy alone. The quality of the evidence for overall and progression or disease-free survival was moderate and was mainly downgraded due to concerns regarding risk of bias in individual trials. The trials in all of the comparisons are at high or moderate risk of bias. More trials that assess identical medical management with and without hysterectomy may test the robustness of the findings of this review as further research is likely to have an important impact on our confidence in the estimates of effect. The meta-analyses in the review found that women who received neoadjuvant chemotherapy plus hysterectomy had less risk of death than those who received radiotherapy alone (HR 0.71, 95% CI 0.55 to 0.93, see Analysis 1.1) but there was no difference in disease progression. However, it is difficult to assess the impact of the hysterectomy given that it was in combination with neoadjuvant chemotherapy, since much of this difference may be due to the chemotherapy component controlling microscopic distant disease rather than improving local control. Using the GRADE approach (GRADE Working Group 2004), the evidence summarised by this review is not sufficient to drive changes in clinical practice. Uncertainty about the additive effects of hysterectomy on a number of different outcomes justify its evaluation in addition to chemoradiotherapy in future clinical trials.

Quality of the evidence

We reviewed seven heterogenous studies, assessing a total of 1217 women, that evaluated the role of hysterectomy with radiotherapy or chemotherapy, or both, in women with locally advanced cervical cancer. Losses to follow-up was small but the trials generally scored poorly for other risk of bias items and were potentially at high risk of bias. The number of women in the trials varied considerably with the largest (Benedetti-Panici 2002) including 409 women and the smallest (Yamauchi 2010) including only 42 women.

We included trials with locally advanced cervical cancer but these trials had a different number of cases for each stage of disease (stage IB2 to stage IIIB), therefore the results may have differed across trials.

The type and dose of medical treatment (chemotherapy, radiotherapy or both) were heterogeneous across the trials.

The baseline indicators to measure the general health of participants in the studies were incompletely reported. The performance status of women was only mentioned in four studies (Benedetti-Panici 2002; Cetina 2013; Chang 2000; Keys 1999) and important clinical details such as the size of the tumour and information on residual disease were not reported in all of the studies.

Primary survival outcomes were largely well reported. HRs were either reported explicitly, deduced or obtained via correspondence so time to event data were analysed using appropriate survival methods in meta-analyses or, where possible, in single study reports. Harms were incompletely reported and quality of life was not reported in any of the studies. Morbidity was reported by treatment arm in five studies (Benedetti-Panici 2002; Cetina 2013; Chang 2000; Keys 2003; Perez 1987), but it was not reported by Morice 2012 and Yamauchi 2010. It is important to describe the side effects of adjuvant hysterectomy in women with locally advanced cervical cancer receiving multiple treatments as the available literature suggests severe morbidity (Touboul 2010).

In Benedetti-Panici 2002 28% of women deviated from the protocol deviation in each arm (58 of 210 in the neoadjuvant chemotherapy and hysterectomy arm, 55 of 199 in the radiotherapy arm), which is high. An additional concern is that of the 210 women in the neoadjuvant chemotherapy and hysterectomy arm 75 received radiotherapy, 37 due to not being suitable for hysterectomy and 38 after hysterectomy. Only 78% (164 of 210) in the neoadjuvant chemotherapy and hysterectomy arm had surgery. This crossover and the protocol deviation are potentially highly significant sources of bias.

Four studies (Benedetti-Panici 2002; Cetina 2013; Chang 2000; Keys 2003) did not mention the route of hysterectomy, that is open or laparoscopic. Morice 2012 indicated how many cases had laparoscopic or open procedures, however the study outcomes, including morbidity, were not subgrouped regarding this factor. Evidence suggests that laparoscopic procedures may have less morbidity than open procedures when performed for the appropriate group of women (Bijen 2009; Colombo 2009; Park 2013). Future studies should ideally consider this factor.

In Keys 2003 surgical staging of lymph nodes was optional and was performed on 57 (22%) women equally divided between the two study arms. Any patient with metastasis to the para-aortic nodes was ineligible for the RCT. Of the 103 women who did not have pre-randomisation surgical staging, 54 (52%) had a hysterectomy and lymph node sampling procedure. Of these, seven (13%) had positive para-aortic nodes. Since the surgical staging of lymph nodes was optional and it was performed in a subgroup of women, it is likely that this study was biased as far as the homogeneity of the staging and the prognosis of included women.

In the Chang 2000 trial there were three different dose ranges for brachytherapy during the study period.

This review identifies that more evidence is needed and there is justification for evaluating the role of hysterectomy in combination with other adjuvant and neoadjuvant treatment options in clinical trials.

The overall quality of the evidence for neoadjuvant chemotherapy and radical hysterectomy versus radiotherapy alone is moderate for survival outcomes and low for adverse events. All other comparisons provided low quality evidence, mainly because of poor reporting of outcomes and sparse data where results were based on single trials. The imprecision in single trials may be due to there being no significant difference between two treatments or an absence of evidence, which may come to light with greater statistical power. Quality of life was not reported in any of the trials and adverse events were incompletely reported, so the quality of the evidence was low or very low for these outcomes in all of the comparisons. The trials in all of the comparisons were at high or moderate risk of bias. Further research is likely to have an important impact on our confidence in the estimates of effects and may change the estimates in the treatment comparisons based on single trial results and for outcomes that were incompletely reported; but we are quite confident of the reliability of the meta-analysis of neoadjuvant chemotherapy and hysterectomy versus radiotherapy alone (N = 571) for the assessment of survival outcomes.

Potential biases in the review process

A comprehensive search was performed, including of electronic databases and the grey literature. All references were assessed and data extracted by two review authors working independently. We restricted the included studies to RCTs, which provide the strongest level of evidence available. Hence we have attempted to reduce bias in the review process.

One significant threat to the validity of the review is the possibility of publication bias, that is studies that had negative results did not find the treatments to have been effective may not have been published. We were unable to assess this possibility as the meta-analyses included just three studies and the review seven studies in total.

Agreements and disagreements with other studies or reviews

Treatment of locally advanced cervical cancer should be individualised and limited to the minimum number of treatment modalities to yield the best cure with minimal complications. The US National Cancer Institute alert in February 1999 stated that chemoradiotherapy should be considered for all women with cervical cancer. This was based on significant improvements in progression-free survival and overall survival when cisplatin-based chemotherapy was administered during radiation for various stages of cervical cancer (Morris 1999; NCI 1999; Rose 1999; Whitney 1999). Chemoradiotherapy is considered by many groups (in North America, Europe) as the standard treatment for locally advanced cervical cancer (CCMAC 2010; Green 2001). This includes pelvic external-beam radiotherapy with concomitant platinum-based chemotherapy followed by brachytherapy to boost the central disease response. Alternatively, locally advanced cervical cancer has been treated with primary radiotherapy alone.

In other countries, the lack of access to radiotherapy and the presumed poor control of metastatic disease has necessitated the use of neoadjuvant chemotherapy and hysterectomy. Chemotherapy is administered before other treatments in order to reduce the tumour volume and therefore to make women with clinically inoperable disease amenable to surgery (Sardi 1990; Sardi 1997).

More questions about neoadjuvant chemotherapy followed by hysterectomy should be answered by the findings of the European Organization for Research and Treatment of Cancer (55994) (EORTC 55994) RCT comparing neoadjuvant chemotherapy followed by surgery with the chemoradiotherapy approach for women with locally advanced cervical cancer (stage IB-II).

With adjuvant hysterectomy the primary site of cervical cancer is removed. This approach may be preferred by women and the physicians as the 'initial site' of the tumour is removed. However, it is not certain if this approach results in improved survival. This systematic review of the currently available published trials found no evidence that adjuvant hysterectomy improves overall survival in women with locally advanced cervical cancer treated with radiotherapy or chemotherapy, or both. In women with a complete response to chemoradiotherapy or radiotherapy there is no obvious benefit. Women with a partial response to chemoradiotherapy or radiotherapy represent a poorer prognostic group; the role of adjuvant hysterectomy in this group of women is still

debated (Azria 2005; Houvenaeghel 2007; Ota 2008; Sun 2014; Touboul 2010). In cases of suboptimal chemoradiotherapy, due to poor radiotherapy resources, adjuvant hysterectomy may have a role (Kundargi 2013).

In the trial of Keys 2003, women with grossly positive hysterectomy specimens progressed and died at almost seven-times the rate of those with negative specimens. A retrospective study (Touboul 2010) assessed the prognostic factors and morbidities in 150 women with locally advanced cervical cancer who had surgery after chemoradiotherapy. They found that the most important prognostic factors for survival were the presence and size of residual disease and histological nodal involvement. It is well recognised that there is a greater risk for extra-cervical disease (nodal spread or distant disease) in women with residual disease. These authors suggested that the survival of women treated using chemoradiotherapy for locally advanced cervical cancer could be potentially enhanced by improving the rate of complete response in the irradiated area (cervix or pelvic nodes) and by initially detecting women with para-aortic spread so that treatment could be adapted. Similarly, Ferrandina 2014 found that women with locally advanced cervical cancer who had adjuvant hysterectomy after chemoradiotherapy had a higher risk of postoperative complications if there was a suboptimal response to chemoradiotherapy and, to a lesser extent, a more advanced stage and para-aortic lymphadenopathy. One of the concerns regarding surgery following chemoradiotherapy is surgery-related morbidity. The CCMAC 2010 meta-analysis showed that chemoradiotherapy on its own can cause severe side effects; chemotherapy can cause significant acute toxicity and radiotherapy can cause late complications which are difficult to reverse. Surgery following these modalities can be challenging as the quality of the tissues and the potential for healing are adversely affected by the preceding treatments. Touboul 2010 and Ferrandina 2014 found that the morbidity following surgery was high, suggesting an under-reporting of morbidity data in the included studies.

In five of the included studies (Cetina 2013; Keys 2003; Morice 2012; Perez 1987; Yamauchi 2010) there was no significant difference in the rate of local and distant recurrences between the two arms. In Chang 2000, a reduction in the local recurrence rate (9% versus 21%) and a slight decrease in the distant recurrence rate (10% versus 13%) were observed in those women who received concurrent radiation and cisplatin and radical hysterectomy compared with those who received radiotherapy alone. The beneficial role of hysterectomy on this difference is not clear because, as mentioned earlier, evidence suggests that it is the addition of cisplatin that reduces the risk of local and distant recurrence (Morris 1999; NCI 1999; Peters 2000; Rose 1999; Whitney 1999).

AUTHORS' CONCLUSIONS

Implications for practice

From the available RCTs, we found insufficient evidence to suggest that hysterectomy improves the survival of women with locally advanced cervical cancer who were treated with radiotherapy or chemoradiotherapy. We did find that women who received neoadjuvant chemotherapy plus hysterectomy had less risk of death than those who received radiotherapy alone, but it is unclear whether that survival benefit was attributable to the hysterectomy or chemotherapy, or because a significant number of these women also received adjuvant radiotherapy.

The trials were at moderate or high risk of bias. The overall quality of the evidence is variable across the different comparisons and outcomes and was often downgraded due to concerns over the risk of bias and incomplete reporting of outcomes. This downgrading was mainly based on poor reporting and sparseness of data for some of the comparisons, where results were based on a single trial. The imprecision in single trials may be due to the small sample sizes and few events.

The decision to offer adjuvant hysterectomy (simple or radical, by open or laparoscopic procedure, with or without lymphadenectomy) needs to be individualised or performed in the context of a clinical trial.

Implications for research

Quality of life was not reported in any of the trials and adverse events were incompletely reported, so the quality of the evidence was low or very low for these outcomes across all comparisons. The trials in all of the comparisons were at high or moderate risk of bias. Further research is likely to have an important impact on our confidence in the estimates of effect and may change the estimates in the treatment comparisons based on single trial results and for outcomes that were incompletely reported.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Benedetti-Panici 2002

Methods	Multi-centre RCT set in Italy
Participants	A total of 409 eligible women with stage IB2 to III cervical cancer were included in the trial **Histopathology type** Squamous cell cancer of the cervix 210 women received neo-adjuvant chemotherapy (neoadjuvant chemotherapy) and radical hysterectomy (Arm A) and 199 received radiotherapy (Arm B) The baseline characteristics did not show any significant differences between the two arms **Median age** 49 years (range 25 to 70) in Arm A and 52 in Arm B (range 28 to 69) **Performance status** The performance status was 0 in the majority of the eligible women: 94% in the neoadjuvant chemotherapy and radical hysterectomy arm and 91% in the radiotherapy arm **FIGO stage** 41% of women had FIGO stage 1B2 to IIA > 4 cm in arm A and 44% in arm B 35% of women had FIGO stage IIB in arm A and 38% in arm B 24% of women had FIGO stage III in arm A and 18% in arm B **Tumour size** The tumour size was > 5 cm in 54% of the neoadjuvant chemotherapy and radical hysterectomy arm and in 58% of the radiotherapy arm **Tumour grade** 63% of women had grade 1 to 2 in Arm A and 62% in Arm B 34% had grade 3 in arm A and 32% in Arm B In the remaining women the grade was ungraded (3% and 6% in arms A and B respectively) **Lymph node status** Negative in 69% in Arm A and 74% in Arm B Positive in 23% in Arm A and 22% in Arm B Positive aortic in 5% in Arm A and 3% in Arm B Unknown in 8% in Arm A and 4% in Arm B.
Interventions	• **Neoadjuvant chemotherapy and radical hysterectomy** The neoadjuvant chemotherapy regimen was not predetermined, but minimal requirements were a cisplatin-containing regimen with a < 240 mg/m^2 total cisplatin dose with a maximum of two additional drugs, administered over a period of 6 to 8 weeks After neoadjuvant chemotherapy, the women were clinically reassessed and classified as suitable or unsuitable for radical hysterectomy. The latter women were treated by radiotherapy Surgery consisted of radical hysterectomy (type III to V) plus systematic (at least 20 nodes to be resected) pelvic lymphadenectomy (aortic lymphadenectomy was optional) Postoperative radiotherapy was given in women with positive surgical resection margins or metastatic nodes, or both

	In the case of node metastasis, the choice of adjuvant treatment was based on the institution's policy (i.e. chemotherapy, external-beam radiotherapy, or no further therapy) • **Radiotherapy** Conventional treatment consisted of external-beam, megavoltage radiotherapy (45 to 50 Gy) to the whole pelvis over 5 to 6 weeks. In the presence of metastatic pelvic nodes, detected by computed tomography or magnetic resonance imaging or lymphangiography, an extra dose of 5 to 7 Gy was administered. Low-dose rate internal radiotherapy (20 to 30 Gy to the tumour volume) was provided 2 to 4 weeks after external radiotherapy Aortic node metastases, when present, were irradiated (45 Gy/5 weeks, followed by a 5 Gy boost to residual disease eventually detected) with extended fields encompassing pelvic and aortic volume or at the end pelvic irradiation, in the case of a pelvic complete remission Salvage treatments were allowed in women who showed progressing disease
Outcomes	Overall survival Progression-free survival Severe morbidity
Notes	The median follow-up of the overall population was 40 months (range 1 to 107). When the analysis was restricted to surviving women, the median duration of follow-up was 53 months (range 3 to 107) Type III and type IV radical hysterectomies were performed Authors described assigned treatment as inadequate in 49 (23%) and 33 women (17%) in the neoadjuvant chemotherapy and hysterectomy and radiotherapy arms, respectively Reasons for inadequate treatment: • In the neoadjuvant chemotherapy and radical hysterectomy arm: more than 20% cisplatin total dose reduction (one patient) or more than 2-week delay of neoadjuvant chemotherapy administration (11 women), in the absence of toxicity; selective (< 20 nodes resected) pelvic lymphadenectomy; and type II radical hysterectomy (40 women) (more than one reason present in three women) • In the radiotherapy arm: a less than 60 Gy total dose (point A) was delivered in 21 women and in 18 women the total treatment time was ≥ 90 days (more than one violation present in six women) The risk ratio of long-term severe complications for chemosurgery versus radiotherapy alone was 0.86 (95% CI 0.49 to 1.50)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Women were randomly assigned to neoadjuvant chemotherapy and radical hysterectomy or radiotherapy by telephoning the trial data centre. Women were stratified at randomisation by disease stage, age and institution but it was unclear whether or not this sequence generation was done adequately

Benedetti-Panici 2002 (*Continued*)

Allocation concealment (selection bias)	Low risk	Women were randomly assigned to neoadjuvant chemotherapy and radical hysterectomy or radiotherapy by telephoning the trial data centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and clinicians to these intervention arms
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per cent analysed: 409/409 eligible women were analysed for primary survival outcomes using appropriate statistical techniques
Selective reporting (reporting bias)	Low risk	All case report forms were reviewed first by two study members and further verified by two independent investigators (one radiotherapist and one surgeon). All pertinent outcomes appear to have been reported by the trial authors
Other bias	High risk	Large deviations from protocol - a quarter of women deviated from protocol and this may have had impact on results 58/210 (26%) in neoadjuvant chemotherapy + radical hysterectomy arm (of those eligible) 55/199 (28%) in radiotherapy (of those eligible)

Cetina 2013

Methods	RCT conducted in Mexico. It was unclear whether or not this was a single or multicentre trial
Participants	A total of 211 eligible women with a histological diagnosis of untreated FIGO stage IB2 to IIB cervical cancer with no evidence of cancer in para-aortic lymph nodes (as evaluated by computed tomography scan) Women were required to be 18 to 70 years of age. Women were ineligible for the study if they had previously received chemotherapy or radiotherapy The baseline characteristics did not show any significant differences between the two arms **Age** The median age was 44 (range 23 to 66) years in the internal radiotherapy group and 45 (range 25 to 62) years in radical hysterectomy group **Karnofsky performance status** The median performance status score was 90 in both arms (range 80 to 100 in internal radiotherapy arm and 70 to 100 in radical hysterectomy arm) **Mean tumour size**

	The median tumour size was 32 mm in both arms (range 12 to 64 mm in internal radiotherapy arm and 12 to 81 mm in radical hysterectomy arm). Table 1 in the publication of Cetina 2013 actually stated that the median tumour size in each group was 32 cm but we assumed this should have been 32 mm **FIGO staging** 18 (18%) women had FIGO stage IB2 disease in the internal radiotherapy arm and 18 (16%) did in the radical hysterectomy arm 12 (12%) women had FIGO stage IIA2 disease in the internal radiotherapy arm and 11 (10%) did in the radical hysterectomy arm 70 (70%) women had FIGO stage IIB disease in the internal radiotherapy arm and 82 (74%) did in the radical hysterectomy arm **Histopathological type** 83 (83%) women had squamous cell cancer in the internal radiotherapy arm and 100 (90%) did in the radical hysterectomy arm 14 (14%) women had adenocarcinoma in the internal radiotherapy arm and 8 (7%) did in the radical hysterectomy arm 3 (3%) women had adenosquamous carcinoma in the internal radiotherapy arm and 3 (3%) in the radical hysterectomy arm **Haemoglobin (g/dl)** Median haemoglobin level was 13.3 (range 10.1 to 18) g/dl in the internal radiotherapy group and 12.8 (range 10 to 16) g/dl in radical hysterectomy group
Interventions	**External-beam chemoradiation with gemcitabine plus cisplatin** Women received 50.4 Gy external-beam radiotherapy to the entire pelvic region in 28 sessions of 1.8 Gy/day, 5 days/week, over the 6 weeks of chemotherapy • **Internal radiotherapy after external-beam chemoradiation with gemcitabine plus cisplatin** Immediately after completion of external-beam radiotherapy and chemotherapy, arm 1 women underwent low-dose rate internal radiotherapy. An internal radiotherapy dose of 30 to 35 Gy was delivered to point A to result in a cumulative dose of 80 to 85 Gy combining external-beam radiotherapy and internal radiotherapy. The cumulative external-beam radiotherapy and internal radiotherapy dose to point B (the pelvic wall) was 55 to 65 Gy • **Radical hysterectomy after external-beam chemoradiation with gemcitabine plus cisplatin** Within 4 to 6 weeks after the external beam radiotherapy and chemotherapy, Arm 2 women were submitted to type III radical hysterectomy and bilateral pelvic lymph node dissection and para-aortic lymph node sampling if the multidisciplinary team judged the disease could be resected obtaining margins free of disease. Postoperative low-dose rate internal radiotherapy was mandated in the surgical arm women only if surgical specimen revealed positive surgical margins and was administered within 4 weeks after surgery at a median dose of 30 Gy to the vaginal mucosa delivered to a depth of 0.5 cm
Outcomes	Overall survival Progression-free survival Pathological response: defined as complete with the absence of viable malignant cells in the surgical specimen Operative complications: defined as intraoperative including: bladder, ureteral, bowel, and vascular injuries and estimated blood loss exceeding 1000 ml

	Early postoperative and long-term complications: defined as any adverse event occurring within or after 30 days from surgery Late complications: including proctitis, cystitis and hydronephrosis Toxicity to chemoradiation with cisplatin and /gemcitabine (not reported by treatment arm)
Notes	Median length of follow-up in the trial was 36 months (3 to 80 months) Dose modification was not allowed for any of the drugs In the surgical arm, 86 (77%) out of 111 women received the full intervention. Fifteen (13.5%) abandoned treatment during external-beam radiotherapy; seven (6%) were judged not to be resectable and three (3%) had medical contraindication to surgery. In the internal radiotherapy arm, 86 (86%) completed treatment as per protocol. Three (3%) women abandoned treatment during external-beam radiotherapy and 11 (11%) had residual tumours after external-beam radiotherapy that prevented application of internal radiotherapy There were no differences between the median dose and days to complete external-beam radiotherapy in both the arms. Both the arms received a median number of five cycles (one to six) of cisplatin-gemcitabine Among the 86 women who received surgery, 62 (72%) had pathological complete response and 24 (28%) had pathological partial response. In 16 of these 24 women, only microscopic foci were found. The median number of pelvic and para-aortic lymph nodes removed was 30 (range 8 to 60) and 14 (range 3 to 32), respectively. Nine women (10%) had positive pelvic lymph nodes (median 3; range 1 to 7) and six of these also had positive para-aortic lymph nodes (median 2; range 1 to 4), and they received para-aortic radiation Progression-free survival rates in the internal radiotherapy arm were 75% and 72% in the surgical arm. Overall survival was 76% in the internal radiotherapy versus 74. 5% in the surgical arm. In the univariate analysis, none of the factors analysed (time to complete external-beam radiotherapy, < 45 versus > 45 days; histology, squamous versus non-squamous; clinical stage IB2-IIA versus IIB; age < 50 versus > 50 years and haemoglobin > 12 versus > 12 gr/dl) for either progression-free survival or overall survival were significant. The multivariate analysis also showed none to be significant Toxicity to chemoradiation: the most frequent toxic effects were hematological and gastrointestinal. Grade 3 leucopenia and neutropenia occurred in 30% and 25% of women **Acute complications in the surgical arm** The median hospital stay was 5 days (4 to 6). The median surgical time was 4 hours (4 to 6). The median blood loss was 450 ml (range 150 to 1600). Twelve women (14%) were transfused. Three women (3.5%) had vascular laceration; one (1.5%) had a urethral tear and two (2%) had section of the ureter. One patient (1.5%) had wound dehiscence and another (1.5%) infection in the surgical wound **Late toxicity** In the internal radiotherapy arm, grade 1 and 2 proctitis and cystitis were registered in nearly half of the women; however, grades 3 and 4 were seen in only 2% and 2%, respectively. In the surgical arm, six women had infection after 30 days from surgery. Three women (3.4%) had unilateral lymphocysts that required treatment with percutaneous drainage in two and lymphocyst resection and drainage in one. In addition, two women had uretero-cutaneous fistulae (2.3%) treated with surgery and double J-stent positioning

Cetina 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported, "After signing an informed consent, women were stratified according to FIGO stage IB2-IIA or IIB and randomly assigned before chemoradiation"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and clinicians to these intervention arms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per cent analysed: 211/211 (100%) eligible women were analysed for efficacy and toxicity and survival outcomes were analysed using appropriate statistical techniques. A total of 18/211 were lost to follow-up
Selective reporting (reporting bias)	Low risk	All pertinent outcomes appear to have been reported by the trial authors
Other bias	Unclear risk	Insufficient information to assess whether an additional risk of bias exists

Chang 2000

Methods	RCT conducted in China. It was unclear whether or not this was a single or multi-centre trial
Participants	A total of 120 eligible women with FIGO stage IB (bulky) to IIA (bulky) cervical cancer The baseline characteristics did not show any significant differences between the two arms **Age** The median age was 46 years in the neoadjuvant chemotherapy and radical hysterectomy group and 47 years in radiotherapy group **Performance status** The performance status was 0 in 85% of the neoadjuvant chemotherapy and radical hysterectomy arm and in 83% of the radiotherapy arm The performance status was 1 in 15% of the neoadjuvant chemotherapy and radical hysterectomy arm and in 15% of the radiotherapy arm The performance status was 2 in 0% of the neoadjuvant chemotherapy and radical

	hysterectomy arm and in 2% of the radiotherapy arm **Mean tumour dimension** The mean tumour dimension was 5.0 ± 0.8 cm in the neoadjuvant chemotherapy and radical hysterectomy arm and 4.9 ± 0.7 cm in the radiotherapy arm The mean tumour dimension was > 6 cm in 10% of the neoadjuvant chemotherapy and radical hysterectomy arm and in 10% of the radiotherapy arm **Tumour type** The tumour type was endophytic in 51% of the neoadjuvant chemotherapy and radical hysterectomy arm and in 54% of the radiotherapy arm The tumour type was exophytic in 49% of the neoadjuvant chemotherapy and radical hysterectomy arm and in 46% of the radiotherapy arm **FIGO staging** 53% of women had FIGO stage IB bulky in the neoadjuvant chemotherapy and radical hysterectomy arm and 50% in the radiotherapy arm 47% of women had FIGO stage IIA bulky in the neoadjuvant chemotherapy and radical hysterectomy arm and 50% in the radiotherapy arm **Histopathological type** 91% had squamous cell cancer in the neoadjuvant chemotherapy and radical hysterectomy arm and 88% in the radiotherapy arm 4% had adenocarcinoma in the neoadjuvant chemotherapy and radical hysterectomy arm and 8% in the radiotherapy arm 4% had adenosquamous carcinoma in the neoadjuvant chemotherapy and radical hysterectomy arm and 4% in the radiotherapy arm **Tumour grade** 3% had tumour grade I in the neoadjuvant chemotherapy and radical hysterectomy arm and 6% in the radiotherapy arm 40% had tumour grade II in the neoadjuvant chemotherapy and radical hysterectomy arm and 27% in the radiotherapy arm 44% had tumour grade III in the neoadjuvant chemotherapy and radical hysterectomy arm and 40% in the radiotherapy arm 9% had undifferentiated grade in the neoadjuvant chemotherapy and radical hysterectomy arm and 6% in the radiotherapy arm 4% had unspecified grade in the neoadjuvant chemotherapy and radical hysterectomy arm and 21% in the radiotherapy arm
Interventions	• **Neoadjuvant chemotherapy and radical hysterectomy** The neoadjuvant chemotherapy in this study consisted of cisplatin and vincristine, followed by bleomycin Two to 4 weeks after the completion of neoadjuvant chemotherapy, women underwent a type III radical abdominal hysterectomy and pelvic lymphadenectomy. The adnexae were usually left in women < 40 years old if they were grossly normal in appearance • **Radiotherapy** The radiotherapy usually included a combination of external irradiation and high dose rate internal radiotherapy. In brief, women received 40 to 44 Gy of whole pelvic irradiation; the para-aortic lymph nodes were not routinely included in the treatment field Parametria received up to 50 Gy The daily fraction was 1.8 to 2 Gy, five fractions per week If bulky tumour persisted after 44 Gy of irradiation, external-beam doses to the lower pelvis were increased to 50 to 54 Gy without central block, followed by internal radio-

	therapy, or to 70 Gy without internal radiotherapy Seven women received external irradiation only **Internal radiotherapy** There were three different dose ranges for internal radiotherapy during this period Before April 1992, internal radiotherapy was given as three fractions with 2-week intervals between each fraction; the dose to point A was 6.5 to 7.2 Gy/fraction. Of the women in the radiotherapy arm, one was treated using this method Between July 1992 and September 1993, five women were transferred to another hospital for internal radiotherapy because our remote control after-loading system was out of order. They received a total of four fractions of high-dose internal radiotherapy by two applicator insertions; on each insertion, two fractions of 7 to 7.5 Gy to point A were given during the same day with an interval of 4 to 6 hours. The median cumulative dose to point A was 72 Gy After August 1993, internal radiotherapy was again performed in our hospital and was given in six fractions at two fractions per week; the dose to point A was 4.3 Gy/fraction. The median cumulative dose to point A in this treatment protocol was 70 Gy. Thirty-seven women were treated using this method The response to radiotherapy was evaluated by a radiation oncologist and a gynaecologic oncologist weekly during treatment The postoperative radiotherapy was given by using techniques similar to those described above, the dose to the whole pelvis was 44 to 45 Gy, and that to the true pelvis was 50 to 54 Gy. After external irradiation, intravaginal internal radiotherapy was given in two to three fractions with a total dose of 4 to 6 Gy/0.5 cm below vaginal mucosa
Outcomes	Overall survival Disease-free survival Response Toxicity
Notes	Women with enlarged para-aortic lymph nodes on image study were ineligible unless results of cytologic or histologic studies were negative Type III radical hysterectomies were performed The median duration of follow-up was 39 months The median disease-free survival for the radiotherapy arm was 68 months, but median for the neoadjuvant chemotherapy arm could not be calculated as more than half of women did not experience a relapse. The difference in disease-free survival for women in the two treatment arms showed no apparent difference (P value = 0.8) The 2-year survival rate was 81% (95% CI 71% to 91%) in the neoadjuvant chemotherapy arm and 84% (95% CI 72% to 95%) in the radiotherapy arm, and the estimated 5-year survival rates were 70% (95% CI 56% to 83%) and 62% (95% CI 43% to 80%) for the neoadjuvant chemotherapy and radiotherapy arms, respectively The disease-free survival and the overall survival of the women who underwent neoadjuvant chemotherapy and radical hysterectomy did not differ significantly from those of women treated with radiotherapy alone. Women in the neoadjuvant chemotherapy arm had a higher incidence of receiving adjuvant therapy, with either radiotherapy or chemotherapy, after the scheduled treatment than those in the radiotherapy arm, who received radical hysterectomy as the adjuvant therapy. Of the 68 women in the neoadjuvant chemotherapy arm 62 underwent radical hysterectomy and 19 of those had adjuvant radiotherapy, 6 had adjuvant chemotherapy and 2 had combined chemotherapy

	and radiotherapy The neoadjuvant chemotherapy and radical hysterectomy group had higher incidence of local versus distant relapse (21% versus 9% respectively), whereas the radiotherapy had equal incidence of local versus distant relapse (12%) Higher incidences of relapse over the vagina and over the lung were noted in the neoadjuvant chemotherapy arm, whereas the radiotherapy arm showed a higher rate of paraaortic node relapse The incidence of acute toxicity, mainly mild to moderate gastrointestinal and hematologic toxicity and urinary retention, was higher in the neoadjuvant chemotherapy arm than in the radiotherapy arm, whereas the incidence of radiation cystitis, radiation proctitis, and lymphedema was higher in the radiotherapy arm

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"Randomisation was conducted by the Biostatistics Consulting Center of Chang Gung Memorial Hospital"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and clinicians to these intervention arms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The authors stated that in order to allocate more women to the presumably favourable treatment arm, they allocated 60% of the women to the neoadjuvant chemotherapy arm and 40% to the radiotherapy arm. This could potentially introduce a bias when clinicians assessed subjective outcomes such as classification of response and toxicity
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per cent analysed: 120/120 eligible women were analysed for primary survival outcomes using appropriate statistical techniques
Selective reporting (reporting bias)	Low risk	All pertinent outcomes appear to have been reported by the trial authors
Other bias	Unclear risk	Insufficient information to assess whether an additional risk of bias exists

Keys 2003

Methods	RCT-US (GOG #71, RTOG #84-12) Multi-centre trial The primary study objective was to determine whether adjuvant hysterectomy following radiation therapy for women with ***bulky*** stage IB cervical cancer improved survival
Participants	256 eligible women It is not mentioned whether the women were evaluated clinically or radiologically after radiotherapy in order to assess the tumour response and residual disease Surgical staging of lymph nodes was optional and was performed on 57 (22%) women, equally divided between the two study arms. Any patient with metastasis to the para-aortic nodes was ineligible for the RCT **Age (yrs)** $\leq$ 30: 9% in the radiotherapy group and 9% in the radiotherapy and hysterectomy group 31 to 40: 37% in the radiotherapy group and 29% in the radiotherapy and hysterectomy group 41 to 50: 32% in the radiotherapy group and 35% in the radiotherapy and hysterectomy group 51 to 60: 17% in the radiotherapy group and 18% in the radiotherapy and hysterectomy group 61 to 70: 4% in the radiotherapy group and 8% in the radiotherapy and hysterectomy group 71 to 80: 1% in the radiotherapy group and 2% in the radiotherapy and hysterectomy group **Race** White: 49% in the radiotherapy group and 52% in the radiotherapy and hysterectomy group African-American: 35% in the radiotherapy group and 27% in the radiotherapy and hysterectomy group Other: 15% in the radiotherapy group and 21% in the radiotherapy and hysterectomy group **GOG performance grade** 0: 77% in the radiotherapy group and 76% in the radiotherapy and hysterectomy group 1: 22% in the radiotherapy group and 20% in the radiotherapy and hysterectomy group 2: 1% in the radiotherapy group and 4% in the radiotherapy and hysterectomy group **Cell type** Adenocarcinoma: 6% in the radiotherapy group and 7% in the radiotherapy and hysterectomy group Adenosquamous carcinoma: 7% in the radiotherapy group and 7% in the radiotherapy and hysterectomy group Squamous cell carcinoma: 86% in the radiotherapy group and 86% in the radiotherapy and hysterectomy group **Tumour type** Exophytic: 48% in the radiotherapy group and 43% in the radiotherapy and hysterectomy group Barrel: 52% in the radiotherapy group and 57% in the radiotherapy and hysterectomy group **Tumour size (cm)** 4: 9% in the radiotherapy group and 13% in the radiotherapy and hysterectomy group 5: 36% in the radiotherapy group and 33% in the radiotherapy and hysterectomy group

	6: 32% in the radiotherapy group and 27% in the radiotherapy and hysterectomy group 7: 10% in the radiotherapy group and 18% in the radiotherapy and hysterectomy group 8+: 12% in the radiotherapy group and 9% in the radiotherapy and hysterectomy group
Interventions	• **Radiotherapy only (external and internal radiotherapy)** • **Radiotherapy and Hysterectomy (attenuated irradiation followed by extrafascial hysterectomy)** **Radiotherapy** Radiation therapy was to be delivered externally Daily fraction size was to be prescribed as 180 Gy and external treatment carried to a total dose of 40 and 45 Gy for the radiation only and the adjuvant hysterectomy regimens, respectively Dose distribution could not vary more than 5% across the treatment volume. These parameters were the same for both treatment arms The intracavitary treatment dose prescription was different between the treatment arms Both groups were to have an intracavitary treatment 1 to 2 weeks after completing external treatment The radiation only group was to receive a dose of 40 Gy to 'point A', while those who were to have hysterectomy received only 30 Gy Interstitial therapy was not permitted on this protocol A total dose of 80 Gy to point A was prescribed for the radiation-alone regimen and 75 Gy for the adjuvant hysterectomy regimen A minimum dose of 55 Gy was prescribed to point B for both regimens A parametrial boost was permitted if necessary to achieve this dose All irradiation was to be completed within 10 weeks **Hysterectomy** The experimental group was then to undergo extrafascial hysterectomy with removal of tubes and ovaries, if present, 2 to 6 weeks after completion of all irradiation This operation was described to include the removal of the corpus and cervix without contiguous parametrial tissue
Outcomes	Overall survival Pelvic-free survival Pelvic recurrence
Notes	A total of 256 eligible women with exophytic or "barrel" shaped tumours measuring 4 cm were randomised to either external and intracavitary radiotherapy (N = 124) or attenuated radiotherapy followed by extrafascial hysterectomy (N = 132) Of the women randomised to receive radiotherapy only, 87% received a total point A dose of 78 Gy or more while 49% had a total duration of treatment of 60 days or less For the radiation and hysterectomy treatment regimen, 90% received a total point A dose of 71 Gy or more while 80% had a total duration of treatment of 60 days or less Regarding the proportion of received to prescribed dose to point A, 96% and 95% of women had proportions greater than 0.80 from the radiation only and the combined treatment regimen, respectively Twenty-two per cent of women (radiation only; 28 of 124 (23%); and radiation and hysterectomy; 29 of 132 (22%)) received the optional up-front surgical staging Of the 103 women who did not have pre-randomisation surgical staging on the hysterectomy regimen, 54 (52%) had a hysterectomy and lymph node sampling procedure.

	Of these, seven (13%) had positive para-aortic nodes Both treatment programs were well tolerated Hysterectomy did not increase the frequency of reported grade 3 and 4 adverse effects (13 (10%) women for each regimen). Slightly more than two-thirds (18 of 26) of these serious adverse effects were from the gastrointestinal or genitourinary tract exclusively. The frequency of any reported adverse effect was higher for the hysterectomy group (63% versus 56%) There were 57 (46%) women who had progression of disease among the radiation-only group and there were 49 (37%) progressions in the adjuvant hysterectomy group The progression-free survival results includes, as failures, not just those with disease progression but 8 and 11 patient deaths that occurred without progression among the radiation-only and the adjuvant hysterectomy regimen, respectively The significance level for the log-rank test is P value = 0.07 (one-tail) The reduction in the risk of progression/death for the combined treatment group to the radiation-only group was 23% (i.e., relative risk is 0.77) with a 90% confidence interval of (-3 to 43) The median progression-free survival was 7.4 years for the radiation only regimen and no estimate is available for the hysterectomy regimen (progression-free survival is 53% at 8.4 years) There were two treatment-related deaths in the radiation only group and one in the hysterectomy group Eight women died of intercurrent disease and 12 died of unknown causes. Those who were last seen alive have a median follow-up time of 9.6 years (range, 0.3 to 16.1 years) Twelve women in each regimen (10% versus 9%) were lost to follow-up by 5 years There was no apparent difference (P value = 0.26, one-tail) in the survival experience of women by treatment regimen The relative risk estimate of the combined-treatment group to the radiation- only group was 0.89 (90% confidence interval, 0.65, 1.21). Fifty-six women have died in each treatment regimen The modelling of survival identified the same prognostic factors with very similar relative risk estimates Adjusting for tumour size, performance status, and age, the relative risk of progression for the combined treatment group to the radiation-only group was statistically significant (i.e., relative risk is 0.72, P value = 0.04, one-tail) The adjusted relative risk estimate of death was 0.84, which was not statistically significant At 5 years the strictly local relapse incidence is up to 27% for the radiation only regimen versus only 14% for the combined treatment regimen, although the combined treatment group was slightly more likely to have distal progression (20% versus 16%). These rates agree with the distribution of progression site To determine if there is any differential effect of adjuvant hysterectomy by tumour size, a test for interaction was performed. The interaction term, when quantified by using the whole centimetre tumour size, was borderline significant (P value = 0.06) for progression-free survival but was statistically significant (P value = 0.007) for survival. The results indicate that women on the hysterectomy regimen had a lower risk of progression and death than the radiation-alone women for tumour sizes of 4, 5, and 6 cm. Combined, the relative risk of death was 0.60 (relative risk of progression, 0.58) for the hysterectomy to the radiation-only group. Those with tumour sizes of 7 cm or larger in the hysterectomy group progressed at a higher rate after 14 months; the relative risk estimate is 1.27

Keys 2003 (*Continued*)

	(relative risk of death, 2.03). The crossover from lower to higher risk for the hysterectomy regimen occurs between 6 and 7 cm for both progression-free survival and survival Histologic evaluation of the cervical specimens for the 123 women who underwent hysterectomy identified 59 (48%) with no detectable malignancy, while 49 (40%) were microscopically positive and 15 (12%) were grossly positive The median time to surgery from study entry was 3.0 months (10th and 90th percentiles, 2.4 and 3.8 months) Comparing progression-free survival and survival of women with negative versus positive specimens were statistically significant. Women with grossly positive hysterectomy specimens progressed and died at almost 7 times the rate compared to those with negative specimens

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization with equal probability of assignment to each treatment regimen was carried out by a block arrangement balancing the treatment assignment within major GOG institutions and the option of paraaortic lymph node sampling"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and clinicians to these intervention arms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	% analysed: 256/256 eligible women were analysed for primary survival outcomes using appropriate statistical techniques. Two women in each arm did not receive radiation and were not examined for adverse effects
Selective reporting (reporting bias)	Low risk	All pertinent outcomes appear to have been reported by the trial authors
Other bias	Unclear risk	Insufficient information to assess whether an additional risk of bias exists

Morice 2012

Methods	RCT conducted in France. It was unclear whether or not this was a single or multi-centre trial, but appears to have been multi-centre FIGO stage IB2 or II cervical cancer received pelvic external radiation therapy and concomitant cisplatin chemotherapy with hysterectomy or without radical hysterectomy
Participants	A total of 61 eligible women having achieved a complete clinical and radiological response after concurrent chemoradiotherapy were randomly allocated to the treatment arms: hysterectomy or no hysterectomy The median age was 45 in the concurrent chemoradiotherapy and hysterectomy arm and 44 in the concurrent chemoradiotherapy and hysterectomy and no hysterectomy arm **FIGO staging** 52% of women had FIGO stage IB2 in the concurrent chemoradiotherapy and hysterectomy arm and 50% in the concurrent chemoradiotherapy and no hysterectomy arm 48% of women had FIGO stage II in the concurrent chemoradiotherapy and hysterectomy arm and 50% in the concurrent chemoradiotherapy and no hysterectomy arm **Histopathology type** 90% had squamous cell cancer in the concurrent chemoradiotherapy and hysterectomy arm and 80% in the concurrent chemoradiotherapy and no hysterectomy arm 10% had adenocarcinoma in the concurrent chemoradiotherapy and hysterectomy arm and 20% in the concurrent chemoradiotherapy and no hysterectomy arm Median (range) dose of external radiotherapy, Gy was 45 in the concurrent chemoradiotherapy and hysterectomy arm and 46 in the concurrent chemoradiotherapy and no hysterectomy arm **Internal radiotherapy** 24 women had one application in the concurrent chemoradiotherapy and hysterectomy arm and 25 in the concurrent chemoradiotherapy and no hysterectomy arm 4 women had two applications in the concurrent chemoradiotherapy and hysterectomy arm and 4 in the concurrent chemoradiotherapy and no hysterectomy arm 3 women had unknown applications in the concurrent chemoradiotherapy and hysterectomy arm and 3 in the concurrent chemoradiotherapy and no hysterectomy arm **Median dose of internal radiotherapy, Gy** 15 in the concurrent chemoradiotherapy and hysterectomy and 15 in the concurrent chemoradiotherapy and no hysterectomy arm Unknown in 9 women **Lateropelvic external-beam radiotherapy boost** 23% in the concurrent chemoradiotherapy and hysterectomy arm and 31% in the concurrent chemoradiotherapy and no hysterectomy arm **Median (range) duration of radiotherapy, days** 51 in the concurrent chemoradiotherapy and hysterectomy arm and 51.5 in the concurrent chemoradiotherapy and no hysterectomy arm Unknown in 5 women **Courses of concurrent chemotherapy** 5 in the concurrent chemoradiotherapy and hysterectomy arm and 5 in the concurrent chemoradiotherapy and no hysterectomy arm Unknown in 6 women **Initial characteristics** Respectively, 26 and 10 women had clinical spread to the parametria or vagina during initial management

	During pre-therapeutic examinations, 18 women had suspicious pelvic nodes (on magnetic resonance imaging or computed tomography scan or both) No patient had suspicious para-aortic nodes Thirteen women underwent an initial para-aortic lymphadenectomy (associated with pelvic node dissection in one) Two women had involved para-aortic nodes and one patient had positive pelvic nodes (of 17 removed) but without para-aortic involvement
Interventions	• **Pelvic external radiation therapy and concomitant cisplatin chemotherapy with hysterectomy** • **Pelvic external radiation therapy and concomitant cisplatin chemotherapy without hysterectomy** **Radiotherapy** Radiotherapy was delivered to the pelvis for a total dose of 45 to 50 Gy, delivered in five fractions of 1.8 to 2 Gy per week followed, 1 to 2 weeks later, by internal radiotherapy This radiation was combined with concomitant chemotherapy using cisplatin during external radiation therapy The use of a sixth course of concomitant chemotherapy during internal radiotherapy was optional Complete clinical and radiological response (based on magnetic resonance imaging) evaluated 6 to 8 weeks after internal radiotherapy **Chemotherapy** Concomitant cisplatin chemotherapy **Hysterectomy** Hysterectomy could be performed using a laparotomy or a laparoscopic approach and could be extrafascial or radical (type II according to the Piver classification) according to the preoperative examination A selective or complete pelvic lymphadenectomy was optional and could be performed if lymphadenopathy was detected during surgery If a para-aortic lymphadenectomy was not performed initially using a laparoscopic approach, it could be done at the time of pelvic surgery in women randomised to arm A It was possible for some of the women randomised to arm B to undergo surgery after internal radiotherapy to carry out a laparotomy or a laparoscopic para-aortic lymphadenectomy, but without pelvic surgery
Outcomes	Overall survival Event-free survival (event referring to recurrence or death) Site of first recurrence Morbidity (the results not published on this or other publication)
Notes	This trial was closed because of poor accrual: only 61 women were enrolled (in 2003-2006) and are reported in this study: 31 in arm A and 30 in arm B The median duration of follow-up was 3.8 years (range 0.4 to 5.8) One patient initially included in arm A did not undergo hysterectomy and one patient included in arm B did undergo hysterectomy After the end of concurrent chemoradiotherapy and internal radiotherapy all women, except four, had a normal clinical examination (but this status was unknown for eight women) In arm A, a laparoscopic hysterectomy was performed in seven cases and a radical hysterec-

	tomy was performed in 10 cases. Sixteen women underwent para-aortic lymphadenectomy. Six women underwent complete bilateral pelvic lymphadenectomy, three had a unilateral pelvic lymphadenectomy with contralateral pelvic selective lymphadenectomy, and four had a selective pelvic lymphadenectomy In arm B, 17 women underwent a para-aortic lymphadenectomy (via a laparoscopic approach for six of them). No patient underwent a complete pelvic lymphadenectomy and one patient had a selective pelvic adenectomy In arm A, 11 women had residual disease after histological analysis (isolated cells for six women, $\leq$ 1 cm for three women, and > 1 cm for two women). Only one of them (with residual disease > 1 cm) had an abnormal pre-randomisation magnetic resonance imaging (ambiguous endocervical lesion measuring 8 mm) In arm A, three women had metastatic pelvic nodes (two had one involved node and one had three involved nodes) and two women had metastatic para-aortic nodes (one had two involved nodes and one had eight involved nodes) In arm B, one patient had metastatic pelvic nodes and no patient had metastatic para-aortic nodes The 3-year EFS rates were, respectively, 72% (95% CI 53 to 85) and 89% (95% CI 75 to 96) (not significant) in arm A and arm B The 3-year OS rates were, respectively, 86% (95% CI 69 to 55) and 97% (95% CI 83 to 99) (not significant) in arm A and arm B The log-rank test did not show any statistical difference between arm A and arm B in terms of the overall survival and event-free survival outcomes Twelve women relapsed (five of them died): eight in arm A and four in arm B The location of recurrent disease was known in 11 women Among two women having a pelvic node recurrence, none had a suspicious pelvic node during initial imaging and one had lateropelvic boost for parametrial spread

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 of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and clinicians to these intervention arms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per cent analysed: 61/61 randomised women were analysed

Morice 2012 (*Continued*)

Selective reporting (reporting bias)	High risk	After contacting the authors we were informed that the morbidity results were not published or available
Other bias	Unclear risk	Insufficient information to assess whether an additional risk of bias exists

Perez 1987

Methods	Single RCT in Washington University, USA Women were randomised to be treated with radiotherapy alone or radiotherapy and radical hysterectomy
Participants	A total of 118 eligible women with stage IB to IIA cervical cancer It is not reported how many women were stage IB1 and how many stage IB2 (the latter group is area of interest for this Cochrane review) Women with barrel-shaped cervix (endocervical lesion with cervix diameter larger than 5 cm) were excluded Age distribution was comparable in the two groups. No additional information is given regarding the age (i.e range, median age, mean age) of the participating women **In women treated with radiotherapy alone (N = 56)** - Stage IB women: 35 had squamous cell carcinoma, 4 had adenocarcinoma and one had adenosquamous carcinoma - Stage IIA women: 16 had squamous cell carcinoma **In women treated with radiotherapy and radical hysterectomy (N = 62)** - Stage IB women: 43 had squamous cell carcinoma, 4 had adenocarcinoma and one had adenosquamous carcinoma - Stage IIA women: 14 had squamous cell carcinoma
Interventions	• **Preoperative radiotherapy and radical hysterectomy** Women treated with preoperative radiation and surgery received 2000 Gy whole pelvis irradiation and one intracavitary insertion for 5000 to 6000 mgh, followed 2 to 6 weeks later by a radical hysterectomy and bilateral pelvic lymphadenectomy (up to the bifurcation of the common iliac chain). The dose to the cervix was about 7000 Gy and to the pelvic lymph nodes 3000 Gy • **Radiotherapy alone** Treatment with irradiation alone consisted of 1000 to 2000 Gy delivered to the whole pelvis and an additional parametrial dose to total of 5000 Gy to the external iliac lymph nodes combined with two intracavitary insertions for a total of approximately 7500 mgh (6500 to 7000 Gy to point A). The dose to the paracervical tissues was about 8500 Gy and to the pelvic lymph nodes 6000 Gy
Outcomes	5 year tumour-free actuarial survival Sites of failure after therapy Complications

Notes	All women were available for 5-year follow-up and the median period of observation is 6 years No women were lost to follow-up In the women with Stage IB, 40 were treated with radiotherapy alone and 48 with preoperative radiotherapy and a radical hysterectomy In women with Stage IIA, 16 were treated with radiotherapy alone and 14 with preoperative radiotherapy and surgery The 5-year, tumour-free actuarial survival for Stage IB women was 89% with radiotherapy alone and 80% in the preoperative radiotherapy and surgery groups In Stage IIA, the 5-year survival was 56% for the irradiation alone group and 79% for the preoperative radiotherapy and hysterectomy women. The difference in these results is not statistically significant An analysis of the chronological distribution of recurrences showed that 85% of the failures occurred within 3 years from therapy, at about the same rate in the radiotherapy alone or radiotherapy and surgery groups The overall incidence of major complications was 16% in the radiotherapy alone group in contrast to 11% in the preoperative radiotherapy and surgery group. This difference is not statistically significant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were ... randomized by the flip of a coin"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and clinicians to these intervention arms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per cent analysed: 118/118 randomised women were analysed and no women were lost to follow-up
Selective reporting (reporting bias)	High risk	Five-year tumour-free survival was reported but overall survival was not, even though the number of deaths would have been known
Other bias	Unclear risk	Insufficient information to assess whether an additional risk of bias exists

Yamauchi 2010

Methods	Single-centre RCT conducted in Japan
Participants	A total of 42 women were enrolled: 20 were assigned to receive neoadjuvant chemotherapy & radical hysterectomy and 22 were assigned to receive radiotherapy. All were exclusively Stage IIIB cervical cancers **Age** The mean age was 53.2 ± 1.7 in the neoadjuvant chemotherapy and radical hysterectomy group and 59.9 ± 1.7 in the radiotherapy group Average age during enrolment was statistically younger in the neoadjuvant chemotherapy & radical hysterectomy group compared to the radiotherapy group (P value < 0.01) The age range was 36 to 69 in the neoadjuvant chemotherapy and radical hysterectomy group and 42 to 70 in the radiotherapy group (unpaired *t* test) **Histopathology** The histopathology type was squamous cell cancer only Keratinizing in 8 in the neoadjuvant chemotherapy and radical hysterectomy group and 4 in the radiotherapy group Non-keratinizing in 12 in the neoadjuvant chemotherapy and radical hysterectomy group and 18 in the radiotherapy group (Fisher test) **Hydronephrosis** Prevalence of hydronephrosis was similar between the two groups Two women in the neoadjuvant chemotherapy and radical hysterectomy group and 2 in the radiotherapy group **Parametrium involvement** Bilateral parametrium involvement was significantly higher in the radiotherapy (P value < 0.05) 5 in the neoadjuvant chemotherapy and radical hysterectomy group and 13 in the radiotherapy group (P value < 0.05)
Interventions	• **Neoadjuvant chemotherapy and radical surgery** **Neoadjuvant chemotherapy** The regimen included the following: The neoadjuvant chemotherapy and radical hysterectomy group received intraarterial infusion chemotherapy, consisting of cisplatin, bleomycin, and mitomycin for three courses every 4 weeks. Evaluations were done after each course of chemotherapy to determine the local tumour size and whether there were free surgical margins of the involved parametrium in the pelvis **Radical surgery (hysterectomy)** If the tumour was surgically removable, a radical hysterectomy was performed with bilateral salpingo- oophorectomy and pelvic lymphadenectomy, and then radiotherapy was given at 40 Gy to the whole pelvic region. If the tumour progressed or relapsed, a combined chemotherapy of bleomycin, vincristine, mitomycin, and cisplatin (BOPM) was given, and then irinotecan with cisplatin as the third line If the local tumour was inoperable (N = 1) radiotherapy was given at 40 Gy to the whole pelvic region and 20 Gy to intracavity, followed by BOPM chemotherapy • **Radiotherapy alone** The radiotherapy group received radiotherapy to the whole pelvic region in 20 fractions totalling 40 Gy The total dose delivered to point B as a boost dose with midline shield coverage was 20 Gy

	Total dose delivered by internal radiotherapy was 24 to 30 Gy The duration of the radiotherapy was 4 weeks Radiotherapy was discontinued if a patient had a white blood cell count of less than 3000/mm^3 In cases with local recurrence or progression of the primary lesion, chemotherapy was added, which included BOMP, irinotecan with cisplatin, and cisplatin, or carboplatin alone When distant metastasis occurred, we added radiotherapy, or the single lesion was surgically removed
Outcomes	5-year survival 5-year disease-free survival The trial authors supplied HR estimates for OS and disease-free survival for inclusion in meta analyses
Notes	In the neoadjuvant chemotherapy and radical hysterectomy arm, if the tumour became operable within three courses, radical hysterectomy was performed The radiotherapy alone group received radiotherapy to the whole pelvis of 40 Gy, midline shield coverage of 20 Gy, and intracavitary of 24 to 30 Gy The median duration of follow-up was 60 months The keratinising type of cervical squamous cell carcinoma responded more poorly to radiation than the non-keratinizing type. However, both keratinising and non-keratinising types responded similarly to neoadjuvant chemotherapy and radical hysterectomy After 15 years of enrolment, they had only 42 eligible women and, furthermore, the recent meta-analysis showed that concurrent chemoradiation therapy was superior to sequential chemotherapy. Thus, it was decided to stop this study before the expected number of women was completed and a follow-up study was performed There were no differences in the recurrence rates and recurrence sites between the two types of treatments The 5-year survival rate was 47% for the neoadjuvant chemotherapy and radical hysterectomy group and 48% for the radiotherapy group There was no statistical difference in the overall survival between the 2 groups

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 of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and clinicians to these intervention arms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Incomplete outcome data (attrition bias) All outcomes	Low risk	Per cent analysed: 42/42 randomised women were analysed and no women were lost to follow-up (including the two women who died)
Selective reporting (reporting bias)	High risk	Adverse event and toxicity data were not reported
Other bias	Unclear risk	Insufficient information to assess whether an additional risk of bias exists

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

Study	Reason for exclusion
Katsamuta 2013	Women in both arms received hysterectomy
Keys 1999	Women in both arms received hysterectomy
Sardi 1997	Women in both arms received hysterectomy or surgical staging
Sun 2013	Women in both arms received hysterectomy
Sundfor 1996	This trial compared surgery or radiotherapy in women with early stage carcinoma of the cervix

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

EORTC 55994

Trial name or title	Chemotherapy Followed By Surgery Vs Radiotherapy Plus Chemotherapy in women With Stage IB or II Cervical Cancer
Methods	Multi-centre RCT
Participants	Disease characteristics: Histologically confirmed cervical cancer, including the following subtypes: • Squamous cell carcinoma • Adenosquamous cell carcinoma • Adenocarcinoma (excluding small cell, clear cell, and other rare variants of the classical adenocarcinoma) FIGO stage IB2, IIA (greater than 4 cm), or IIB Patient characteristics: Age: • 18 to 75 years Performance status:

EORTC 55994 (*Continued*)

	• WHO 0 to 2
Interventions	• **Neoadjuvant chemotherapy and radical hysterectomy** Women receive neoadjuvant cisplatin-based chemotherapy on day 1. Treatment repeats every 21 days. Within 6 weeks after the last chemotherapy course, women undergo a type III-V Piver-Rutledge radical hysterectomy. Women with positive lymph nodes or tumour invasion into the parametria or less than 5 mm from the resection borders after surgery receive standard adjuvant external-beam radiotherapy once daily, 5 days a week, for 5 to 5.6 weeks (25 to 28 treatment days) followed by external boost radiotherapy or internal radiotherapy for 1 or 2 days • **Concurrent chemoradiotherapy** Women receive standard therapy comprising radiotherapy as in arm I concurrently with cisplatin-based chemotherapy once weekly for 6 weeks. Adjuvant hysterectomy is allowed, but not recommended, in cases of histologically proven residual tumour
Outcomes	• Compare the overall and progression-free survival of women with stage IB2, IIA, or IIB cervical cancer treated with neoadjuvant cisplatin-based chemotherapy followed by radical hysterectomy versus standard therapy comprising concurrent radiotherapy and cisplatin-based chemotherapy • Compare the toxicity of these regimens in these women • Compare the quality of life of women treated with these regimens
Starting date	March 2002
Contact information	Trial Lead Organizations/Sponsors European Organization for Research and Treatment of Cancer Fabio Landoni, MD Study Chair Alessandro Colombo, MD Study Chair Stefano Greggi, MD, PhD Study Chair Gemma Kenter, MD Study Chair
Notes	Estimated Enrollment: 686 Estimated Study Completion Date: April 2018 Estimated Primary Completion Date: September 2014 (Final data collection date for primary outcome measures)

DATA AND ANALYSES

Comparison 1. Neoadjuvant chemotherapy and radical hysterectomy versus radiotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3	571	Hazard Ratio (Random, 95% CI)	0.71 [0.55, 0.93]
2 Disease or progression-free survival	3	571	Hazard Ratio (Random, 95% CI)	0.75 [0.53, 1.05]

Analysis 1.1. Comparison 1 Neoadjuvant chemotherapy and radical hysterectomy versus radiotherapy alone, Outcome 1 Overall survival.

Review: Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer

Comparison: 1 Neoadjuvant chemotherapy and radical hysterectomy versus radiotherapy alone

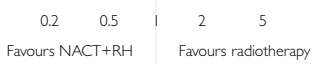
Outcome: 1 Overall survival

Study or subgroup	NACT plus RH N	Radiotherapy alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Benedetti-Panici 2002	210	199	-0.405 (0.153)		78.8 %	0.67 [0.49, 0.90]
Chang 2000	68	52	-0.11 (0.39)		12.1 %	0.90 [0.42, 1.92]
Yamauchi 2010	20	22	-0.08 (0.45)		9.1 %	0.92 [0.38, 2.23]
Total (95% CI)	**298**	**273**			**100.0 %**	**0.71 [0.55, 0.93]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.86$, df = 2 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 2.50 (P = 0.012)

Test for subgroup differences: Not applicable

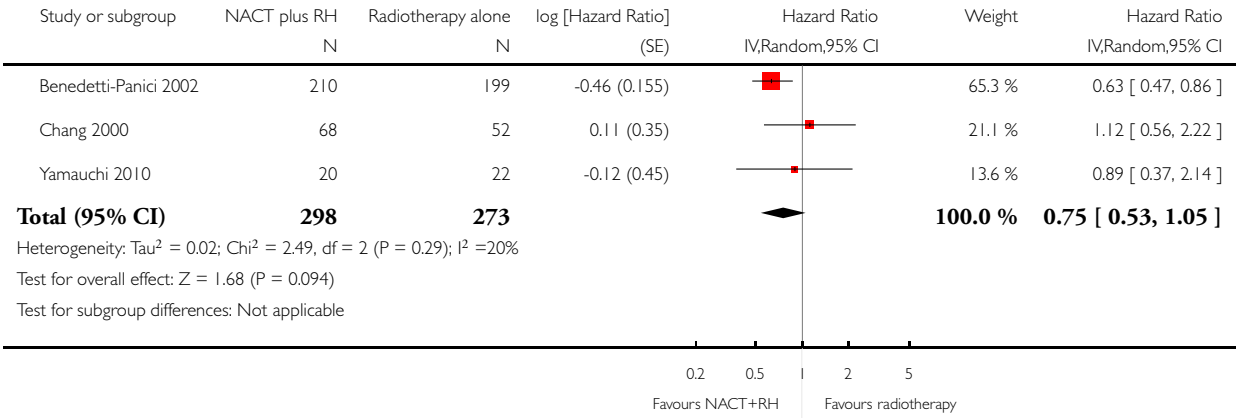


Analysis 1.2. Comparison 1 Neoadjuvant chemotherapy and radical hysterectomy versus radiotherapy alone, Outcome 2 Disease or progression-free survival.

Review: Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer

Comparison: 1 Neoadjuvant chemotherapy and radical hysterectomy versus radiotherapy alone

Outcome: 2 Disease or progression-free survival



APPENDICES

Appendix 1. FIGO staging

	FIGO Classification for Cervical Cancer
STAGE	***CHARACTERISTICS***
I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
IA	Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not > 7.0 mm. Depth of invasion should not be > 5.0 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging
IA_1	Measured stromal invasion of not > 3.0 mm in depth and extension of not > 7.0 mm
IA_2	Measured stromal invasion of > 3.0 mm and not > 5.0 mm in depth with an extension of not > 7.0 mm

(*Continued*)

IB	Clinical lesions confined to the cervix or preclinical lesions > IA. All gross lesions even with superficial invasion are stage IB cancers
IB_1	Clinical lesions not > 4 cm in size
IB_2	Clinical lesions > 4 cm in size
II	The carcinoma extends beyond the cervix, but has not extended onto the pelvic wall; the carcinoma involves the vagina, but not as far as the lower third
IIA	No obvious parametrial involvement. Involvement of up to the upper two-thirds of the vagina
IIB	Obvious parametrial involvement, but not into the pelvic sidewall
III	The carcinoma has extended onto the pelvic wall; on rectal examination there is no cancer-free space between the tumour and the pelvic wall; the tumour involves the lower third of the vagina; all cases with a hydronephrosis or non-functioning kidney should be included, unless they are known to be due to other causes
IIIA	No extension onto the pelvic wall, but involvement of the lower third of the vagina
IIIB	Extension onto the pelvic wall or hydronephrosis or nonfunctioning kidney
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

Appendix 2. CENTRALsearch strategy

CENTRAL

1. MeSH descriptor Uterine Cervical Neoplasms explode all trees
2. (cervi* near/5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*))
3. (#1 OR #2)
4. MeSH descriptor Hysterectomy explode all trees
5. hysterectom*
6. (#4 OR #5)
7. MeSH descriptor Antineoplastic Agents explode all trees
8. MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
9. MeSH descriptor Chemotherapy, Adjuvant, this term only
10. chemotherap*
11. cisplatin
12. carboplatin
13. gemcitabine
14. paclitaxel
15. etoposide
16. fluorouracil
17. bleomycin

18. ifosphamide
19. (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)
20. MeSH descriptor Radiotherapy explode all trees
21. radiotherap*
22. radiation
23. (#20 OR #21 OR #22)
24. chemoradi* or radiochemo*
25. (#19 OR #23 OR #24)
26. (#3 AND #6 AND #25)

Appendix 3. MEDLINE search strategy

MEDLINE (Ovid)

1. exp Uterine Cervical Neoplasms/
2. (cervi* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. exp Hysterectomy/
5. hysterectom*.mp.
6. 4 or 5
7. exp Antineoplastic Agents/
8. exp Antineoplastic Combined Chemotherapy Protocols/
9. Chemotherapy, Adjuvant/
10. chemotherap*.mp.
11. cisplatin.mp.
12. carboplatin.mp.
13. gemcitabine.mp.
14. paclitaxel.mp.
15. etoposide.mp.
16. fluorouracil.mp.
17. belomycin.mp.
18. ifosphamide.mp.
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp Radiotherapy/
21. radiotherap*.mp.
22. radiation.mp.
23. 20 or 21 or 22
24. (chemoradi* or radiochemo*).mp.
25. 19 or 23 or 24
26. 3 and 6 and 25
27. randomized controlled trial.pt.
28. controlled clinical trial.pt.
29. randomized.ab.
30. placebo.ab.
31. clinical trials as topic.sh.
32. randomly.ab.
33. trial.ti.
34. 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 26 and 34

key:
mp=title, original title, abstract, name of substance word, subject heading word, unique identifier
pt=publication type
ab=abstract

sh=subject heading

Appendix 4. EMBASE search strategy

EMBASE Ovid

1. exp uterine cervix tumor/
2. (cervi* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. exp hysterectomy/
5. hysterectom*.mp.
6. 4 or 5
7. exp antineoplastic agent/
8. exp chemotherapy/
9. chemotherap*.mp.
10. cisplatin.mp.
11. carboplatin.mp.
12. gemcitabine.mp.
13. paclitaxel.mp.
14. etoposide.mp.
15. fluorouracil.mp.
16. belomycin.mp.
17. ifosphamide.mp.
18. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp radiotherapy/
20. radiotherap*.mp.
21. radiation.mp.
22. 19 or 20 or 21
23. (chemoradi* or radiochemo*).mp.
24. 18 or 22 or 23
25. 3 and 6 and 24
26. crossover procedure/
27. double-blind procedure/
28. randomized controlled trial/
29. single-blind procedure/
30. random*.mp.
31. factorial*.mp.
32. (crossover* or cross over* or cross-over*).mp.
33. placebo*.mp.
34. (double* adj blind*).mp.
35. (singl* adj blind*).mp.
36. assign*.mp.
37. allocat*.mp.
38. volunteer*.mp.
39. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 25 and 39

key:

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

Appendix 5. LILACS search strategy

LILACS
(MH:hysterectomy or hysterectom$) AND ((cervi$ and (cancer$ or tumor$ or tumour$ or malignan$ or carcinoma$ or neoplas$)) or MH:Uterine Cervical Neoplasms)

CONTRIBUTIONS OF AUTHORS

FK and AB searched for relevant trials and individually examined each potentially relevant full text reference. AB extracted data on risk of bias items. FK and AB drafted the full review; AB drafted methodological and statistical sections of the review as well as various sections of the discussion; FK drafted clinical sections of the review, added expertise and drafted some of the discussion.

EB provided clinical advice and expertise, offered critical comments and contributed to the discussion.

MP and DO reviewed the final version of the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol title was, 'To assess the effectiveness and safety (surgery-related complications) of hysterectomy with radiotherapy, chemotherapy or both in locally advanced cervical cancer (stages IB2 to III)' but was modified to the following title: 'To determine whether hysterectomy, in addition to standard treatment with radiation and/or chemotherapy in women with locally advanced cervical cancer (stage IB2-III), is safe and effective compared with standard treatment alone'. The original title was reworded for clarity.

Types of outcome measures

Primary outcomes

The primary outcome definition was expanded to incorporate definitions by trialists.

- Overall survival: survival until death from all causes was assessed from the time when women were enrolled in the study or as defined by the trial authors.

Secondary outcomes

Progression-free (PFS) and disease-free survival were listed as separate outcomes in the protocol but in the review PFS was preferred. We subsequently defined trials using disease-free survival and PFS as a subgroup analysis that was of interest (see below). Local control was specified as an outcome of interest in the protocol but was omitted in the review after discussion about its importance and our wanting to restrict outcomes to those that are important and pertinent.

- Progression-free survival.
- If authors reported disease-free survival rather than progression-free survival then this was assessed.
- Quality of life measured using a scale that has been validated through reporting of norms in a peer-reviewed publication by a validated scale.
- Adverse events:

Complications of chemotherapy and radiotherapy were added to the review as only surgery-related complications were listed in the protocol but complications from these medical agents are important.

Chemotherapy and radiotherapy-related complications

Grades of chemotherapeutic and radiotherapeutic toxicity were extracted and grouped as:

- haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage);
- gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver toxicity, proctitis);
- genitourinary;
- skin (stomatitis, mucositis, alopecia, allergy);
- neurological (peripheral and central); and
- pulmonary.

Search methods for identification of studies

Some of the methods for searching were not implemented, namely approaching major co-operative trials groups active in this area. Continuous outcome data were not reported in any of the trials so the following sections in the protocol which discussed the handling of the data of such outcomes were removed as they were unnecessary (dichotomous data was not meta-analysed so was removed in the data synthesis section).

Data extraction and management

We extracted data on outcomes as below:

- for continuous outcomes (e.g. quality of life), we will extract the final value and standard deviation of the outcome of interest and the number of women assessed at the endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean difference (if trials measured outcomes on different scales) between treatment arms and its standard error.

Measures of treatment effect

We used the following measures of the effect of treatment:

- for continuous outcomes, we will use the mean difference between treatment arms.

Data synthesis

If sufficient clinically similar trials were available, their results were pooled in meta-analyses.

- For any dichotomous outcomes, the RR will be calculated for each study and will then be pooled.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences will be pooled.

If any trials have multiple treatment groups, the 'shared' comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analysis according to:

- the type of hysterectomy undergone (simple versus radical);
- the type of radiotherapy used;
- the chemotherapeutic regimen used;
- the histopathological types of cervical cancer cases;
- whether the trial measured progression or disease-free survival. This was added after the protocol after going through the searches; it was likely to be important but in the end subgroup analysis by outcome definition was not possible.

Sensitivity analysis

If a sufficient number of trials are included in the review, we will conduct sensitivity analyses to examine the possible contribution of other clinical or methodological differences between the trials, specifically:

1. trials at low risk of bias versus those at high and unclear risk of bias;
2. trials that seem to differ from the others in their clinical criteria for defining survival.