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Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer.
Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD010401.
DOI: 10.1002/14651858.CD010401.pub2.

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[Intervention Review]

Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer

Siriwan Tangjitgamol[1], Kanyarat Katanyoo[2], Malinee Laopaiboon[3], Pisake Lumbiganon[4], Sumonmal Manusirivithaya[5], Busaba Supawattanabodee[5]

[1]Department of Obstetrics and Gynaecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. [2]Department of Radiology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. [3]Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand. [4]Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. [5]Research Facilitation Divison, Faculty of Medicine Vajira Hospital, Khon Kaen, Thailand

Contact address: Siriwan Tangjitgamol, Department of Obstetrics and Gynaecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, 681 Samsen Road, Dusit District, Bangkok, 10300, Thailand. siriwanonco@yahoo.com.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2019.

Citation: Tangjitgamol S, Katanyoo K, Laopaiboon M, Lumbiganon P, Manusirivithaya S, Supawattanabodee B. Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No.: CD010401. DOI: 10.1002/14651858.CD010401.pub2.

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ABSTRACT

Background

Current standard treatment for patients with cervical cancer who have locally advanced stage disease (International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IVA) is concurrent chemoradiation therapy (CCRT). However, less than two-thirds of patients in this group survive for longer than five years post treatment. Adjuvant chemotherapy (ACT) can be given in an attempt to improve survival by eradicating residual disease in the pelvis and treating occult disease outside the pelvic radiation field. However, inconsistency in trial design, inclusion criteria for participants, interventions and survival benefit has been noted among trials of ACT after CCRT for locally advanced cervical cancer (LACC).

Objectives

To evaluate the effect of adjuvant chemotherapy (ACT) after concurrent chemoradiation (CCRT) on survival of women with locally advanced cervical cancer compared with CCRT alone.

Search methods

We searched the Cochrane Gynaecological Review Group Trial Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and conference proceedings to March 2014. We handsearched citation lists of relevant studies.

Selection criteria

Randomised controlled trials (RCTs) comparing CCRT alone versus CCRT plus ACT were included. Patients were diagnosed with cervical cancer FIGO stage IIB to IVA with a histopathology of squamous cell carcinoma, adenosquamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma.

Data collection and analysis

Two review authors (ST, KK) selected relevant trials, extracted data, assessed risk of bias independently, compared results and resolved disagreements by discussion.

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Main results

We identified two RCTs involving 978 women with cervical cancer stage IIB to IVA. As the trials were significantly different clinically, we did not perform meta-analyses. One industry-funded trial involving 515 women compared CCRT (cisplatin) versus CCRT (cisplatin and gemcitabine) plus ACT (two additional cycles). This trial reported significant improvement in progression-free survival (PFS) and overall survival (OS) in women who were given CCRT plus ACT compared with those treated with CCRT alone: Three-year PFS was 74.4% versus 65.0% (hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.49 to 0.95, P value 0.027), and three-year OS was 80% versus 69% (HR 0.68, 95% CI 0.49 to 0.95, P value 0.022). However, as the CCRT chemotherapy differed between the two arms, we considered the findings to be at high risk of bias.

The second trial was a four-arm study from which we extracted data on 463 women in two study arms receiving CCRT (intravenous mitomycin C and oral 5-fluorouracil (5-FU)) or CCRT plus ACT (oral 5-FU for three cycles). The HR for OS in women who received ACT after CCRT compared with the HR for OS in those who were given CCRT alone was 1.309 (95% CI 0.795 to 2.157), and the HR for disease-free survival (DFS) was 1.125 (95% CI 0.799 to 1.586).

Haematological adverse events were more common in the ACT arms of both trials. Quality of life (QoL) was not reported in either trial.

Authors' conclusions

With limited data from only two trials, we found insufficient evidence to support the use of ACT after CCRT. Future large trials are required to demonstrate efficacy, toxicities and QoL.

PLAIN LANGUAGE SUMMARY

Can additional chemotherapy after initial treatment for locally advanced stage cervical cancer reduce recurrence and extend life?

The issue

Standard treatment for locally advanced stage cervical cancer (stage IIB to IVA) is 'concurrent chemoradiation' when anticancer drugs are given during the same treatment period as pelvic radiotherapy (radiation therapy to lower abdomen). However, the tumour may remain (residual cancer) or may come back (recurrent cancer) after this standard treatment. This review evaluated whether giving additional anticancer drugs (ACTs) after standard treatment could help women with locally advanced cervical cancer to live longer compared with standard treatment alone.

How we conducted the review

We searched the literature to March 2014 and identified two randomised controlled trials comparing standard treatment versus standard treatment plus ACT in women with locally advanced cervical cancer. Two review authors assessed these studies and collected data independently.

Findings

The two studies were very different; therefore we could not pool their data. One trial conducted internationally between 2002 and 2004, involving 515 women, found that cancer took longer to return in women receiving ACT (cisplatin and gemcitabine), and more women in the ACT group were alive after three years than in the standard treatment group (80% versus 69%). We considered the findings to be at high risk of bias in this trial, as women were given different drugs during standard treatment, and so the overall effect of the study treatment could not be attributed to the ACT alone. The other trial, which was conducted in several hospitals in Thailand between 1988 and 1994, involved 463 women. ACT (5-fluorouracil) did not improve the length of survival or the time taken for cancer to return in women in this trial. A trend towards increased side effects was reported in the ACT arms of both studies.

Conclusions

We found insufficient evidence to support giving additional anticancer drugs to women who have received standard treatment for locally advanced cervical cancer, as currently only limited data are available from two very different trials.

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BACKGROUND

Description of the condition

Worldwide, cervical cancer is the fourth most common cancer in women, with an estimated 528,000 new cases and 266,000 deaths in 2012 (Ferlay 2013). Most cervical cancer cases (84%, or 445,000 cases) and deaths (87%, or 230,000 cases) occurred in less developed regions (Ferlay 2013). In addition to a higher incidence of cervical cancer in less developed regions, patients in these areas have a higher proportion of locally advanced stages, including stage IIB to IVA of the International Federation of Gynecology and Obstetrics (FIGO) staging classification, or advanced stage IVB cancers (Moore 2010). This is due in part to lack of co-ordinated screening programmes and/or lack of access to radiotherapy, leading to poorer overall survival. Thus, seeking further means of improving treatment outcomes for advanced or locally advanced cervical cancer (LACC) is required.

Description of the intervention

Concurrent chemoradiation therapy (CCRT) is a type of treatment in which chemotherapy is given at the same time as radiation therapy. Chemotherapy serves as a radiosensitiser that enhances the activity of radiation, and as a direct cytotoxin to local tumour cells and subclinical distant metastases beyond the radiation area (Rose 2002). It is currently a standard treatment for patients with LACC. This combined treatment appeared to improve survival outcomes compared with radiation therapy alone (Green 2005), with overall survival rates ranging from 60% to 65% (Cochrane Meta-Analysis Collaboration 2008). However, local and distant failures (17% and 18%, respectively) of LACC after CCRT were still encountered (Eifel 2004). Interventions provided to improve treatment outcomes include chemotherapy administered before CCRT (neoadjuvant chemotherapy) (McCormack 2013 (a); McCormack 2013 (b); Singh 2013) and additional chemotherapy given after the standard treatment, which is referred to as 'consolidation chemotherapy' or 'adjuvant chemotherapy' (ACT) (Choi 2007; Dueñas-González 2011; Lorvidhaya 2003; Tang 2012; Vrdoljak 2005; Vrdoljak 2006; Zhang 2010).

How the intervention might work

The objective of adjuvant chemotherapy after completion of radiation therapy, or CCRT, is to eradicate tumour cells outside of the radiation field. The role of ACT has been explored in several studies or trials involving LACC (Choi 2007; Choi 2010; Domingo 2009; Dueñas-González 2011; Lorvidhaya 2003; Tang 2012; Vrdoljak 2006; Wong 1999; Zhang 2010). All single-arm phase II studies (Choi 2007; Domingo 2009; Vrdoljak 2006; Zhang 2010) that evaluated the role of ACT in LACC reported a higher response rate than those that evaluated the role of CCRT alone. Overall survival rates greater than 80% to 90% achieved with CCRT followed by ACT were higher than the 60% to 65% rates obtained with CCRT alone (Cochrane Meta-Analysis Collaboration 2008).

Why it is important to do this review

Concurrent chemoradiation therapy (CCRT) is the current standard treatment for locally advanced cervical cancer (LACC); however, it can yield only a 60% to 65% survival rate (Cochrane Meta-Analysis Collaboration 2008). Adjuvant chemotherapy after CCRT is therefore one possible way to extend the survival of patients with LACC because it may further reduce or eradicate any residual disease, including occult disease outside the pelvic radiation field. Although the survival benefit derived from ACT after CCRT has been demonstrated in some studies, evidence is limited. Furthermore, each study has specific characteristics vis-à-vis the population included and the different types of chemotherapy regimen given, especially between two study arms in the same trial. Without clear benefit of ACT after CCRT, no definitive recommendation or clinical practice guideline can be provided for its use. As chemotherapy can cause toxicities, potential survival advantages must outweigh these disadvantages, hence a systematic review to evaluate the efficacy and toxicity of this treatment option is warranted.

OBJECTIVES

To evaluate the effect of adjuvant chemotherapy (ACT) after concurrent chemoradiation (CCRT) on survival of women with locally advanced cervical cancer compared with CCRT alone.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women ≥ 18 years of age with a diagnosis of cervical cancer, FIGO stage IIB to IVA, and a histopathology of squamous cell carcinoma, adenosquamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma. All patients had concurrent chemoradiation (CCRT) before receiving adjuvant chemotherapy (ACT).

Types of interventions

- Intervention: adjuvant or additional chemotherapy (ACT) given after standard treatment of chemotherapy and radiation during the same period (CCRT).
- Comparator: standard treatment with CCRT, then no further treatment.

Types of outcome measures

Primary outcomes

- Overall survival, analysed from date of randomisation until death or the participant's last visit.
- Progression-free survival analysed from date of randomisation until appearance of a new lesion during treatment, or a greater than 20% or 25% increase in local tumour size by RECIST (Response Evaluation Criteria In Solid Tumors) (Eisenhauer 2009) or WHO (World Health Organization) (Miller 1981) criteria, respectively.

Secondary outcomes

- Response rates after completion of CCRT, and after ACT.
- Recurrence rate after treatment with CCRT, and after ACT.
- Quality of life, measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.
- Severe toxicities and adverse events in study arm versus control arm, classified according to CTCAE 2006.

Grades of toxicity were grouped as:

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

Search methods for identification of studies

We searched for papers without restriction of languages and arranged translation as necessary.

Electronic searches

We searched the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 1) (Appendix 1).
- MEDLINE to March 2014 (Appendix 2).
- EMBASE to March 2014 (Appendix 3).

We identified all relevant articles on PubMed using the 'related articles' feature and performed further searches for other published articles.

Searching other resources

Unpublished and grey literature

We searched the following for ongoing trials.

- *meta*Register of Controlled Trials (*m*RCT) (http://www.controlled-trials.com/mrct/).
- Physicians Data Query (http://www.cancer.gov/cancertopics/pdq/cancerdatabase).
- ClinicalTrials.gov (http://clinicaltrials.gov/).
- National Cancer Institute (http://www.cancer.gov/clinicaltrials).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/).

We identified ongoing trials with published information on study design and inclusion and exclusion criteria (Mileshkin 2010; Tangjitgamol 2014). We found that recruitment for both trials is ongoing.

We searched electronic databases such as Zetoc (http://zetoc.mimas.ac.uk/) and Ohio College Library Center (OCLC) WorldCat Dissertations and Theses (WorldCatDissertations) (http://www.oclc.org/support/documentation/firstsearch/databases/dbdetails/details/worldcatdissertations.htm) for conference proceedings and abstracts.

Handsearching

We handsearched the citation lists of included studies and key textbooks and contacted experts in the field to identify further reports of trials. We also handsearched the following sources for previous systematic reviews and reports of conferences.

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncologists).
- *International Journal of Gynecological Cancer* (Biannual Meeting of the International Gynecologic Cancer Society and Biannual Meeting of the European Society of Gynaecologic Oncology).
- *British Journal of Cancer.*
- British Cancer Research Meeting.
- Annual Meeting of European Society of Medical Oncology.
- Annual Meeting of the American Society of Clinical Oncology.

Data collection and analysis

Selection of studies

Two review authors (ST, KK) independently examined search results and obtained and excluded records that clearly did not meet our inclusion criteria. We obtained copies of the full text of potentially relevant references. The two review authors (ST, KK) independently assessed eligibility of the retrieved full-text articles. Disagreements were resolved by discussion between the two review authors and by consultation with a third review author (PL). Reasons for exclusion were documented.

Data extraction and management

Two review authors (ST, KK) extracted data independently using a data abstraction form specially designed for the review. The two review authors resolved differences by discussion or by appeal to a third review author (PL) when necessary. For included studies, the following data were extracted.

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population (total number enrolled; participant characteristics; participant age; co-morbidities; other baseline characteristics).
- Intervention details (CCRT—regimen, dosage, cycles of treatment; radiation therapy—radiation therapy technique (external pelvic radiation therapy, extended field radiation therapy, brachytherapy), radiation machine or instrument (cobalt, linear accelerator), type of brachytherapy (low-dose or high-dose rate), doses; ACT—regimen, dosage, cycles of treatment).
- Comparison (primary and secondary outcomes between the two arms).
- Risk of bias in the study (Assessment of risk of bias in included studies).
- Duration of follow-up.
- Outcomes (outcome definition and unit of measurement (if relevant); for adjusted estimates, we recorded variables adjusted for during analyses).
- Results (number of participants allocated to each intervention group, total number analysed for each outcome, missing participants).

Data on all participants in the groups to which they were originally randomly assigned (intention-to-treat) were extracted. We noted

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the time points at which outcomes were collected and reported. Results were extracted as follows.

- Time-to-event data (survival and disease progression): We estimated the log of hazard ratio using the methods of Parmar 1998.
- Dichotomous outcomes (e.g. adverse events or deaths): We extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, to estimate the risk ratio.
- Continuous outcomes (e.g. quality of life measures): No data were available.

Assessment of risk of bias in included studies

Risk of bias in included trials was assessed using the tool of The Cochrane Collaboration for assessing risk of bias (Higgins 2011; Appendix 4).

- Selection bias (random sequence generation and allocation concealment).
- Performance bias (not applicable because clinicians were aware of interventions).
- Detection bias (blinding of outcome assessment).
- Attrition bias (high rates of incomplete outcome data and trials with ≥ 20% missing data were assessed as having high risk of bias).
- Reporting bias (selective reporting of outcomes).

Two review authors (ST, KK) applied the risk of bias tool independently; differences were resolved by discussion or by appeal to the third and fifth review authors (PL, ML). We summarised results in both a risk of bias graph and a risk of bias summary. Results of meta-analyses were interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

We planned to pool the results of included studies in meta-analyses if adequate numbers of clinically similar studies were available. We would use the following measures of the effects of treatment.

- Dichotomous outcomes: Risk ratio (RR) and 95% confidence interval (CI) were calculated for each trial.
- Time-to-event data: Hazard ratio (HR) and 95% CI were calculated for each study.

Dealing with missing data

We did not impute missing outcome data.

Assessment of heterogeneity

We planned to assess heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage of inconsistency 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).

Assessment of reporting biases

We intended to examine funnel plots corresponding to meta-analyses of the primary outcome to assess the potential for small-study effects such as publication bias if a sufficient number of studies (i.e. more than 10) were identified.

Data synthesis

We intended that if sufficient clinically similar studies were available, we would conduct meta-analyses using the Cochrane Collaboration's statistical software (Review Manager 2012) using a fixed-effect model. If data were statistically or clinically heterogeneous, we planned to use the random-effects model with inverse variance weighting (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

To investigate heterogeneity of the primary outcomes, we planned to perform subgroup analyses with trials grouped by:

- type of chemotherapeutic regimen (platinum versus non–platinum-based);
- stage of disease (stage IIB versus stage III to IVA);
- radiation therapy technique (external pelvic radiation therapy, radiation machine (cobalt or linear accelerator), brachytherapy, extended field radiation therapy); and
- histopathology (squamous cell carcinoma versus others).

Factors such as age, stage, type of intervention, length of follow-up and risk of bias status in interpretation of any heterogeneity would be considered.

Sensitivity analysis

We would perform sensitivity analyses by excluding studies at high risk of bias.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

A MEDLINE search identified 598 studies. A similar search of EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Specialised Register revealed 941 studies, 263 studies and 253 studies, respectively. Reference lists were checked, and handsearching of journals and congress abstracts yielded five additional studies.

A total of 74 articles were selected from the first sift. After 18 duplicates and 39 other abstracts were removed, 17 possibly eligible studies were retrieved for more detailed analysis. We found eight RCTs (Chiara 1994; Dueñas-González 2011; Kantardzic 2004; Lorvidhaya 2003; Tang 2012; Vishnevskaia 1999; Wang 2010; Wong 1999). Two RCTs met the inclusion criteria and were included in this review (Dueñas-González 2011; Lorvidhaya 2003). One study (Dueñas-González 2011) subsequently reported a subgroup analysis to determine prognostic factors for participants (Dueñas-González 2012). Six trials were excluded for one or more of the following reasons: Neoadjuvant chemotherapy was given as well as adjuvant chemotherapy (Chiara 1994; Tang 2012; Vishnevskaia 1999); only radiation was used in either of the control arms (Kantardzic 2004; Vishnevskaia 1999; Wang 2010; Wong 1999) or in both arms (Chiara 1994).

The eight remaining non-randomised studies were excluded for the following reasons: only radiation provided or phase II studies

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without a comparative arm (Choi 2007; Domingo 2009; Kim 2012; Mahasittiwat 2011; McCaffrey 2011; Vrdoljak 2006); prospective matched case comparison without randomisation (Choi 2010); or a preliminary report of one study (Vrdoljak 2005). See QUOROM (Quality of Reporting of Meta-analyses) statement flow diagram (Figure 1).

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Figure 1. Study flow diagram.

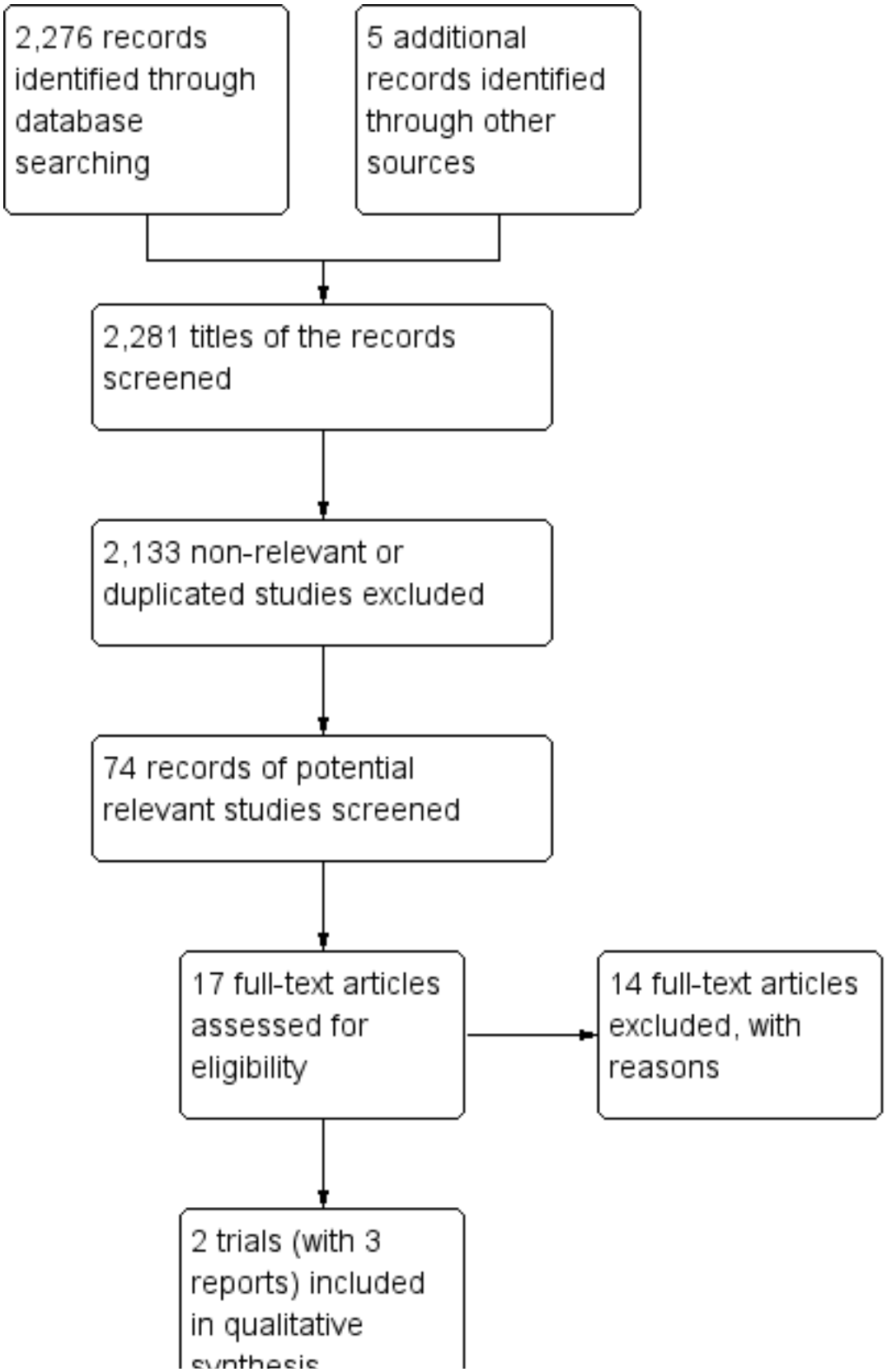

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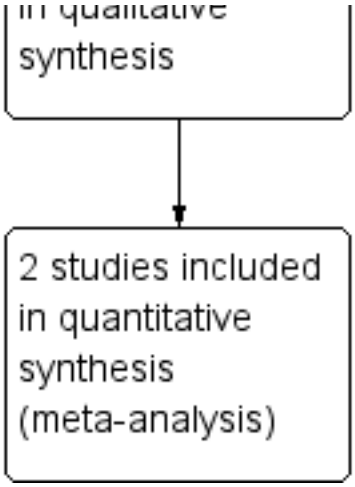
Figure 1. (Continued)



Included studies

We found three reports from two RCTs (Dueñas-González 2011; Lorvidhaya 2003). Dueñas-González 2011 described the results of their subgroup analysis in a subsequent report (Dueñas-González 2012), details of which are provided in the Characteristics of included studies.

Design and setting

Two RCTs were included. One (Lorvidhaya 2003) was undertaken in Thailand as a multi-centre trial between January 1988 and November 1994. The other (Dueñas-González 2011) was conducted in Argentina, Bosnia and Herzegovina, India, Mexico, Pakistan, Panama, Peru and Thailand between May 2002 and March 2004.

Participants

Two trials included a total of 978 participants with stage IIB to IVA cervical cancer.

Lorvidhaya 2003 included in the study 926 women with a performance status 2 or less, according to the Eastern Cooperative Oncology Group. The histopathology had to be squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma. For women with stage IIB disease, the central tumour had to be larger than 3 cm and/or had to involve more than half of the parametrium.

Dueñas-González 2011 included 515 women with cervical cancer who had Karnofsky performance score ≥ 70. Tumours of squamous cell carcinoma, adenocarcinoma, adeno/squamous carcinoma and poorly differentiated carcinoma were included. Women with enlarged para-aortic lymph node > 1 cm, proven by fine-needle aspiration to have metastatic cancer, were excluded.

Intervention

The Lordvithaya trial (Lorvidhaya 2003), which aimed mainly to study the efficacy of CCRT and the role of ACT, randomly assigned participants with LACC to four treatment arms. The standard arm received only radiation therapy (RT) (arm 1, n = 242), while the three study arms received RT with ACT (arm 2, n = 221) and CCRT without (arm 3, n = 233) or with ACT (arm 4, n = 230). Radiation was given with Co-60 or a linear accelerator machine. The external beam pelvic radiation (EBRT) dose was 40 to 50 Gy given to whole pelvis and pelvic lymph node. Intracavitary radiation was given according to the practice in each participating centre as four applications of high dose rate or one to two applications of medium dose rate. Chemotherapy given during radiation therapy consisted of intravenous mitomycin C plus oral 5-FU. The drug used in an adjuvant setting was oral 5-FU given for three cycles: drug taken for four weeks with a two-week rest between cycles. Only two arms (CCRT plus ACT versus CCRT alone) were relevant to our review question, therefore only data on the 233 participants given CCRT (arm 3) and the 230 participants receiving CCRT plus ACT (arm 4) were extracted for the review.

The Dueñas-González trial (Dueñas-González 2011) randomly assigned participants to two treatment arms. The study arm received CCRT followed by ACT (arm A, n = 259), while the control arm was given only CCRT (arm B, n = 256). Radiation equipment consisted of cobalt-60 (Co-60) or a linear accelerator. The EBRT dose was 50.4 Gy, and a low or intermediate dose rate of brachytherapy was given immediately after chemoradiation. Chemotherapy used concurrently with RT included six cycles of intravenous weekly cisplatin plus gemcitabine in the study arm and only cisplatin in the control arm. Two weeks after completion of brachytherapy, participants in the study arm received two additional cycles of tri-weekly cisplatin plus gemcitabine.

Compliance and follow-up

In Lorvidhaya 2003, 13 participants with small cell carcinoma (six in the CCRT group and seven in the CCRT plus ACT group; approximately 3% both) were excluded from the analysis. After a median follow-up of 89 months, 12 (5%) and 19 (8%) of the participants in both arms were lost to follow-up and received incomplete treatment. Reasons were not specified. These participants were censored as having failure of treatment. No information was provided on the compliance of participants taking oral chemotherapy.

In Dueñas-González 2011, the median follow-up was 46.9 months. The numbers of participants who discontinued treatment were 42 in arm A (CCRT plus ACT) and 11 in arm B (CCRT alone) (P value < 0.001), most commonly as the result of adverse effects. In the CCRT phase, the median number of gemcitabine and cisplatin cycles

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received in arm A was five (range one to six cycles), and the median number of cycles of cisplatin administered in arm B was six (range one to six cycles). In the ACT phase of arm A, 86.2% of participants received at least one cycle, and 76.5% received both cycles of ACT. Although median radiation doses were similar in the two treatment arms, the period of RT was longer in arm A: 49 days versus 45 days (P value < 0.001).

Outcomes

Lorvidhaya 2003 reported overall survival and progression-free survival (PFS). Dueñas-González 2011 reported overall survival, disease-free survival (DFS) and adverse events.

Excluded studies

Of 17 possibly eligible studies, 14 were excluded: six were RCTs, and eight were phase II prospective trials.

Six RCTS were excluded for one or more of the following reasons: neoadjuvant chemotherapy was also given aside from ACT (Chiara 1994; Tang 2012; Vishnevskaia 1999); only radiation was used in either the control arm (Kantardzic 2004; Vishnevskaia 1999; Wang 2010; Wong 1999) or both arms (Chiara 1994).

Of the eight remaining non-randomised studies, all were excluded for the following reasons: providing radiation only, phase II studies without a comparative arm (Choi 2007; Domingo 2009; Kim 2012; Mahasittiwat 2011; McCaffrey 2011; Vrdoljak 2006), prospective matched case comparison without randomisation (Choi 2010) or a preliminary report of one study (Vrdoljak 2005).

See Characteristics of excluded studies.

Risk of bias in included studies

Allocation

In Lorvidhaya 2003, randomisation was stratified according to each individual centre among the six centres joining in the trial. No information was provided regarding the method and the centre or site responsible for randomisation as well as allocation concealment. We assessed this as unclear risk.

In Dueñas-González 2011, participants were randomly assigned to CCRT plus ACT or CCRT alone at week 0 according to the Pocock and Simon algorithm by disease stage (IIB versus III to IVA), tumour diameter (< versus ≥ 5 cm), investigational centre, radiation equipment (cobalt-60 versus linear accelerator) and age (< versus ≥ 55 years). The random allocation sequence was generated by central telephone of the pharmaceutical company providing the research funding (Eli Lilly, Indianapolis, IN, USA). Allocation was concealed until interventions were assigned. This has been deemed to show low risk of bias.

Blinding

No blinding during treatment was reported in either trial (Dueñas-González 2011; Lorvidhaya 2003). This is believed to show high risk of bias.

Incomplete outcome data

After randomisation, Lorvidhaya 2003 identified six participants in the CCRT group and seven in the CCRT plus ACT group (approximately 3% both) who had small cell carcinoma and were excluded from the analysis. After a median follow-up of 89 months, 31 participants in both arms (12% or 5% in the CCRT group and 19% or 8% in the CCRT plus ACT group) were lost to follow-up and received incomplete treatment. Reasons were not specified. Participants were censored as having failure of treatment.

Among the 515 participants who were randomly assigned in Dueñas-González 2011, one who was allocated to CCRT was given both CCRT and adjuvant chemotherapy. A total of 53 participants (approximately 10%) discontinued treatment. After a median follow-up period of 46.9 months, a total of 56 participants (approximately 11%) were lost to follow-up by the end of the study. Numbers and reasons for loss to follow-up were similar in the two treatment arms.

We determined both trials as having low risk of bias.

Selective reporting

All outcomes in Lorvidhaya 2003 were reported according to the protocol. Nevertheless, no information was provided on the timing of adverse events.

Alhough the primary endpoint in Dueñas-González 2011 was changed from OS to PFS after completion of enrolment, all outcomes specified in the protocol were reported. Survival analyses were performed by an intention-to-treat approach (including the one participant who had a treatment cross-over), and toxicities were analysed for safety according to the actual treatment received.

We determined that both trials had low risk of bias.

Other potential sources of bias

No imbalance in baseline characteristics between the two arms was reported in either of the two studies (Dueñas-González 2011; Lorvidhaya 2003). However, an important difference in CCRT treatment between groups was found in one study (Dueñas-González 2011). The control arm received only single-agent chemotherapy (cisplatin), and the study arm was given two drugs (cisplatin and gemcitabine) during CCRT. We determined this to show high risk of bias, as it is likely to have had a significant effect on the outcomes.

Effects of interventions

We were unable to pool data because one of the included trials (Dueñas-González 2011) used different interventions during CCRT between the two arms (study arm received a combination of gemcitabine and cisplatin; control arm received cisplatin alone). In addition, different types of ACT were used in the two included studies; one trial used 5-fluorouracil (5-FU) (Lorvidhaya 2003), and the other (Dueñas-González 2011) used a combination of gemcitabine and cisplatin.

Survival

Lorvidhaya 2003 found no benefit for ACT over CCRT alone. Using the Parmar method to estimate hazard ratio, we found that the HR for OS was 1.309 (95% confidence interval (CI) 0.795 to 2.157) and for DFS was 1.125 (95% CI 0.799 to 1.586) among participants who received adjuvant chemotherapy (ACT).

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Dueñas-González 2011 showed significant improvement in PFS and OS among those who received CCRT plus ACT compared with those given CCRT alone (HR 0.68, 95% CI 0.49 to 0.95 for PFS, P value 0.027; HR 0.68, 95% CI 0.49 to 0.95 for OS, P value 0.022). The benefit of ACT was demonstrated in all subgroups. Subsequent analyses (Dueñas-González 2012) showed that benefit from ACT, PFS in particular, was greater in women with more advanced disease, larger tumour size and age younger than 55 years. The hazard ratio of PFS among participants with stage III to IVA disease who were given CCRT and ACT compared with those who received only CCRT was 0.59 (95% CI 0.37 to 0.97, P value 0.036).

Data on survival from both studies are summarised in Additional tables: Table 1.

No meta-analysis was performed. Data on progression-free survival for each individual trial are shown in Figure 2 and on overall survival in Figure 3.

Figure 2. Forest plot of comparison: 1 Survival, outcome: 1.1 Progression-free survival.

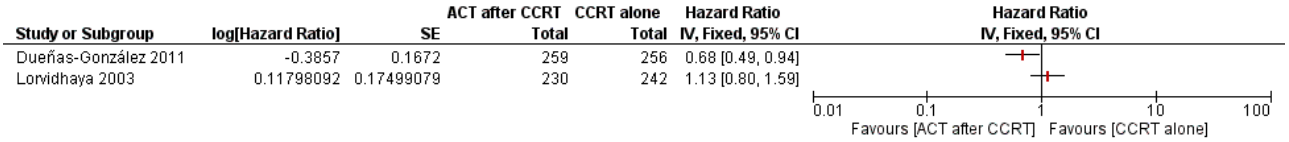
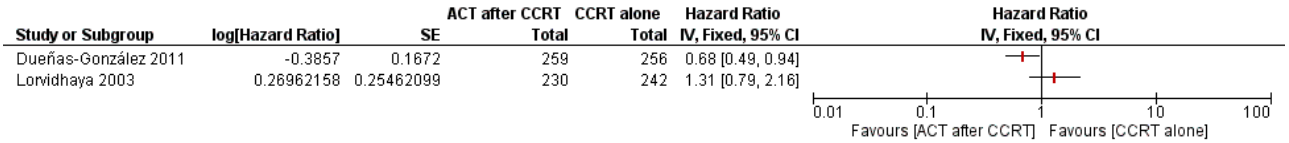


Figure 3. Forest plot of comparison: 1 Survival, outcome: 1.2 Overall survival.



Failure after treatment

Lorvidhaya 2003 did not demonstrate that the addition of chemotherapy could decrease total failure rate or loco-regional or distant failure after CCRT. Total failure rates were 29.0% among participants who received CCRT (arm 3), and 31.2% among those given CCRT plus ACT (arm 4). No significant differences in loco-regional or distant recurrence were noted among participants who were treated with CCRT alone or CCRT plus ACT: 14.3% versus 17.6% (P value not given) for local recurrence, and 17.7% versus 19.5% (P value not given) in arm 3 and arm 4, respectively.

Rates of local failure in Dueñas-González 2011 were not different (11.2% versus 16.4%, P value 0.097). However, distant failure rate was lower in the ACT group: 8.1% versus 16.4% (P value 0.005). Differences in chemotherapy during CCRT should be noted; it is not possible to determine whether differences were due to ACT given alone.

Data on recurrences from both studies are summarised in Additional tables: Table 2.

No meta-analysis was performed. Data on treatment failure at all sites for each individual trial are shown in Analysis 2.1 (Figure 4), local failure in Analysis 2.2 (Figure 5) and distant failure in Analysis 2.3 (Figure 6).

Figure 4. Forest plot of comparison: 2 Failure after treatment, outcome: 2.1 Total failure after treatment.

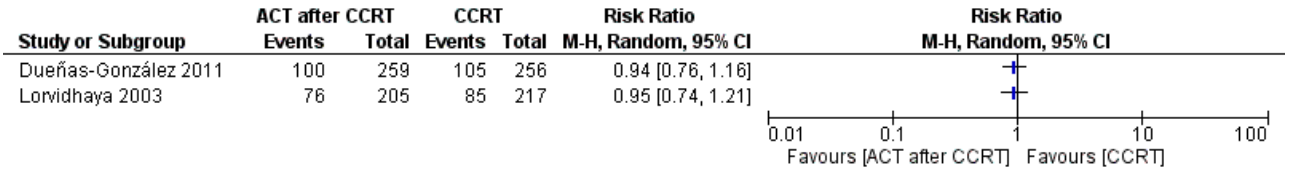


Figure 5. Forest plot of comparison: 2 Failure after treatment, outcome: 2.2 Local failure.

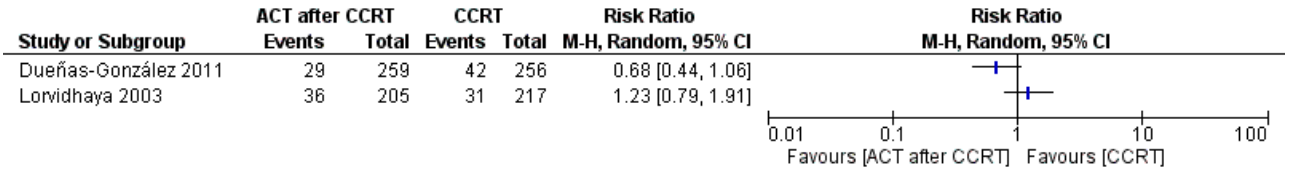


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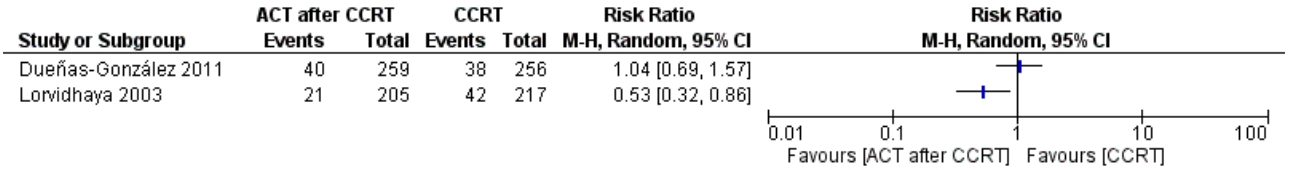
Figure 6. Forest plot of comparison: 2 Failure after treatment, outcome: 2.3 Distant failure.



Response rate

Only Dueñas-González 2011 reported response rates in the two treatment arms. These did not differ (95.8% in the CCRT plus ACT arm versus 93.4% in the CCRT arm, P value 0.249) (Additional tables: Table 3). No information on response rates was available for Lorvidhaya 2003.

Adverse events

Lorvidhaya 2003 reported that one participant in the CCRT arm died from persistent thrombocytopenia and leucopenia. Gastrointestinal symptoms were greater in the CCRT arm, but study authors stated that most women tolerated the treatment well (actual numbers not given). Haematological toxicities were not increased by ACT after CCRT. Anaemia of grade 2 was 24.2% among participants given CCRT plus ACT and 20.6% in those treated with only CCRT. Respective grade 3 and 4 leucopenia was 2.9% and 4.1%, and grade 3 and 4 thrombocytopenia was 1.5% and 2.3% (Additional tables: Table 4). No differences in late side effects were observed among studied arms (Additional tables: Table 5).

Dueñas-González 2011 reported detailed toxicities in both treatment arms. It should be noted that chemotherapy during CCRT differed when added to ACT. More women who had CCRT plus ACT were hospitalised: 30 women versus 11 who had CCRT only (P value 0.003). Women who received CCRT plus ACT also had a greater number of grade 3 or 4 overall toxicities (87.0% vs 46.0%, P value < 0.001). Rates of grade 3 and 4 toxicities in women who received CCRT and ACT versus CCRT alone were 71.9% versus 23.9% for haematological and 34.6% versus 10.6% for gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain/cramping, anorexia and proctitis), respectively. More women in the study arm had received one or more blood transfusions: 49.2% versus 27.5% (P value < 0.001). Overall, three deaths occurred in the CCRT plus ACT arm during or 30 days after treatment. Two deaths were attributed to the ACT. When study authors assessed toxicities from the preadjuvant and adjuvant treatments separately, they found that the CCRT plus ACT arm had greater toxicity than the CCRT alone arm during the preadjuvant phase. However, the incidence of new toxicity during ACT was generally low.

No meta-analysis was performed. Data on anaemia and thrombocytopenia from each individual study are shown in Analysis 3.1 (Figure 7) and Figure 8, respectively.

Figure 7. Forest plot of comparison: 3 Adverse events, outcome: 3.1 Anaemia.

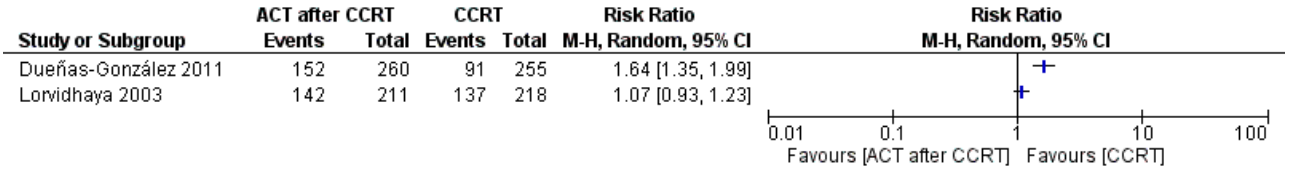
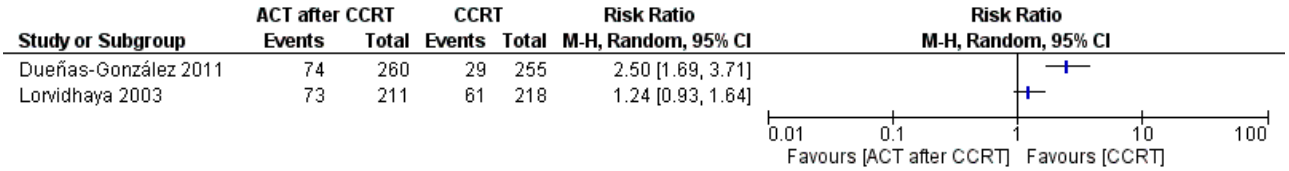


Figure 8. Forest plot of comparison: 3 Adverse events, outcome: 3.2 Thrombocytopenia.



Other outcomes

No information on QoL was reported in either study (Dueñas-González 2011; Lorvidhaya 2003).

DISCUSSION

Summary of main results

Results from the two studies were not amenable to meta-analysis for evaluation of the effect of adjuvant chemotherapy (ACT) after concurrent chemoradiation therapy (CCRT) in terms of survival and total failure rate after treatment.

Overall completeness and applicability of evidence

Two studies met the inclusion criteria (Dueñas-González 2011; Lorvidhaya 2003). We observed important differences between the two studies, which did not allow us to perform a meta-analysis to address all the objectives as planned.

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The studies were conducted in the 1990s and 2000s. This resulted in different trial designs as the computed tomography (CT) scanner was not used consistently as an investigative tool. Although CT scan has never been included in the International Federation of Gynecology and Obstetrics (FIGO) staging process, it is used routinely and impacts treatment decisions in clinical practice and modern research settings. Lorvidhaya 2003 conducted their study from 1988 to 1994, when CT scan of the abdomen was not routinely practiced. This may have led to heterogeneous participant characteristics or risk features. Some participants with locally advanced cervical cancer (LACC) may already have had distant disease beyond the pelvis, particularly the para-aortic lymph nodes. This could affect the incidence and detection of systemic failure, as standard physical examination and plain film chest imaging during follow-up may not detect subtle disease, especially in retroperitoneal nodes. This is likely to affect the progression-free period. Dueñas-González 2011, who conducted their study from 2002 to 2004, included CT scanning in all participants as an evaluation tool and excluded cases with para-aortic lymph node metastasis. This is likely to have resulted in a different participant cohort than was seen in the Lorvidhaya 2003 study, with reduced risk of failure after treatment. CT scanning was also used during surveillance and is likely to have detected recurrence earlier than standard evaluation. This tended to reduce the progression-free interval compared with clinical follow-up.

The second difference was the chemotherapy used in each study. Lorvidhaya 2003 used non-platinum drugs in their study, and Dueñas-González 2011 used platinum-based chemotherapy, which is the current standard of care.

Given these differences, it was believed inappropriate to perform a meta-analysis of data extracted from the two studies.

Quality of the evidence

Evidence from our review neither supports nor refutes the use of adjuvant chemotherapy to improve survival outcomes or to decrease failure after treatment. Some issues, which were observed in each trial as detailed below, were considered 'flaws' that prevented a definitive conclusion.

Oral adjuvant chemotherapy was used in Lorvidhaya 2003 (oral 5-FU) post combination with mitomycin during CCRT. This study did not report measures used to ascertain participant compliance. This might be reflected by similar rates of toxicity among participants who received or did not receive ACT after CCRT. These factors may have decreased the potential activity of ACT. Dueñas-González 2011 described an imbalance in chemotherapy concurrent with radiation therapy between the two study arms. Single-agent cisplatin was given to participants in the control arm, whereas cisplatin and gemcitabine were given to participants in the study arm. The combined drug was also given as ACT in the study arm. Hence, it is not possible to attribute any survival advantage in the study arm to ACT alone, as this may be due to the effects of more chemotherapy during CCRT rather than to the effects of ACT.

The other issue was the means of tumour assessment. All participants in Lorvidhaya 2003 underwent only chest x-ray and intravenous pyelography, as allowed by the FIGO staging system. Computed tomography scan was not required. This is likely to have contributed to heterogeneous participant characteristics compared with those in Dueñas-González 2011, because some women may already have had systemic spread of disease before treatment. All women in Dueñas-González 2011 underwent whole abdominal CT scanning as part of the baseline evaluation and post-treatment follow-up. This was done to assess the para-aortic lymph nodes, and women with confirmed nodal involvement (confirmed by fine-needle aspiration) were excluded. This is likely to have decreased any bias due to imbalance between the two arms, as only participants without proven preexisting systemic spread were included.

Regarding the other outcomes, numbers of local and systemic failures and limited aspects of toxicity (anaemia and thrombocytopenia) were consistently reported in both studies (Dueñas-González 2011; Lorvidhaya 2003). However, we determined that the results were inconclusive because substantial heterogeneity was observed in the analyses.

The last observation was the duration of follow-up in both studies, which was relatively short, so outcomes from long-term follow-up are necessary.

Potential biases in the review process

The authors of this review, with support from the Cochrane Gynaecological Cancer Group, performed a comprehensive search. All studies were sifted and data were extracted by two review authors independently. Only RCTs were included in this review, as they provide the best available evidence. RCTs conducted when CCRT was not used as standard treatment for LACC with only radiation therapy used in the control arm (Kantardzic 2004; Vishnevskaia 1999; Wang 2010; Wong 1999) or in both arms (Chiara 1994) were excluded because radiation alone at present is considered suboptimal standard treatment for patients with LACC. Data from the study arms of these studies (Kantardzic 2004; Vishnevskaia 1999; Wang 2010; Wong 1999) or from both arms (Chiara 1994), using CCRT plus ACT, were not reported. Randomised controlled trials using other treatment (e.g. neoadjuvant chemotherapy) in addition to CCRT and ACT were also excluded because this treatment approach may obviate the effects of ACT. No other potential biases were noted in the review process.

The review authors' judgements about each risk of bias item for each included study are shown in Figure 9 and Figure 10.

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Figure 9. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

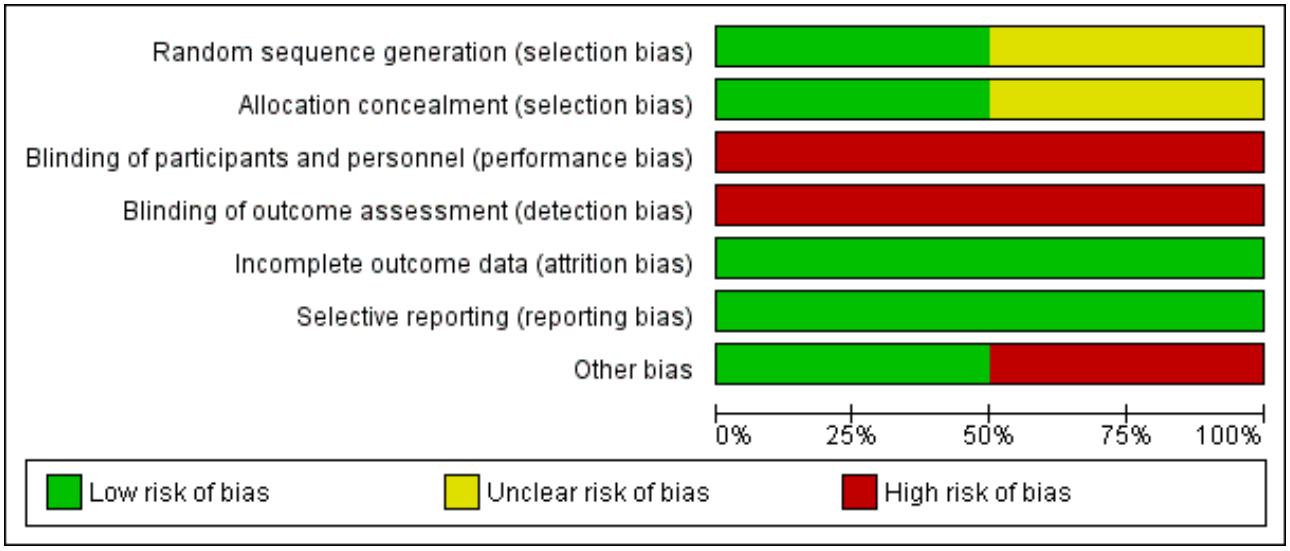

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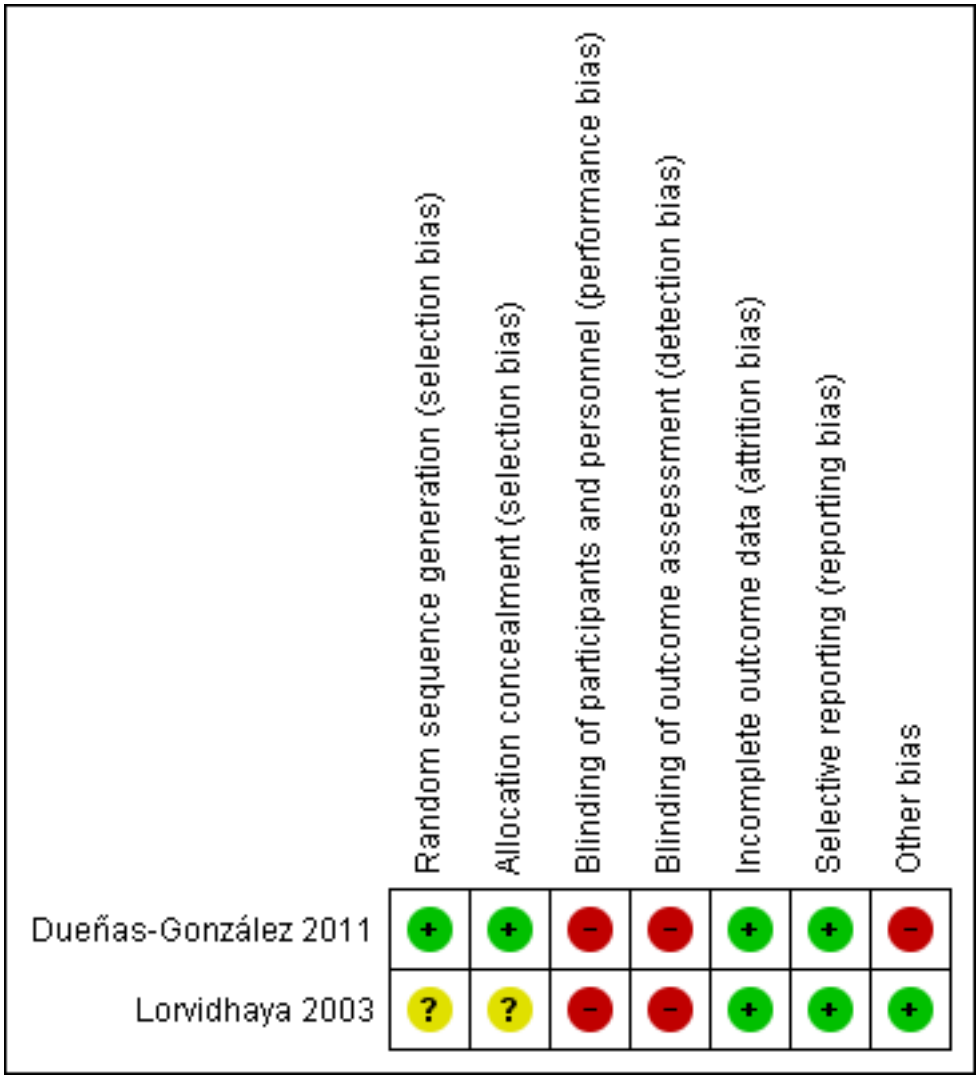
Figure 10. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Agreements and disagreements with other studies or reviews

One of the authors of this review performed a narrative review (Tangjitgamol 2011) on this topic, including three prospective single-arm studies (Choi 2007; Vrdoljak 2006; Zhang 2010), one matched-case comparison (Choi 2010) and four RCTs (Dueñas-González 2011; Kantardzic 2004; Lorvidhaya 2003; Wong 1999). Most of these studies were excluded from our review for reasons stated in the section on Characteristics of excluded studies.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence is insufficient to support the use of ACT after standard CCRT outside of clinical trials.

Implications for research

Along with standard CCRT, alternative or additional treatments are required for patients with LACC to improve survival outcomes. Very few trials have explored this topic, so additional research, focused on the role of adjuvant chemotherapy after standard concurrent chemoradiation, is required. Future studies should aim to ensure balance in treatments given before ACT and to exclude participants with evidence of distant disease by using appropriate imaging modalities (CT scan, positron emission tomography (PET) CT, etc).

ACKNOWLEDGEMENTS

We thank Jo Morrison for providing clinical advice; Jane Hayes for designing the search strategy; Gail Quinn, Andrew Bryant, Tess Lawrie and Clare Jess for contributing to the editorial process and Janice Hamman for assisting with English language presentation.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group.

The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the NIHR, the National Health Service (NHS) or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Dueñas-González 2011

Methods	Multi-centre randomised international controlled trial in 8 countries: Argentina, Bosnia and Herzegovina, India, Mexico, Pakistan, Panama, Peru and Thailand. Stratified randomisation was done by using the Pocock and Simon algorithm according to disease stage (IIB versus III to IVA), tumour diameter (< versus ≥ 5 cm), investigational centre, radiation equipment (cobalt-60 versus linear accelerator) and participant age (< versus ≥ 55 years)
Participants	515 eligible participants 18 to 70 years of age who had: • cervical cancer stage IIB to IVA • Karnofsky performance score ≥ 70 • tumours of squamous cell carcinoma, adenocarcinoma, adeno/squamous carcinoma and poorly differentiated carcinoma • no enlarged para-aortic lymph node > 1 cm that was proven on fine-needle enlargement to show metastatic cancer • normal complete blood count and renal function
Interventions	Arm A—CCRT plus ACT: 259 participants with mean age of 45 years • Cisplatin 40 mg/m^2 by IV infusion over 60 minutes, followed immediately by gemcitabine 125 mg/m^2 administered by IV infusion once weekly for 6 weeks as concurrent chemotherapy with radiation. Adjuvant chemotherapy given 2 weeks after brachytherapy was cisplatin 50 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1 and 8 for 2 consecutive 21-day cycles Arm B—CCRT alone: 256 participants with mean age of 46 years • Single-agent cisplatin 40 mg/m^2 by IV infusion once weekly for 6 weeks as concurrent chemotherapy with radiation
Outcomes	Primary endpoint: progression-free survival (PFS) at 3 years Secondary efficacy measures: overall survival (OS), time to progressive disease (TtPD), TRR, local failure rate (LFR), clinical adverse events (AEs)
Notes	All participants had whole abdominal CT scan as part of baseline evaluation and post-treatment follow-up. This was used to assess the para-aortic lymph node and was to be excluded in the presence of metastasis confirmed by FNA

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Dueñas-González 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation was generated by central telephone of the pharmaceutical company providing research funding (Eli Lilly, Indianapolis, IN, USA)
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned using the Pocock and Simon algorithm according to disease stage (IIB versus III to IVA), tumour diameter (< versus ≥ 5 cm), investigational centre, radiation equipment (cobalt-60 versus linear accelerator) and participant age (< versus ≥55 years) Allocation was concealed until interventions were assigned
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was performed during treatment because of the nature of the intervention. No information was provided on the blinding process during follow-up or surveillance
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were objective findings and were clearly defined in the trial but were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	After a median follow-up period of 46.9 months, a total of 56 participants (approximately 11%) were lost to follow-up by the end of the study. Reasons for loss to follow-up were similar in the 2 treatment arms
Selective reporting (reporting bias)	Low risk	Although the primary endpoint was changed from OS to PFS after completion of enrolment, all outcomes specified in the protocol were reported
Other bias	High risk	No imbalance between baseline characteristics was observed in the 2 arms. However, chemotherapy schedules in the CCRT phase are also different, and this is likely to have had a major bearing on study results

Lorvidhaya 2003

Methods	Multi-centre randomised controlled trial
Participants	926 eligible participants younger than 65 years of age who had: • cervical cancer with stage IIB, III, IVA (particularly for stage IIB, the central tumour must be larger than 3 cm and/or must have involved more than half of the parametrium) • squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma histopathology • performance status < or = to 2 according to the Eastern Cooperative Oncology Group • normal complete blood count and renal function
Interventions	4 arms of treatment: arm 1—RT only; arm 2—RT plus ACT; arm 3—CCRT; arm 4—CCRT plus ACT Note: • Only data from arm 3 (233 participants with mean age of 48 years) and arm 4 data (230 participants with mean age of 50 years) were extracted and used in this review • Chemotherapy given concurrently with RT (arm 3 and arm 4) consisted of mitomycin C 10 mg/m^2 IV days 1 and 29 plus oral 5-FU 300 mg/d on days 1 to 14 and 29 to 42 in the first 673 participants, then 5 days per week during radiation in subsequent participants

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Lorvidhaya 2003 *(Continued)*

	• 3. Adjuvant chemotherapy given (arm 2 and arm 4) was oral 5-FU 200 mg/d for 3 courses (given 4 weeks with a 2-week rest every 6 weeks)
Outcomes	Overall survival and progression-free survival
Notes	All participants had only chest-x ray and intravenous pyelography, as allowed in the FIGO staging system. CT scan was not performed in all participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified according to each individual centre of the six participating centres. Method and the centre or site responsible for randomisation were not detailed
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding during treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were objective findings and were clearly defined in the trial but were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	• 13 participants with small cell carcinoma (6 in the CCRT group and 7 in the CCRT plus ACT group; approximately 3% both) were excluded from the analysis • After a median follow-up of 89 months, 12 (5%) and 19 (8%) of the participants in both arms were lost to follow-up and received incomplete treatment. Reasons were not specified. Participants were censored as having failure of treatment
Selective reporting (reporting bias)	Low risk	PFS and OS were reported according to the protocol
Other bias	Low risk	No imbalance in baseline characteristics between the 2 arms was noted

ACT: adjuvant chemotherapy.
AE: adverse event.
CCRT: concurrent chemoradiation therapy.
CT: computed tomography.
FIGO: International Federation of Gynecology and Obstetrics.
FNA: fine-needle aspiration.
LFR: local failure rate.
OS: overall survival.
PFS: progression-free survival.
RT: radiation therapy.
TtPD: time to progressive disease.

Characteristics of excluded studies [author-defined order]

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Study	Reason for exclusion
Chiara 1994	This trial randomly assigned 64 participants with stage IIB to III cervical cancer to receive RT alone as control arm or sequential chemotherapy (biweekly cisplatin) given 2 cycles before and 4 cycles after RT in the study arm. It was excluded because (1) In addition to ACT, the drug was given before RT as neoadjuvant chemotherapy in the study arm; and (2) standard treatment in both arms was only RT (not CCRT)
Choi 2007	This phase II study treated 30 participants with cervical carcinoma of FIGO stage IB2 to IVA with CCRT (cisplatin and 5-FU) followed by 3 more cycles of the same chemotherapy. It was excluded because it was a single-arm study without a comparative group
Choi 2010	This prospective study included 78 participants with stage IIB to IVA cervical cancer. The control arm received only CCRT (tri-weekly cisplatin and 5-FU or weekly cisplatin). The study arm received the same CCRT followed by chemotherapy (either 3 tri-weekly cisplatin and 5-FU or 6 weekly cisplatin). It was excluded because it was a matched-case comparison study without randomisation
Domingo 2009	This prospective study included 60 participants with stage IIB to IIIB cervical cancer who received CCRT (capecitabine) followed by ACT (same drug but increased dose) for 6 more cycles. It was excluded because it was a single-arm phase II study without a comparator group
Kantardzic 2004	This trial randomly assigned 80 participants with stage IIB to III cervical cancer to RT alone or CCRT (cisplatin and bleomycin) followed by additional cycles of the same chemotherapy. It was excluded because only RT was given in the control arm
Kim 2012	This prospective study evaluated the efficacy and toxicity of consolidation chemotherapy (paclitaxel and carboplatin) after CCRT in 35 participants with stage IB1 to IVA cervical cancer. It was excluded because (1) It was a phase II study without randomisation; (2) different stages and primary treatment were given to participants in each group (group 1 comprised 19 participants with stage IB1 to IIA cervical cancer who had risk factors identified from surgery and received adjuvant CCRT, and group 2 consisted of 18 participants with stage IIB to IVA cervical cancer who received CCRT); and (3) all participants with cervical cancer in both groups, who received 3 cycles of consolidation chemotherapy
Mahasittiwat 2011	This prospective study included 19 participants with cervical carcinoma of FIGO stage IIB and IIIB who received CCRT. Only 9 received 3 cycles of consolidation chemotherapy (cisplatin and ifosfamide). It was excluded because it was a phase II single-arm study without a comparator group
McCaffrey 2011	This phase II study evaluated the activity of a 4-drug regimen of chemotherapy (cisplatin, bleomycin, methotrexate and 5-FU) in 67 participants with cervical cancer stage IB to IIIB. It was excluded because (1) it was a phase II study without randomisation; (2) participants were selected to have different primary and adjuvant treatment according to their clinical features (one group (42 participants) received neoadjuvant chemotherapy before surgery and consolidated with RT; the other group (25 participants) had primary surgery followed by ACT (and optional radiation) if pathological risk factors were identified); and (3) The primary treatment in both groups was not CCRT
Tang 2012	This trial randomly assigned 880 participants with cervical cancer stage IIB to IVA of adenocarcinoma histology to received CCRT as the control arm or 1 cycle of neoadjuvant chemotherapy (paclitaxel and cisplatin) followed by CCRT (cisplatin or cisplatin and 5-FU) and 2 cycles of consolidation chemotherapy with the same drugs as the study arm. This study was excluded because neoadjuvant chemotherapy was given along with additional chemotherapy after CCRT
Vishnevskaia 1999	This trial randomly assigned 100 participants with locally advanced cervical carcinoma to the control arm to receive only RT or to the study arm to receive multi-modality treatment, including immunotherapy (epithalamin), neoadjuvant chemotherapy (cisplatin and 5-FU) and CCRT followed by ACT (multiple drugs). It was excluded because (1) the study arm received neoadjuvant chemotherapy along with CCRT and ACT; and (2) the control arm did not receive CCRT—only RT

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Study	Reason for exclusion
Vrdoljak 2006	This prospective study included 62 participants with stage IB2 to IVA cervical cancer who received CCRT (cisplatin and ifosfamide) followed by consolidation chemotherapy (same drug). It was excluded because it was a single-arm study without a comparator arm
Wang 2010	This trial randomly assigned 156 participants with stage IIa to IIIb cervical squamous cell carcinoma to receive RT alone or CCRT (weekly cisplatin) followed by 3 cycles of ACT (docetaxel and cisplatin). It was excluded because only RT was given in the control arm
Wong 1999	This trial randomly assigned 220 participants with bulky stage I, II and III cervical cancer to receive standard pelvic RT or CCRT (epirubicin) followed by 5 additional cycles of the same chemotherapy. It was excluded because only RT was given in the control arm
Zhang 2010	This prospective study included 34 participants with stage IIB to IIIB cervical cancer, who received CCRT (paclitaxel and nedaplatin) followed by 4 additional cycles of consolidation chemotherapy (same drug). It was excluded because it was a single-arm study without a comparator control arm
Vrdoljak 2005	This was a preliminary report of a single-arm prospective study by Vrdoljak et al, which described findings in 44 out of 62 total participants with stage IB2 to IVA cervical cancer, who received CCRT (cisplatin and ifosfamide) followed by consolidation chemotherapy (same drug)

5-FU: 5-Fluorouracil
ACT: adjuvant chemotherapy
CCRT: concurrent chemoradiation therapy
FIGO: International Federation of Gynecology and Obstetrics
RT: radiation therapy

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

Mileshkin 2010

Trial name or title	A phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for patients with locally advanced cervical cancer compared with chemoradiation alone: the outback trial
Methods	A randomised controlled multi-centre clinical trial (ANZGOG 0902/GOG-0274/RTOG 1174)
Participants	780 participants with locally advanced cervical cancer suitable for primary treatment with chemoradiation. Histologically confirmed diagnosis of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the cervix with stage IB1 and positive nodes, IB2, II, IIIB or IVA disease. Participants must have received no previous pelvic radiotherapy or chemotherapy for this tumour and must not have needed interstitial brachytherapy treatment at presentation
Interventions	Participants are randomly assigned to 2 groups. All participants receive cisplatin weekly for 6 weeks concurrent with pelvic radiation followed by observation in the control arm or an additional 4 cycles of chemotherapy (paclitaxel and carboplatin every 3 weeks) in the study arm
Outcomes	Progression-free survival, overall survival, adverse events, prognostic biomarkers
Starting date	2/22/2012
Contact information	outback@ctc.usyd.edu.au
Notes	

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Tangjitgamol 2014

Trial name or title	Randomised controlled trial comparing concurrent chemoradiation versus concurrent chemoradiation followed by adjuvant chemotherapy in patients with locally advanced cervical cancer
Methods	Randomised controlled multi-centre trial (TCTR 20140106001)
Participants	500 participants with locally advanced cervical cancer (FIGO stage IIB to IVA). Histologically confirmed diagnosis of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the cervix. Participants must have ECOG performance score of 0 to 2 and adequate bone marrow, liver and renal function. Participants with suspicious para-aortic lymph node metastasis, presence of adnexal mass or chronic illness (e.g.renal impairment, neuropathy, immunosuppressive disorders) will be excluded
Interventions	Participants are randomly assigned to 2 arms. After receiving concurrent pelvic radiation and cisplatin weekly for 6 weeks, the control arm will be observed, while the study arm will receive 3 cycles of paclitaxel and carboplatin every 4 weeks
Outcomes	Progression-free survival, overall survival, response rate, cost-utility analysis
Starting date	January 2014
Contact information	siriwanonco@yahoo.com
Notes	

ECOG: Eastern Cooperative Oncology Group.
FIGO: International Federation of Gynecology and Obstetrics.

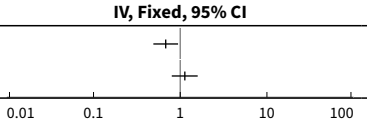
DATA AND ANALYSES

Comparison 1. Survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression-free survival	2		Hazard Ratio (Fixed, 95% CI)	Totals not selected
2 Overall survival	2		Hazard Ratio (Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Survival, Outcome 1 Progression-free survival.

Study or subgroup	ACT after CCRT N	CCRT alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Dueñas-González 2011	259	256	-0.4 (0.167)		0.68[0.49,0.94]
Lorvidhaya 2003	230	242	0.1 (0.175)		1.13[0.8,1.59]



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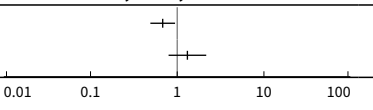
Analysis 1.2. Comparison 1 Survival, Outcome 2 Overall survival.

Study or subgroup	ACT after CCRT N	CCRT alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Dueñas-González 2011	259	256	-0.4 (0.167)		0.68[0.49,0.94]
Lorvidhaya 2003	230	242	0.3 (0.255)		1.31[0.79,2.16]

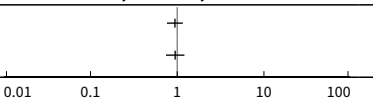


Comparison 2. Failure after treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure after treatment	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Local failure	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Distant failure	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

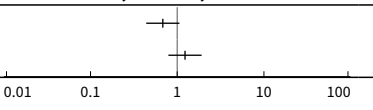
Analysis 2.1. Comparison 2 Failure after treatment, Outcome 1 Total failure after treatment.

Study or subgroup	ACT after CCRT n/N	CCRT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dueñas-González 2011	100/259	105/256		0.94[0.76,1.16]
Lorvidhaya 2003	76/205	85/217		0.95[0.74,1.21]



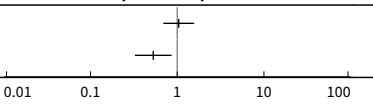
Analysis 2.2. Comparison 2 Failure after treatment, Outcome 2 Local failure.

Study or subgroup	ACT after CCRT n/N	CCRT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dueñas-González 2011	29/259	42/256		0.68[0.44,1.06]
Lorvidhaya 2003	36/205	31/217		1.23[0.79,1.91]



Analysis 2.3. Comparison 2 Failure after treatment, Outcome 3 Distant failure.

Study or subgroup	ACT after CCRT n/N	CCRT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dueñas-González 2011	40/259	38/256		1.04[0.69,1.57]
Lorvidhaya 2003	21/205	42/217		0.53[0.32,0.86]



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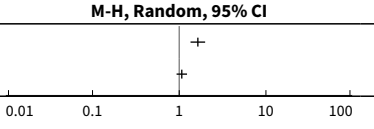
Comparison 3. Adverse events

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Anaemia	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Thrombocytopenia	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

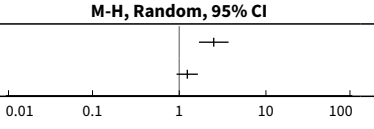
Analysis 3.1. Comparison 3 Adverse events, Outcome 1 Anaemia.

Study or subgroup	ACT after CCRT n/N	CCRT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dueñas-González 2011	152/260	91/255		1.64[1.35,1.99]
Lorvidhaya 2003	142/211	137/218		1.07[0.93,1.23]



Analysis 3.2. Comparison 3 Adverse events, Outcome 2 Thrombocytopenia.

Study or subgroup	ACT after CCRT n/N	CCRT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dueñas-González 2011	74/260	29/255		2.5[1.69,3.71]
Lorvidhaya 2003	73/211	61/218		1.24[0.93,1.64]



ADDITIONAL TABLES

Table 1. Survival outcome

Study	Lordvithaya	Dueñas-Gonzalez
N (CCRT versus CCRT/ACT)	233 versus 230	256 versus 259
FU	89 months	46.9 months
Outcomes (CCRT versus CCRT/ACT)		
1. OS		
· 3-year OS	85% versus 79% (estimated from graph), P value NS HR 1.309, 95% CI 0.795 to 2.157 (by Parmar method)	69% versus 78% (estimated from graph) HR 0.68, 95% CI 0.49 to 0.95, P value 0.0224
· 5-year OS	82.7% (79.0 to 86.4) versus 73.6 (67.1 to 80.1), P value NS	-

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Table 1. Survival outcome *(Continued)*

2. PFS		
· 3-year PFS	68% versus 63% (estimated from graph), P value NS HR 1.125, 95% CI 0.799 to 1.586 (by Parmar method)	65.0% (58.5 to 70.7) versus 74.4 % (68 to 79.8) HR 0.68, 95% CI 0.49 to 0.95), P value 0.0227
· 5-year PFS	64.5% (60.6 to 68.0) versus 59.7% (53.6 to 65.8), P value NS	-

Table 2. Recurrence

Study	Lordvithaya	Dueñas-Gonzalez
N (CCRT versus CCRT/ ACT)	233 versus 230	256 versus 259
· Local (with or without DR)	31 (14.3%) versus 36 (17.6%), P value NS	16.4% versus 11.2%, P value 0.097
· Distant (with or without LR)	38 (17.7%) versus 40 (19.5%), P value NS	16.4% versus 8.1%, P value 0.005
· Local and/ or distant	63 (29.0%) versus 64 (31.2%), P value NS	-

Table 3. Response rate

Study	Lordvithaya	Dueñas-Gonzalez
Response rate	NA	93.4 (89.6 to 96.1) in CCRT arm versus 95.8 (92.5 to 97.9) in CCRT + ACT arm, P value 0.249

Table 4. Acute adverse event

Adverse events/Study	Lordvithaya n (%)		Dueñas-Gonzalez n (%)	
	CCRT (N = 218)	CCRT + ACT (N = 211)	CCRT (N = 255)	CCRT + ACT (N = 260)
Acute adverse event (grade 1 to 2)				
1. Haematological				
• Leucopenia	110 (50.4)	139 (65.8)	NA	
• Anaemia	137 (62.8)	142 (67.3)	86 (33.8)	128 (49.3)
• Neutropenia	NA		62 (24.3)	80 (30.8)

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Table 4. Acute adverse event *(Continued)*

• Febrile neutropenia	NA		0	1 (0.4)
• Thrombocytopenia	56 (25.7)	70 (33.5)	26 (10.2)	58 (32.4)
• Haemorrhage	NA		NA	
2. Gastrointestinal				
• Nausea	NA		148 (58.0)	153 (58.8)
• Vomiting	NA		116 (45.5)	129 (49.6)
• Anorexia	NA		37 (14.5)	46 (17.7)
• Diarrhoea	NA		119 (46.7)	121 (46.5)
• Liver	NA		6 (1.6)	33 (12.6)
• Proctitis	NA		20 (7.9)	29 (11.2)
3. Genitourinary (increased Cr level)	NA		2 (0.8)	5 (1.9)
4. Skin	NA		40 (15.7)	45 (17.3)
5. Neurological	NA		NA	
6. Pulmonary	NA		NA	
Acute adverse event (grade 3 to 4)				
1. Haematological				
• Leucopenia	9 (4.1)	6 (2.9)	NA	
• Anaemia	0		5 (2.0)	24 (9.2)
• Neutropenia	NA		15 (5.9)	133 (51.2)
• Febrile neutropenia	NA		1 (0.4)	6 (2.3)
• Thrombocytopenia	5 (2.3)	3 (1.5)	3 (1.2)	16 (6.2)
• Haemorrhage	NA		NA	
2. Gastrointestinal				
• Nausea	NA		7 (2.7)	11 (4.2)
• Vomiting	NA		7 (2.8)	20 (7.7)
• Anorexia	NA		0	1 (0.4)
• Diarrhoea	NA		12 (4.7)	46 (17.7)
• Liver	NA		0	4 (1.6)

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Table 4. Acute adverse event *(Continued)*

• proctitis	NA	1 (0.4)	9 (3.5)
3. Genitourinary (increased Cr level)	NA	2 (0.8)	4 (1.5)
4. Skin	NA	27 (10.6)	29 (11.2)
5. Neurological	NA	NA	
6. Pulmonary	NA	NA	

Table 5. Late adverse event

Study	Lordvithaya n (%)	Dueñas-Gonzalez n (%)
Late adverse event (grade 3 to 4)		
1. Bowel	3.1% vs 5.8%	1 (0.5) vs 5 (2.3)
2. Bladder		1 (0.5) vs 3 (1.4)
3. Mucous membrane	NA	1 (0.5%) vs 1 (0.5)
4. Subcutaneous		0 vs 1 (0.5)

APPENDICES

Appendix 1. CENTRAL

#1 MeSH descriptor: [Uterine Cervical Neoplasms] this term only
#2 (cervi* near/5 (cancer* or neoplas* or carcinoma* or tumor* or tumour* or malignan*))
#3 #1 or #2
#4 Any MeSH descriptor with qualifier(s): [Radiotherapy - RT]
#5 MeSH descriptor: [Radiotherapy] explode all trees
#6 MeSH descriptor: [Chemoradiotherapy] explode all trees
#7 (radiotherap* or radiat* or irradiat* or chemoradi* or radiochemo*)
#8 #4 or #5 or #6 or 7
#9 Any MeSH descriptor with qualifier(s): [Drug therapy - DT]
#10 MeSH descriptor: [Antineoplastic Agents] explode all trees
#11 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] this term only
#12 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees
#13 chemo*
#14 #9 or #10 or #11 or #12 or #13
#15 #3 and #8 and #14

Appendix 2. MEDLINE search strategy

1. Uterine Cervical Neoplasms/
2. (cervi* adj5 (cancer* or neoplas* or carcinoma* or tumor* or tumour* or malignan*)).mp.
3. 1 or 2
4. radiotherapy.fs.
5. exp Radiotherapy/
6. exp Chemoradiotherapy/

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7. (radiotherap* or radiat* or irradiat* or chemoradi* or radiochemo*).mp.
8. 4 or 5 or 6 or 7
9. drug therapy.fs.
10. exp Antineoplastic Agents/
11. Antineoplastic Combined Chemotherapy Protocols/
12. Chemotherapy, Adjuvant/
13. chemo*.mp.
14. 9 or 10 or 11 or 12 or 13
15. 3 and 8 and 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized.ab.
19. placebo.ab.
20. clinical trials as topic.sh.
21. randomly.ab.
22. trial.ti.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 15 and 23
25. exp animals/ not humans.sh.
26. 24 not 25

key: mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier, pt=publication type, ab=abstract, ti=title, sh=subject heading, fs=floating subheading, exp=exploded term

Appendix 3. EMBASE

1. exp uterine cervix tumor/
2. (cervi* adj5 (cancer* or neoplas* or carcinoma* or tumor* or tumour* or malignan*)).mp.
3. 1 or 2
4. rt.fs.
5. exp radiotherapy/
6. exp chemoradiotherapy/
7. (radiotherap* or radiat* or irradiat* or chemoradi* or radiochemo*).mp.
8. 4 or 5 or 6 or 7
9. dt.fs.
10. exp antineoplastic agent/
11. exp chemotherapy/
12. chemo*.mp.
13. 9 or 10 or 11 or 12
14. 3 and 8 and 13
15. crossover procedure/
16. double-blind procedure/
17. randomized controlled trial/
18. single-blind procedure/
19. random*.mp.
20. factorial*.mp.
21. (crossover* or cross over* or cross-over*).mp.
22. placebo*.mp.
23. (double* adj blind*).mp.
24. (singl* adj blind*).mp.
25. assign*.mp.
26. allocat*.mp.
27. volunteer*.mp.
28. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 14 and 28
30. (exp animal/ or nonhuman/ or exp animal experiment/) not human/
31. 29 not 30

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

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Appendix 4. The Cochrane Collaboration tool for assessing risk of bias in included studies

Random sequence generation

- Low risk of bias: e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers.
- High risk of bias: e.g. participants assigned to treatments on basis of date of birth, clinic ID number or surname or no attempt to randomly assign participants.
- Unclear risk of bias: e.g. not reported, information not available.

Allocation concealment

- Low risk of bias: e.g. where the allocation sequence could not be foretold.
- High risk of bias: e.g. allocation sequence could be foretold by participants, investigators or treatment providers.
- Unclear risk of bias: e.g. not reported.

Blinding of participants and personnel (not applicable)

Blinding of outcomes assessors

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

Incomplete outcome data

We recorded the proportions of participants whose outcomes were not reported at the end of the study. We coded a satisfactory level of loss to follow-up for each outcome as follows.

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

Selective reporting of outcomes

- Low risk of bias: e.g. review reports all outcomes specified in the protocol.
- High risk of bias: e.g. it is suspected that outcomes have been selectively reported.
- Unclear risk of bias: e.g. it is unclear whether outcomes had been selectively reported.

Other bias

- Low risk of bias if no source of bias is suspected and the trial appears to be methodologically sound.
- High risk of bias if the trial is suspected to have an additional bias.
- Unclear risk of bias if it is uncertain whether an additional bias may have been present.

Adopted from Higgins 2011.

WHAT'S NEW

Date	Event	Description
6 March 2019	Amended	Most recent search date March 2014. The review will be updated once the ongoing studies have been published (NCT02036164 - estimated study completion date January 2019) (ACTRN12610000732088 - anticipated last data collection July 2022).

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CONTRIBUTIONS OF AUTHORS

Siriwan Tangjitgamol and Kanyarat Katanyoo developed the review, searched for and determined the relevance of trials for the review, assessed their methodological quality, collected and extracted data and wrote the review. Pisake Lumbiganon supervised the drafts, provided methodological advice throughout the review, arbitrated over disagreements and advised over the content and presentation of the review. Sumonmal Manusirivithaya developed the protocol and reviewed the drafts and the final manuscript. Malinee Laopaiboon and Busaba Supawattanabodee developed the protocol and ensured scientific purity.

DECLARATIONS OF INTEREST

The review authors and their colleagues are conducting an RCT entitled 'Randomized controlled trial comparing concurrent chemoradiation versus concurrent chemoradiation followed by adjuvant chemotherapy in locally advanced cervical cancer patients.'.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine Vajira Hospital, University of Bangkok Metropolis, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.
- Thai Cochrane Network, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Failure after treatment, which was not stated in the protocol, was included in the review and meta-analysis. We determined that two main reasons justified the change. First, adjuvant chemotherapy is generally expected to have a systemic effect in controlling distant failure, and evidence from the meta-analysis should be useful for clinical practice. Second, data on this outcome were completely reported in both trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [*therapeutic use]; Chemoradiotherapy [*methods] [mortality]; Chemotherapy, Adjuvant [adverse effects] [methods] [mortality]; Cisplatin [administration & dosage]; Deoxycytidine [administration & dosage] [analogs & derivatives]; Fluorouracil [administration & dosage]; Mitomycin [administration & dosage]; Neoplasm Staging; Randomized Controlled Trials as Topic; Uterine Cervical Neoplasms [mortality] [pathology] [*therapy]

MeSH check words

Female; Humans

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