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Chemotherapy for metastatic and recurrent cervical cancer (Review)

Scatchard K, Forrest JL, Flubacher M, Cornes P, Williams C

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[Intervention Review]

Chemotherapy for metastatic and recurrent cervical cancer

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ABSTRACT

Background

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. A woman's risk of developing cervical cancer by 65 years of age ranges from 0.69% in developed countries to 1.38% in developing countries. Although screening by Pap smear should mean early detection at a curable stage for most women, many still present with advanced or metastatic disease with a worse prognosis. The addition of platinum-based chemotherapy to radiotherapy has improved outcome compared to radiotherapy alone; however, 30% to 50% fail to respond to treatment or develop recurrent disease. There are no standard treatment options for these patients, although platinum-based chemotherapy is frequently used and trials are on-going.

Objectives

To compare different types and combinations of cytotoxic chemotherapy for the treatment of metastatic/recurrent cervical cancer.

Search methods

We searched the Cochrane Gynaecological Cancer Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1, 2012), MEDLINE (1950 to January 2012) and EMBASE (1980 to January 2012). The reference lists from these and those of review articles were also checked.

Selection criteria

All randomised controlled trials (RCTs) involving chemotherapy for metastatic/recurrent cervical cancer. Trials involving radiotherapy, chemoradiotherapy, intra-arterial chemotherapy, biological agents or immunomodulators were excluded.

Data collection and analysis

Three review authors independently reviewed trials for inclusion and data extraction and assessed risk of bias.

Main results

There were no data comparing best supportive care with chemotherapy. Cisplatin-based regimens are the most widely used and therefore we have concentrated on these trials. In terms of response rates some non-platinum regimens are equivalent but toxicity is higher. The most common cisplatin regimen was 50 mg/m^2 day 1 q21days. Higher doses had similar survivals. There was no direct comparison between single-agent cisplatin and carboplatin. Overall survival (OS) and progression-free survival (PFS) were not adequately reported and quality of life (QoL) outcomes were incompletely documented. Combination regimens were more toxic than single agents, but in the limited reported data this did not appear to adversely affect QoL.

No significant difference in response rate by site of recurrence was found, although there was a trend towards improved response when the main site of disease was beyond the previously irradiated pelvis.

Authors' conclusions

Combination cisplatin-based chemotherapy could be a viable option for patients of good performance status with recurrent/metastatic cervical cancer, but further trials that report adequate survival and QoL data are sought. Response rates and improvements in survival are low. Cisplatin-based combinations have significant toxicity. Outcomes are poor and novel cytotoxic/biological agents and optimal scheduling need further investigation. Future trials need to stratify for and perform planned subgroup analysis with respect to previous treatment and site of recurrence.

PLAIN LANGUAGE SUMMARY

Chemotherapy primarily aimed at improving length of life while maintaining quality of life for incurable cervical cancer

Cervical cancer often affects young women. Cancer that has come back after initial treatment (recurrent) or has already spread around the body at diagnosis (metastatic) is incurable so chemotherapy is aimed at improving length of life, while maintaining good quality of life. A literature search was conducted identifying 30 potential trials; four trials were excluded. The 26 clinical trials included in this review encompass a large range of different drugs, doses and combinations in a mixed group of patients over a long time period (1976 to 2011), making it difficult to compare treatment options. Although there are no trials directly comparing chemotherapy with symptomatic management alone, chemotherapy is widely used in this setting and assumed to be of benefit. Cisplatin and carboplatin chemotherapy were shown to shrink the cancer in 10% to 30% of patients and are widely used in current practice. Cisplatin chemotherapy when combined with other drugs has been shown to prolong survival by a few months compared with cisplatin alone, but with the cost of increased side effects. Other chemotherapy has been used, but has been found to be less effective or more toxic. Quality of life for patients on chemotherapy appears to be similar for cisplatin and cisplatin-based combinations. Nearly all patients in these studies were relatively fit and well prior to starting treatment, despite their cancer; these results may not be the same in patients who are not fit and well.

BACKGROUND

Description of the condition

Cervical carcinoma arises in the uterine cervix and 60% to 70% of cases are squamous cell carcinomas, approximately 25% to 30% are adenocarcinomas or adenosquamous carcinomas, with a very small number of rarer cancers, such as small cell tumours and neuroendocrine tumours (Jemal 2008; Meta-analysis Collaboration 2008).

Cervical cancer is the second most common cancer among women aged up to 65 years and is the most frequent cause of death from gynaecological cancers worldwide. A woman's risk of developing cervical cancer by 65 years of age ranges from 0.69% in developed countries to 1.38% in developing countries (GLOBOCAN 2008). In Europe, about 60% of women with cervical cancer are alive five years after diagnosis (EUROCARE-3). The stage of disease at diagnosis determines survival rates; lesions less than 4 cm in diameter and confined to the cervix (FIGO (International Federation of Gynecology and Obstetrics) Stage Ib1) at presentation have a five-year survival rate of 92%, while women with cancer spread beyond the true pelvis to adjacent organs (FIGO Stage IVa) have a five-year survival rate of only 17% (Jemal 2008; Meta-analysis Collaboration 2008).

The overwhelming risk factor for development of cervical cancer is the presence of human papilloma virus (HPV), particularly subtypes 16 and 18. Vaccines against HPV have become available and introduced in some countries. In the future it is hoped this will significantly reduce the incidence of cervical cancer. HPV causes the cervical epithelium to become increasingly abnormal (graded as cervical intra-epithelial neoplasia (CIN) grades I to III), this then becomes invasive in 30% to 70% of women over 10 to 12 years, although this process can be much faster in a small minority (< one year). Invasive cancer then spreads directly by invading adjacent structures and metastasising via regional lymph nodes and, less commonly, via the bloodstream to distant sites such as the lungs.

Description of the intervention

Early-stage cancer confined to the cervix, or with extension into upper vagina (Stage I to IIa), can be successfully treated by radical surgery (with or without neoadjuvant chemotherapy) or concomitant chemoradiation, giving five-year survival rates of 80% to 90% (Eifel 2001). A European Organisation for Research and Treatment of Cancer (EORTC) trial (EORTC 55994) of chemoradiotherapy versus neoadjuvant chemotherapy plus surgery is on-going. For more advanced cancer, Stages IIb to IVa the treatment of choice is chemoradiotherapy; as a Cochrane meta-analysis has shown that the addition of platinum-based chemotherapy significantly improves survival compared to radiotherapy alone (Green 2005). Combined chemoradiotherapy will cure 50% to 70% of patients with locally advanced carcinoma of the cervix (Meta-analysis Collaboration 2008; Willmott 2009) and can be used for local control of metastatic disease.

Palliative chemotherapy is used for the management of Stage IVb patients whose disease has spread to distant sites, or for patients with inoperable recurrent or persistent disease (de la Motte Rouge 2006; Pectasides 2008). A number of chemotherapeutic options have been used either as single agents or in combination including cisplatin, adriamycin, ifosfamide, paclitaxel, irinotecan, topotecan, vinorelbine and gemcitabine with responses in the range of 15% to 46% (Moore 2006; Tewari 2005).

How the intervention might work

The aim of chemotherapy is to slow cancer growth, improve survival with minimal toxicity so there is an improvement in quality of life (QoL).

Why it is important to do this review

There are no standard treatments for patients with persistent, recurrent or metastatic cervical cancer. In this group of patients, who are often young and otherwise fit and well, it is important to establish chemotherapy regimens that have the greatest chance of response with tolerable side effects and an improvement in QoL. In the era of chemoradiation as primary management for locally advanced cervical cancer the role of chemotherapy in this setting becomes even more important to establish.

OBJECTIVES

To investigate the effectiveness of single-agent and combination chemotherapy in the treatment of patients with metastatic or recurrent cervical cancer with regards to progression-free survival (PFS), overall survival (OS), adverse effects of treatment and QoL.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials (RCTs).

Types of participants

Adult women (aged 18 years or over) with metastatic (FIGO Stage IVb) or recurrent cervical carcinoma who are suitable for chemotherapeutic treatment.

Types of interventions

- Single-agent cytotoxic chemotherapy.
- Multi-agent cytotoxic chemotherapy.
- Best supportive care.

For the purposes of this review chemotherapy refers to any cytotoxic drug given intravenously or orally with the intent of producing tumour regression as defined by World Health Organization (WHO) criteria for assessing response (Miller 1981); thus biological and immunomodulators were excluded. Trials involving concomitant radiotherapy were excluded because this could complicate assessment of response to chemotherapy, which is the primary objective of the review, particularly as most trials involving radiotherapy compare radiotherapy with radiotherapy plus chemotherapy. Intra-arterial chemotherapy regimens were excluded as this was felt to be a local rather than systemic therapy and so not comparable. We included trials that used both platinum and non-platinum chemotherapy and planned to subgroup based on whether the chemotherapy was platinum or non-platinum based (see Subgroup analysis and investigation of heterogeneity). Best supportive care is not a clearly defined term, but is generally considered to include any interventions that palliate symptoms and optimise QoL, without treating the underlying cancer, such as pain relief or psychological support (www.WHO.int). Where

there is no standard treatment option for a particular disease new treatments are often compared with best supportive care (i.e. symptom control) alone.

Types of outcome measures

Primary outcomes

- Response rate (percentage of patients with evidence of reduction in tumour size following treatment, usually assessed by computerised tomography (CT) scan within one to three months).
- OS (length of time from completing treatment to death from whatever cause).

Secondary outcomes

- Time to progression (length of time from start of chemotherapy to evidence of cancer progression).
- QoL, measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.
- Toxicity, classified according to CTCAE 2006:
  - haematological (leukopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage);
  - gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis);
  - genitourinary;
  - skin (stomatitis, mucositis, alopecia, allergy);
  - neurological (peripheral and central);
  - pulmonary;
  - other.

Search methods for identification of studies

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

Electronic searches

See Cochrane Gynaecological Cancer Group methods used in reviews.
The following electronic databases were searched:

- the Cochrane Gynaecological Cancer Review Group's Trial Register
- the Cochrane Central Register of Controlled Trials (CENTRAL), Issue 1, 2012
- MEDLINE to January 2012
- EMBASE to January 2012

The MEDLINE, EMBASE and CENTRAL search strategies based on terms related to the review topic are presented in Appendix 1, Appendix 2 and Appendix 3, respectively.

All relevant articles found were identified on PubMed and using the 'related articles' feature, a further search was carried out for newly published articles.

Searching other resources

Unpublished and grey literature

Meta-Register, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials were searched for ongoing trials.

Reference lists and Correspondence

The citation lists of included studies were checked and experts in the field contacted to identify further reports of trials.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to the reference management database Endnote, duplicates were removed and the remaining references were examined by three review authors (KS, JF and MF) independently. Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers were assessed independently by three review authors (KS, JF and MF). Disagreements were resolved by discussion between the three review authors. Reasons for exclusion are documented. No blinding of review authors to article author or journal title occurred.

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). This included data on the following:

- author, year of publication and journal citation (including language);
- country;
- setting;
- inclusion and exclusion criteria;
- study design, methodology;
- patient characteristics (age, histology, grade, extent of disease, previous therapy, performance status, whether disease lies within an area previously treated with radiotherapy);
- cervical cancer details at diagnosis:
  - FIGO Stage;
  - histological cell type;
  - tumour grade;
- number of participants in each arm of the trial;
- number excluded from analysis;
- type of intervention (drug, dose, regimen, frequency, number of cycles);
- proportion of participants who received all/ part/none of the intended treatment;
- delays in treatment;
- risk of bias in study (see below);
- length of follow-up;

- outcomes: response rate, OS, time to progression, QoL and toxicity:
  - for each outcome: outcome definition (with diagnostic criteria if relevant);
  - unit of measurement (if relevant);
  - for scales: upper and lower limits, and whether high or low score is good;
  - results: number of participants allocated to each intervention group;
  - for each outcome of interest: sample size; missing participants;
  - the time points at which outcomes were collected and reported will be noted.

Data on outcomes were extracted as below:

- for time to event (OS and time to progression) data, we planned to extract the log of the hazard ratio [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. response rate, toxicity), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at end point, in order to estimate a risk ratio (RR);
- for continuous outcomes (e.g. QoL), we planned to extract the final value and standard deviation of the outcome of interest and the number of patients assessed at end point 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.

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

Data were abstracted independently by three review authors (KS, JF and MF) onto a data abstraction form specially designed for the review. Differences between review authors were resolved by discussion or arbitration of a third party (CW or PC).

Assessment of risk of bias in included studies

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

- selection bias:
  - random sequence generation;
  - allocation concealment;
- performance bias:
  - blinding of participants and personnel (patients and treatment providers);
- detection bias:
  - blinding of outcome assessment;
- attrition bias:
  - incomplete outcome data: we recorded the proportion 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:
    - low risk of bias, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
    - high risk of bias, if more than 20% of patients 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;
- reporting bias:
  - selective reporting of outcomes;
- other possible sources of bias.

The 'Risk of bias' tool was applied independently by three review authors (KS, JF and MF) and differences resolved by discussion or by appeal to a third review author (CW or PC). Results are presented in a 'Risk of bias' summary graph. Results of meta-analyses were interpreted with consideration of the findings with respect to risk of bias.

Measures of treatment effect

We used the following measures of the effect of treatment:

- for time to event data, we planned to use the HR;
- for dichotomous outcomes, we used the RR;
- for continuous outcomes, we planned to use the mean difference between treatment arms.

Dealing with missing data

We did not impute missing outcome data for the primary outcome.

Assessment of heterogeneity

Heterogeneity between trials was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that cannot 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 this were investigated and reported.

Assessment of reporting biases

There was an insufficient number of included trials to assess the potential for small study effects such as publication bias adequately.

Data synthesis

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

- For time-to-event data, HRs would have been pooled using the generic inverse variance facility of RevMan 5 (RevMan 2011).
- For any dichotomous outcomes, the RR was calculated for each trial and these were then pooled.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up would have been pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences would have been pooled.

Random-effects models with inverse variance weighting was used for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

We included trials that used both platinum and non-platinum chemotherapy and planned subgroup analyses, grouping the trials based on whether the chemotherapy was platinum or non-platinum based.

Sensitivity analysis

We planned to perform sensitivity analyses excluding trials at high risk of bias

RESULTS

Description of studies

Results of the search

Five hundred and sixty eight references were identified by searching the electronic databases (excluding duplicates). Reviewing the abstracts for these references identified 30 potentially eligible studies. Three trials were excluded (Baker 1978; Greggi 2000; Kumar 1998) owing to non-randomisation of participants. One trial was excluded as it was a trial of differing Bryostatin-1 schedules showing no activity (Armstrong 2003). Thus 26 eligible trials were included in this review (see Characteristics of included studies), comprising of 3766 randomised participants of which 631 were excluded from analysis in the published papers or abstracts. Thirteen trials were sufficiently similar and were included in meta-analyses. No unpublished data from completed trials were identified.

Included studies

The RCTs included in this review dated from the 1970s to the present day with the number of patients ranging from five to 581. The trials included patients with locally recurrent, persistent or metastatic disease. Most of the patients had previously received radiotherapy to the primary site; however, since 1999 chemoradiotherapy has been the gold standard treatment for locally advanced disease and so patients included in more recent trials were likely to have previously received concurrent chemotherapy (generally platinum-based) with radiotherapy.

The trials used a wide variety of designs and chemotherapy schedules. Five trials compared single-agent platinum with a platinum-containing combination (Alberts 1987; Cadron 2005; Long 2005; Moore 2004; Omura 1997) generally cisplatin, four trials compared single-agent platinum with different formulations or doses (Bonomi 1985; Lira-Puerto 1991; McGuire 1989; Thigpen 1989), two trials compared single-agent platinum with a non-platinum (Long 2006; Pfeiffer 1998), 10 trials compared a variety of non-platinum-containing regimens (Bond 1976; Freedman 1980; Greenberg 1977; Malkasian 1981; Moseley 1976; Omura 1978; Omura 1981; Palo 1976; Wallace 1978; Weiss 1992), four trials compared differing platinum combinations (Bloss 2002; Edmonson 1988; Monk 2008; Mountzios 2009) and the remaining trial compared non-platinum single-agent with platinum-containing combination (Bezwoda 1986).

Outcomes were incompletely reported, with only response rate and some adverse event components being reported to an adequate level to include in meta-analyses. Time to event data were poorly reported with most trials presenting median and quartile statistics. Median survival in all trials ranged from four months to 17 months. The intention was to compare survival data and time to progression data by comparing HRs, but these were only reported in two studies. Where data were not reported, we had hoped to be able to calculate them using the method described by Parmar 1998, by extracting the log rank P value, number of events and the number of subjects in the treatment and control groups; however, insufficient trial data (mean survival, probabilities or individual patient data) had been reported for this. Michiels 2005 showed that median survival times are not reasonable surrogate measures for meta-analysis of survival. Eighteen of the 26 trials did not perform intention-to-treat analyses.

It had been anticipated that the majority of trials would be reporting toxicity with reference to Common Toxicity Criteria version 3.0 (CTCv3.0); however, this only became available in 2003 (replacing version 2.0, which ran from 1998 to 2003) and the majority of included trials (18/26) were published prior to 2003. Of these pre-1998 studies eight made no attempt to grade toxicity (Bezwoda 1986; Bond 1976; Edmonson 1988; Freedman 1980; Greenberg 1977; Malkasian 1981; Moseley 1976; Omura 1978), two used an unspecified grading system (Palo 1976; Wallace 1978), and remainder used Eastern Cooperative Oncology Group (ECOG) (Lira-Puerto 1991), Southwest Oncology Group (SWOG) (Alberts 1987; Weiss 1992) and Gynecologic Oncology Group (GOG) (Bonomi 1985; McGuire 1989; Omura 1981; Omura 1997; Thigpen 1989). None of the included trials published after 2003 (8/23) used CTCv3.0 and only two (Long 2005; Monk 2008) used CTCv2.0. The remainder using WHO (Mountzios 2009; Pfeiffer 1998), SWOG (Weiss 1992) or GOG (Bloss 2002; Moore 2004) scales. This wide variety made it very difficult to compare toxicities between regimens despite an attempt to convert all the differing grading scales into the CTCv2.0 equivalent.

Excluded studies

Four references were excluded, after obtaining the full text, for the following reasons:

- Baker 1978, Greggi 2000 and Kumar 1998 were excluded as they were not randomised trials;
- Armstrong 2003 was excluded as trial drugs were not cytotoxic agents.

For further details of all the excluded trials see the Characteristics of excluded studies.

Risk of bias in included studies

For risk of bias summary see Figure 1 and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

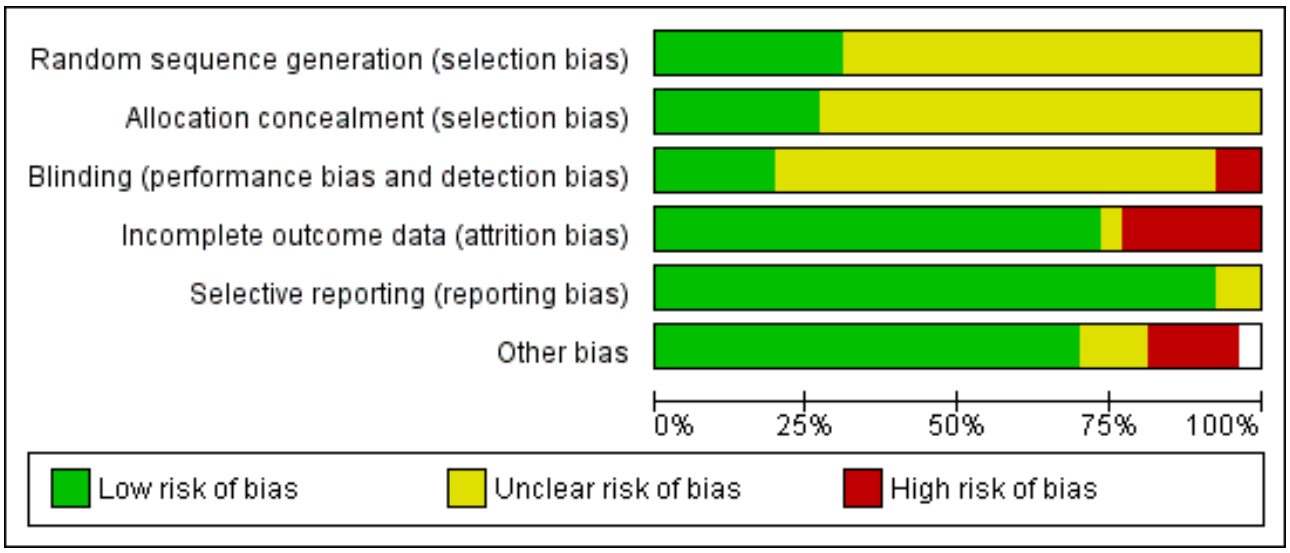


Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

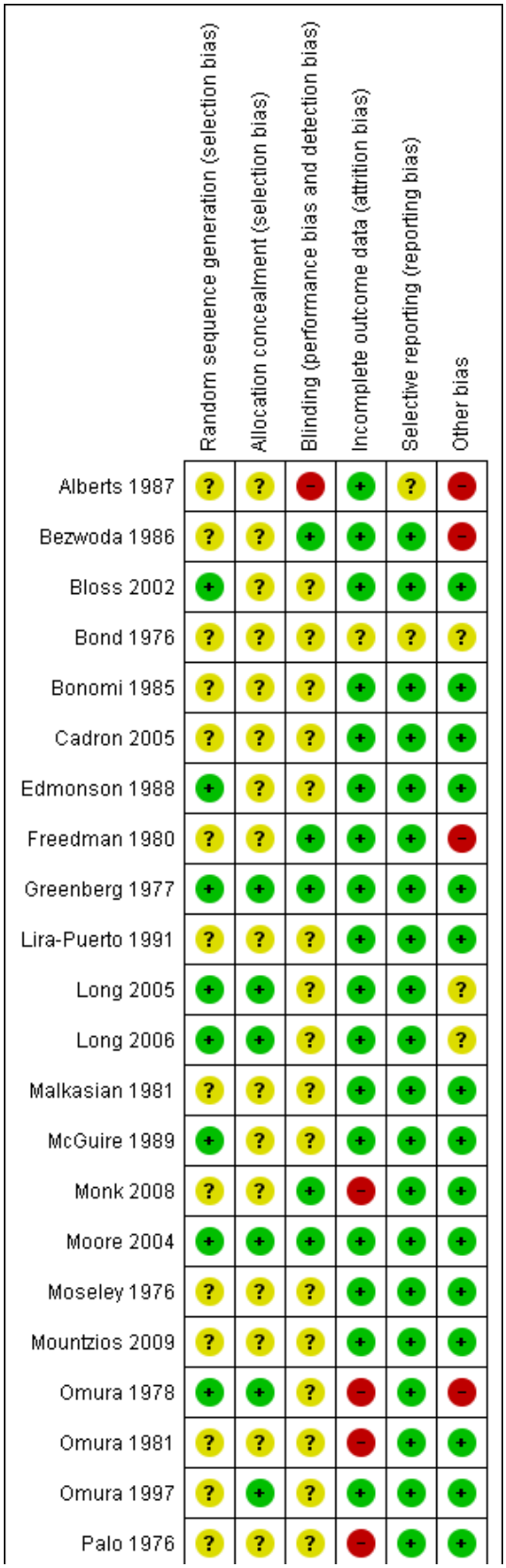
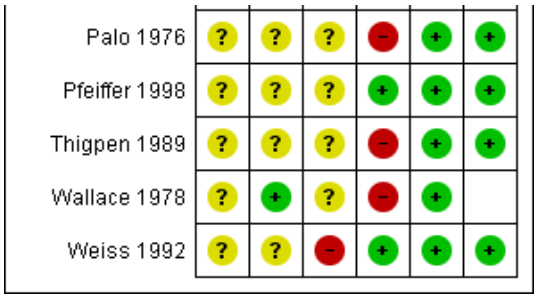


Figure 2. (Continued)



Allocation

All included trials were described as randomised or involved the randomised assignment of treatment; however, there was only sufficient detail given in 10 (Bloss 2002; Greenberg 1977; Long 2005; Long 2006; McGuire 1989; Moore 2004; Omura 1978; Omura 1997; Thigpen 1989; Wallace 1978) out of the 26 trials to confirm that the randomisation procedure was adequate. Of these trials only five also gave details of allocation concealment, which was by central randomisation (Greenberg 1977; Long 2005; Omura 1997) or closed envelope technique (Omura 1978; Wallace 1978).

Blinding

Adequacy of blinding could not be assessed in any of the trials. Many trials reported using physical examination as part of the assessment of response introducing potential for significant bias. Whether or not the outcome assessor was blinded was not reported in any of the trials.

Incomplete outcome data

Twelve trials excluded 5% or less of their participants (Alberts 1987; Bloss 2002; Edmonson 1988; Freedman 1980; Greenberg 1977; Lira-Puerto 1991; Long 2005; Long 2006; Malkasian 1981; Mountzios 2009; Omura 1997; Weiss 1992), eight trials excluded 6% to 19% (Bezwoda 1986; Cadron 2005; McGuire 1989; Monk 2008; Moore 2004; Omura 1981; Pfeiffer 1998; Thigpen 1989) and five trials excluded 20% to 49% (Bonomi 1985; Moseley 1976; Omura 1978; Palo 1976; Wallace 1978). In one trial (Bond 1976) the total number of participants was not given neither was it stated how many patients were excluded from the final analysis. Frequent reasons for exclusion were given as ineligibility, loss to follow-up, inadequate data, lack of easily assessable disease and missing data.

In the older trials particularly there was a large drop-out rate, such that in three trials nearly half the patients randomised were not evaluated (Bond 1976; Omura 1978; Wallace 1978). Patients were sometimes excluded because of a lack of measurable disease.

Selective reporting

All trials reported response rates but survival data reporting was inconsistent. Twenty-one of 26 trials reported OS with two further trials reporting median survival (Alberts 1987; Bond 1976), but were not reported in sufficient detail to allow inclusion in meta-analyses. Survival data were not reported in four trials (Moseley 1976; Omura 1981; Omura 1997; Weiss 1992). PFS was only reported in 11 trials (Bloss 2002; Bonomi 1985; Monk 2008; Moore 2004; Mountzios 2009; Omura 1981; Omura 1997; Palo 1976; Pfeiffer 1998; Thigpen 1989; Wallace 1978).

Where full survival data were not reported there was no justification for the choice of end points. Only two trials (Long 2005; Monk 2008) reported HRs and there was insufficient detail in the other trials to calculate using Parmars methods (Michiels 2005; Parmar 1998). This is discussed in more detail in the Results section.

Other potential sources of bias

A variety of first-line treatment was given prior to these trials with a historical bias. In the older trials (patients enrolled pre-1999) the majority of first-line treatment was radiotherapy whereas post-1999 most patients received primary chemoradiotherapy. In some trials (Bond 1976; Edmonson 1988; Palo 1976) cross-over was allowed between arms.

Effects of interventions

In the meta-analysis comparing various forms of chemotherapy, two trials (Bezwoda 1986; Greenberg 1977) assessing response rate and three trials (Alberts 1987; Omura 1997; Moore 2004) assessing toxicity had no responses in one of the arms, so we added 0.5 to these cells to allow calculation of an RR. This is the default zero-cell correction within RevMan (RevMan 2011), and biases the result of the meta-analysis towards no difference between the two types of chemotherapy being compared.

The methods of assessing response rates were variable, many of the older trials used clinical evaluation to a large extent with some radiological imaging (e.g. pelvic x-ray) while more modern trials focused on CT or magnetic resonance imaging (MRI). Criteria for determining response also vary; however, three (Long 2005; Moore 2004; Omura 1997) of the five trials included in the meta-analysis used the GOG definition based on the best response achieved at any point during treatment that had to be maintained for at least four weeks (complete response: disappearance of all lesions for at least four weeks; partial response: a greater than 50% reduction in the product of bi-dimensional measurement of each lesion for at least four weeks; progressive disease: a greater than 50% increase in the product of the bi-dimensional measurement of any lesion). One study (Alberts 1987) used SWOG criteria where the difference in size of lesions had to be 25% or greater to be progressive or partially responsive disease. Cadron 2005 used WHO criteria for determining response but gave no further details as to what this entailed. Response rates are early, easily measurable indicators often used as a surrogate for benefit but do not necessarily correlate with a survival advantage.

In Analysis 1.3, Analysis 1.4, Analysis 1.5, Analysis 1.6 and Analysis 1.7 complete and partial response were grouped together and were deemed 'response'.

Single-agent versus combination chemotherapy

Meta-analysis of 10 RCTs (Alberts 1987; Bezwoda 1986; Cadron 2005; Greenberg 1977; Long 2006; Malkasian 1981; Moore 2004; Omura 1981; Omura 1997; Wallace 1978), assessing 1438 participants, did not find any statistically significant difference in response rate between women who received single-agent chemotherapy and those who received combination therapy (RR 0.94; 95% CI 0.57 to 1.55). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than chance may represent substantial heterogeneity (I^2 = 67%). A wide variety of chemotherapy agents and doses were used across trials (see Table 1). Many of the trials were from an era when activity of agents was not known and so included inactive agents. The trials of Bezwoda 1986 and Greenberg 1977 were removed because of this in a sensitivity analysis, but the results were largely unchanged (RR 0.94; 95% CI 0.59 to 1.50; I^2 = 66%). In addition many of these older trials were of poor quality, where more stringent reporting guidelines were not introduced until after these trials were completed.

There were no data comparing best supportive care with chemotherapy. Bezwoda 1986 compared hydroxyurea with cisplatin methotrexate and found no response to hydroxyurea and a difference in OS of nine versus four months. Moseley 1976 compared different CCNU-based combinations again with no response (see Analysis 1.1; Analysis 1.2).

Cisplatin single-agent versus cisplatin combination chemotherapy

Meta-analysis of five RCTs (Alberts 1987; Cadron 2005; Long 2005; Moore 2004; Omura 1997), assessing 1114 participants, found that the proportion of women who responded to treatment was significantly lower in the group who received chemotherapy as a single agent than in the group who received combination chemotherapy (RR 0.60; 95% CI 0.44 to 0.81) (Table 2). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than sampling error (chance) was of little importance (I^2 = 25%) (Analysis 1.3).

Platinum versus non-platinum chemotherapy

Meta-analysis of three RCTs (Bezwoda 1986; Long 2005; Pfeiffer 1998), assessing 413 participants, did not find any statistically significant difference in response rate between women who received platinum-based chemotherapy and those who received non-platinum chemotherapy (RR 1.33; 95% CI 0.50 to 3.54). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than chance may represent moderate heterogeneity (I^2 = 52%) (Table 3). Exclusion of the Bezwoda 1986 trial data (which was generally of poor quality and showed no response at all to hydroxyurea) following a sensitivity analysis removed all of the heterogeneity (I^2 = 0%). It should be noted that the MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) arm of the Long 2005 trial was stopped early because of toxicity and patient numbers are small (see Analysis 1.4; Analysis 1.5).

Cisplatin combination with or without paclitaxel

Meta-analysis of two RCTs (Monk 2008; Mountzios 2009), assessing 587 participants, found that the proportion of women who responded to treatment was statistically significantly lower in the group who received platinum plus paclitaxel than in the group who received combination platinum-containing regimens that did not include paclitaxel (RR 1.47; 95% CI 1.01 to 2.15). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than chance may represent moderate heterogeneity (I^2 = 52%) (Table 4). However, in one trial a paclitaxel triplet was compared with a no-paclitaxel doublet and so this explains some of the heterogeneity. Thus a combined plot should be interpreted with caution (see Analysis 1.6).

In-field versus out-of-field responses with platinum-containing chemotherapy

Some authors hypothesised that response rates to chemotherapy will be less in previously irradiated areas therefore some trials performed a subgroup analysis to compare in-radiotherapy-field versus out-of-field response rates. In order to attempt to explore this it was decided to only look at platinum-containing regimens, which were selected because they are the most widely used clinically and have demonstrable activity. Meta-analysis of six RCTs (Bloss 2002; Cadron 2005; Edmonson 1988; Lira-Puerto 1991; McGuire 1989; Moore 2004), assessing 1062 participants, found that the proportion of women who responded to treatment was significantly lower for recurrences within the pelvic field compared with disease outside of the pelvic radiotherapy field (RR 0.62; 95% CI 0.46 to 0.83). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than chance may represent moderate heterogeneity (I^2 = 34%). Two trials were excluded from the meta-analysis because of incomplete data (Bezwoda 1986; Pfeiffer 1998). Of note the majority of patients had not received prior chemotherapy (77.2%) with their radiotherapy. Where patients had had previous chemotherapy this was generally cisplatin as part of chemoradiotherapy, rather than chemotherapy alone with palliative intent (see Analysis 1.7 and Table 5).

Overall survival, progression-free survival and time to progression

OS and PFS was incompletely reported and there was insufficient information across trials to allow pooling of results.

OS with cisplatin alone was 6.5 to 9 months (> 11 trials) with PFS of approximately three months (additional tables). With cisplatin combination OS was 7 to 10 months with PFS of 4.6 to 4.9 months. The Alberts 1987 and Cadron 2005 trials were excluded as the numbers were small and appeared to be outliers to other studies with greater numbers.

When comparing cisplatin-containing regimens with non-platinum-containing regimens there was marked heterogeneity owing to different activities. Again ranges of OS were 4 to 9.6 months and PFS 2.9 to 4.6 months.

The addition of a taxane led to OS of 12.9 to 15.4 months with PFS of 5.8 to 7.9 months. However, these were based on more recent trials (Monk 2008; Mountzios 2009) rather than older trials.

Some trials compared different cisplatin or carboplatin doses. The most commonly used was cisplatin 50 mg/m^2 day one every 21 days with median OS of eight months and median response rates of 19%. This is a relatively low dose compared with cisplatin doses in other tumour sites. Higher doses of cisplatin were explored by Bonomi 1985 yielding a higher response rate of 31% but no difference in OS (seven months). However, this was one study with limited power to detect differences owing to low patients numbers and high drop-out rates and so the question remains unanswered. Carboplatin gave similar median response rates of 26% with median OS of 7.5 months.

HRs were only reported in two trials (Monk 2008; Long 2005). Long 2005 found a survival advantage of cisplatin/topotecan over cisplatin alone in patients with recurrent or metastatic cervical cancer; with a PFS of 2.9 versus 4.6 months (HR 0.76) and OS of 6.5 versus 9.4 months (HR 0.76). Monk 2008 compared three chemotherapy doublets (cisplatin/vinorelbine, cisplatin/gemcitabine and cisplatin/topotecan) with the standard of cisplatin/paclitaxel. They found that no one doublet was statistically significantly superior but there was a trend in PFS, OS and response rate favouring the control arm of cisplatin/paclitaxel (Table 6).

Toxicity

Among all the studies there were 23 deaths from non-cancer-related causes. Fifteen of these were reported as treatment-related with seven deaths from neutropenic sepsis (often with secondary acute renal failure), two from haemorrhage owing to severe thrombocytopenia, two from pulmonary toxicity owing to bleomycin, one from acute renal failure following cisplatin and one death owing to ifosfamide-induced encephalopathy. Four deaths owing to severe haematological toxicity were reported in patients receiving MVAC in the GOG179 trial (Long 2006) causing this arm in the trial to be closed early after only sixty-three patients had been treated with the regimen. Eight other non-cancer deaths were reported although not linked directly to treatment by the authors, including two fatal pulmonary emboli (Long 2005) and six deaths in one trial (Edmonson 1988) owing to cardiac arrests and cerebrovascular accidents in patients who had been receiving cisplatin/bleomycin (two deaths) or cisplatin/bleomycin/doxorubicin/cyclophosphamide (four deaths)).

Because of the heterogeneity in types and combinations of cytotoxic agents used, with many trials only containing small patient numbers and with a wide variety of toxicity scoring systems used it was difficult to analyse and compare the toxicity data. With these provisos an attempt was made to compare toxicities between trials were reported in sufficient detail. This was only possible for the trials involving single-agent cisplatin versus cisplatin-containing combinations.

Cisplatin single-agent versus cisplatin-combination chemotherapy

Unsurprisingly cisplatin combinations generally tended to produce higher rates of toxicity than cisplatin alone.

Grade 3/4 neutropenia

Meta-analysis of four RCTs (Alberts 1987; Long 2005; Moore 2004; Omura 1997), assessing 1073 participants, found that there was significantly less risk of severe neutropenia in women who received chemotherapy as a single agent than those who received combination chemotherapy (RR 0.04; 95% CI 0.02 to 0.12). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than chance may represent moderate heterogeneity (I^2 = 32%) (Analysis 2.1).

Grade 3/4 thrombocytopenia

Meta-analysis of four RCTs (Alberts 1987; Long 2005; Moore 2004; Omura 1997), assessing 1104 participants, found that there was significantly less risk of severe thrombocytopenia in women who received chemotherapy as a single agent than those who received combination chemotherapy (RR 0.16; 95% CI 0.05 to 0.48). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than chance may represent moderate heterogeneity (I^2 = 49%) (Analysis 2.2).

Grade 3/4 infection

Meta-analysis of two RCTs (Long 2005; Moore 2004), assessing 552 participants, found that there was significantly less risk of severe infection in women who received chemotherapy as a single agent than those who received combination chemotherapy (RR 0.42; 95% CI 0.22 to 0.81). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than chance was not important (I^2 = 0%) (see Analysis 2.3).

Grade 3/4 renal dysfunction

Meta-analysis of three RCTs (Long 2005; Moore 2004; Omura 1997), assessing 980 participants, did not find any statistically significant difference in the risk of severe renal dysfunction between women who received single-agent chemotherapy and those who received combination chemotherapy (RR 0.81; 95% CI 0.46 to 1.41). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than chance was not important (I^2 = 0%) (see Analysis 2.4).

Grade 3/4 neuropathy

Meta-analysis of two RCTs (Long 2005; Moore 2004), assessing 552 participants, did not find any statistically significant difference in the risk of severe neuropathy between women who received single-agent chemotherapy and those who received combination chemotherapy (RR 1.39; 95% CI 0.45 to 4.33). The percentage of the variability in effect estimates that was because of heterogeneity between studies rather than chance was not important (I^2 = 0%) (Analysis 2.5).

In those trials using carboplatin at 400 mg/m^2 there was a tendency for severe toxicity in those patients with pre-existing renal impairment highlighting the importance of calculating carboplatin dose based on creatinine clearance using the Calvert formula rather than a milligram per square metre of body surface area (mg/m^2) dose as with other cytotoxic agents (see Analysis 2.5).

Quality of life

The effect of treatment of QoL is of key importance when deciding on treatment of patients where cure is not a realistic goal. Only three trials (Long 2005; Monk 2008; Moore 2004) out of 26 reported any QoL information on trial patients. Similar tools were used by these three trials for monitoring (Functional Assessment of Cancer Therapy - General (FACT-G), Functional Assessment of Cancer Therapy - Cervix (FACT-Cx), NEUROTOX, Brief Pain Inventory (BPI)).

Long 2005 and Moore 2004 found that patients with metastatic or recurrent disease had reduced QoL scores compared to the general population prior to starting treatment (particularly with respect to loss of function and physical wellbeing). In the trial of cisplatin with or without topotecan (Long 2005) there was an association between higher QoL scores at baseline and OS with those in the highest scoring quartile having a 47% lower hazard of death when compared with the lowest scoring quartile (HR 0.53; 95% CI 0.36 to 0.78; P = 0.001). Among patients who complete protocol therapy the serial measurements of QoL scores tend to remain stable no matter which treatment arm they had been allocated to. There was also no difference in QoL scores when comparing single-agent cisplatin with different cisplatin combinations at any time point. The authors hypothesised that improved response rates compensate for the increased toxicity of combination regimens.

DISCUSSION

Summary of main results

- There are no data comparing best supportive care with chemotherapy.
- Survival data were incompletely reported so there is an absence of evidence for important outcomes such as OS and PFS.
- Numerous older trials had small patient numbers and significant potential for bias.
- Large numbers of different chemotherapy agents and combinations have been explored making for heterogeneous data. It is thus difficult to interpret pooled results satisfactorily. Cisplatin-based regimens are the most widely used currently and historically and therefore this review has concentrated on these trials.
- In terms of response rates some non-platinum regimens were equivalent but toxicity was significantly higher, for example the MVAC arm was closed early owing to four treatment-related deaths (of 63 patients) (Long 2006).
- The most widely used cisplatin regimen was 50 mg/m^2 day 1 q21days. Some trials hinted that higher doses had similar survivals, but this could not be confirmed or refuted owing to poor reporting of time to event data. There was no direct comparison between cisplatin and carboplatin but response rate with single-agent carboplatin was similar to single-agent cisplatin.
- Evidence to suggest that cisplatin combination improves response rates when compared with single-agent cisplatin, but further trials are needed to ascertain whether this is the case for OS and PFS. However no one combination is significantly different from others (Monk 2008), although some outcomes may be improved with cisplatin/paclitaxel. Thus toxicity profile, scheduling and co-morbidity are important when individualising therapy.
- Combination regimens are more toxic than single-agent regimens but in the limited reported data this does not appear to impact on QoL, although further trials reporting QoL outcomes are required.
- Nine of the 23 included trials performed subgroup analyses comparing response rates between previously irradiated and non-irradiated sites. Eight of these found no significant difference in response rate by site of recurrence although there was a trend towards improved response when the main site of disease was beyond the previously irradiated pelvis.

Overall completeness and applicability of evidence

This review included patients enrolled into trials with local relapse, distant relapse and primary metastatic disease. The relapsed patients may have had primary treatment with surgery, radiotherapy or chemoradiotherapy. There are no data comparing responses in these different groups. Since 1999, cisplatin-based chemoradiotherapy has been the preferred treatment in patients presenting with Stage 1b2 or above. In this analysis less than 30% of patients had received prior chemoradiotherapy and thus the generalisability of these results remains uncertain. It is likely that response will be less especially in patients with short disease-free intervals or in previously irradiated sites. Conversely there are no data to suggest that there is a lack of response in all patients who have received prior chemoradiotherapy.

There is no direct evidence documenting a comparison of chemotherapy and best supportive care. Cisplatin-based combinations appear to have the highest response rates but median OS remains poor at nine to 12 months with PFS of four to five months. Thus metastatic cervical cancer remains relatively chemo-insensitive.

There is a lack of data on QoL and also survival outcomes. Optimising QoL is essential in this group of palliative patients. Only three trials reported QoL data and new trials need to include this as an outcome. The limited data reported have indicated that cisplatin combination chemotherapy is not detrimental to patient experience, but in the absence of adequate QoL and survival data results need to be interpreted with caution.

Quality of the evidence

The quality of the evidence is low as important outcomes such as OS were incompletely reported and the chemotherapeutic agents used in the different trials varied markedly making comparisons difficult and the presence of heterogeneity across trials a problem. More recent trials, which are most relevant to our results and reflect current practice, are of a more acceptable quality, but most still did not report outcomes satisfactorily.

For example, the most widely used cisplatin regimen was 50 mg/m^2 day 1 q21days. It is not possible to comment on optimal cisplatin owing to inadequate survival data. There were no direct comparisons between cisplatin and carboplatin. Although response rates with single-agent carboplatin were similar to single-agent cisplatin there is insufficient evidence to conclude their equivalence. Further trials on the optimal platinum compound and dose would be clinically useful.

Only in very recent studies, comparing cisplatin combinations, are survival and QoL outcomes reported adequately. Toxicity was reported using different scales and the data were very heterogeneous

Potential biases in the review process

An extensive literature search was performed in EMBASE, MEDLINE, LILACS, CENTRAL, Physician Data Query and Meta-Register. No un-published data were identified. In order to minimise bias a thorough search of grey literature was performed. Strict inclusion and exclusion criteria were also used to make sure that all appropriate trials were included. We restricted the included studies

to RCTs as they provided the strongest level of evidence available. Hence we have attempted to reduce bias in the review process.

The greatest threat to the validity of the review is likely to be the possibility of publication bias, that is studies that did not find the treatment to have been effective may not have been published. We were unable to assess this possibility as the number of trials in each comparison was limited.

Agreements and disagreements with other studies or reviews

Other reviews and meta-analyses of chemotherapy in metastatic or recurrent cervical cancer have been undertaken, all of which concur with the importance of basing treatment on a platinum compound and highlighting the improved PFS when cisplatin used in combination rather than as a single agent (Tewari 2005).

Pectasides 2008 reviewed chemotherapy for recurrent cervical cancer, including Phase II non-randomised data that has not been included in this review. His conclusions of single-agent and combination therapy were similar to those of this review. That is, cisplatin appears to have the highest response rates and analogues of cisplatin, such as carboplatin or iproplatin, were active. Doxorubicin, paclitaxel and topotecan showed significant activity as single agents with 15% to 20% response rates. For combination chemotherapy cisplatin has been combined with 5-fluorouracil (5-FU) Weiss 1990, bleomycin, ifosfamide, gemcitabine, vinorelbine, paclitaxel and topotecan in Phase II and III trials. Many of these trials showed an advantage in terms of response rate for combination when compared with single-agent cisplatin and in some there was also a PFS advantage (cisplatin plus ifosfamide (Omura 1997), cisplatin plus paclitaxel (Moore 2004) and cisplatin plus topotecan (Long 2006)). Only cisplatin plus topotecan showed a survival advantage over single-agent cisplatin.

Many centres are using carboplatin-based combinations in this group of patients despite there being no randomised evidence published to support this. Thus as part of this review of RCTs the Phase II data is not represented. Non-randomised Phase II data suggest that carboplatin in combination with paclitaxel is active and well tolerated (Pectasides 2008; Tinker 2005). Moore 2007 published a retrospective study comparing cisplatin with carboplatin in combination with paclitaxel suggesting equivalent efficacy. One Phase III randomised trial (Saito 2010) is currently recruiting comparing carboplatin/paclitaxel with cisplatin/paclitaxel, which will provide further information on whether carboplatin can be substituted for cisplatin, improving toxicity profile without compromising outcome. This is a particularly important question because of the high frequency of renal impairment in patients with locally recurrent disease limiting their suitability for cisplatin-containing regimens.

Mutch 2003 reviewed the role of gemcitabine in cervical cancer; the majority of the data being non-randomised Phase II trials that are not represented in this paper. They conclude that gemcitabine has demonstrated little activity as a single agent but that it appears to act synergistically with cisplatin. Monk 2008 found similar results in terms of response rate, PFS and OS between cisplatin plus gemcitabine, cisplatin plus paclitaxel, cisplatin plus vinorelbine and cisplatin plus topotecan.

Cisplatin-based combinations are currently the most widely used internationally, making the results of this review applicable.

AUTHORS' CONCLUSIONS

Implications for practice

When treating patients with metastatic or recurrent cervical cancer combination cisplatin-based chemotherapy could be a viable treatment option, but further trials that report adequate survival and QoL data are sought. The role of carboplatin in this context is not established. There is a trend to improved outcome with cisplatin plus paclitaxel combinations but the different toxicity profiles of the various combinations should be discussed individually.

Response rates and improvements in survival were low, therefore chemotherapy may not be appropriate for all patients, especially those with poorer performance status. The majority of patients in these trials were performance status 0 to 1, only small numbers of performance status 2 to 3 patients were included. Cisplatin-based combination chemotherapy had significant toxicity.

Implications for research

There is one ongoing randomised Phase III trial that should address the question of substitution of cisplatin by carboplatin in patients with metastatic and recurrent cervical cancer (Saito 2010). QoL, toxicity and survival will be critical end points for this trial and others.

In other tumour sites weekly regimens have shown better responses and toxicity profiles. This should be explored for cervical cancer.

Overall response rates and survival are poor and novel cytotoxic and biological agents need investigation. The evaluation of existing biological agents was outside the scope of this review; however, agents targeting angiogenesis, epidermal growth factor receptors, histone deacetylases, COX-2 and m-TOR are currently in clinical development. Far fewer molecularly targeted agents have been trialed in cervical cancer compared with other tumour sites, especially at the Phase III level and therefore none of these agents are currently approved for use in clinical practice.

Future trials need to stratify for and perform planned subgroup analysis with respect to previous treatment and site of recurrence.

Future trials should report HRs for survival data to facilitate meta-analysis of pooled data.

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CHARACTERISTICS OF STUDIES

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

Alberts 1987

Methods	Randomised Phase II trial
Participants	119 women with incurable squamous cell carcinoma unsuitable for surgery or radiotherapy. No previous chemotherapy exposure
Interventions	Arm 1: mitomycin C 10 mg/m^2 iv d2, 44, vincristine 0.5 mg/m^2 iv d2, 4, 44, 46, bleomycin 30 mg continuous iv infusion over 24 h for 4 days d1-4, 43-46, cisplatin 50 mg/m^2 iv d1, 22, 43, 64 Arm 2: mitomycin C 12 mg/m^2 iv d1, 43, cisplatin 50 mg/m^2 iv d1, 22, 43, 64 Arm 3: cisplatin 50 mg/m^2 iv d1, 22, 43, 64
Outcomes	Response rate Response duration Median survival Toxicity (SWOG)
Notes	5 ineligible patients (reasons not stated). Arm 3 stopped early owing to slow accrual. Not clear whether ITT analysis performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	High risk	Not documented
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 ineligible patients (reasons not stated). Arm 3 stopped early owing to slow accrual. Not clear whether ITT analysis performed
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Alberts 1987 *(Continued)*

Other bias	High risk	Cisplatin arm stopped early despite appearing to have better results so only 9 patients evaluable

Bezwoda 1986

Methods	Randomised Phase II trial 1982 to 1984
Participants	50 women with recurrent or metastatic cervical cancer
Interventions	Arm 1: hydroxyurea 1.5 g/m^2 po d1-10, 14-d rest period then maintenance with 1 g/m^2 po d1-14 q28 Arm 2: cisplatin 20 mg/m^2 iv daily d1-3 and methotrexate 100 mg/m^2 iv d3 with leucovorin rescue
Outcomes	OS Response rates Toxicity
Notes	3 patients were excluded (refused chemotherapy after randomisation). No ITT analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Low risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients were excluded
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	High risk	Hydroxyurea (arm 1) arm stopped early owing to lack of response, only 12 patients randomised to cisplatin + methotrexate arm (arm 2), the remainder entered that arm as only treatment option once the hydroxyurea arm closed. Thus many randomised and trial results not used in meta-analyses

Bloss 2002

Methods	Randomised Phase II trial

Bloss 2002 *(Continued)*

Participants	303 women with advanced, recurrent or persistent squamous cell cancer of the cervix not suitable for curative treatment with radiotherapy or surgery
Interventions	Arm 1: cisplatin 50 mg/m^2 d1 and ifosfamide 5 g/m^2 over 24 h with mesna 6 g/m^2 q21 max 6 cycles Arm 2: cisplatin 50 mg/m^2 d1 and ifosfamide 5 g/m^2 over 24 h with mesna 6 g/m^2 and bleomycin 30 U over 24 h q21 maximum 6 cycles
Outcomes	Response rate OS PFS Toxicity
Notes	16 patients ineligible (11 wrong histology, 1 wrong primary tumour site, 2 inadequate pathology material, 1 inadequate renal function, 1 inadequate performance status). All patients were included in ITT analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised with equal probability
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 patients ineligible (11 - wrong histology, 1 - wrong primary tumour site, 2 - inadequate pathology material, 1 - inadequate renal function, 1 - inadequate performance status). All patients were included in ITT analysis
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Bond 1976

Methods	Randomised Phase II trial
Participants	Number of participants not stated in the paper. Number included in the analysis was 41. Women with histologically confirmed squamous cell carcinoma of the cervix. Most had previously received radical radiotherapy followed by recurrence of local disease, distant metastases or both
Interventions	Arm 1: doxorubicin 50 mg iv, vincristine 2 mg iv, methotrexate 50 mg iv all d1 q28 Arm 2: doxorubicin 50 mg iv, vincristine 2 mg iv, methotrexate 50 mg iv, bleomycin 15 mg iv all d1 q28
Outcomes	Toxicity

Bond 1976 *(Continued)*

	Response rates Median survival
Notes	Standard doses of drugs given regardless of height, weight or surface area in order to avoid risk of incorrect dose calculation when treatment administered by junior staff. No ITT analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants not stated in the paper. Number included in the analysis was 41
Selective reporting (reporting bias)	Unclear risk	Total number of trial participants not stated only those evaluable
Other bias	Unclear risk	No comparison of patient characteristics between the 2 groups given

Bonomi 1985

Methods	Randomised Phase II trial
Participants	581 women with squamous cell carcinoma of the cervix considered incurable with surgery or radiation
Interventions	Arm 1: cisplatin 50 mg/m^2 iv q21 Arm 2: cisplatin 100 mg/m^2 q21 Arm 3: cisplatin 20 mg/m^2 iv daily d1-5 q21 All arms to a maximum dose of 400 mg/m^2
Outcomes	Response rates Toxicity OS PFS
Notes	54 excluded (5 no histological confirmation of tumour, 32 wrong cell type, 3 inadequate renal function, 8 second or wrong primary tumour, 2 inadequate performance status, 4 improper pre-protocol treatment). There were a further 30 women who could not be evaluated (8 inadequate pathological material, 3 improper randomisation, 2 clerical error, 11 never received cisplatin, 1 removed by investigator, 5 inadequate data). ITT analysis not performed

Bonomi 1985 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	54 excluded. There were a further 30 women who could not be evaluated. ITT analysis not performed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No hint at any other possible biases

Cadron 2005

Methods	Randomised Phase III trial
Participants	24 women with histologically confirmed cervical cancer with distant metastases after surgery or recurrence after radiotherapy
Interventions	Arm 1: cisplatin 37.5 mg/m^2 iv d1-2 q28 Arm 2: cisplatin 37.5 mg/m^2 iv d1-2 and Ifosfamide 2 g/m^2 iv d1-2, mesna 0.5 g/m^2, 5-fluorouracil 500 mg/m^2 d1-2, folinic acid 30 mg/m^2 d1-2 q28
Outcomes	Response rates Toxicity (WHO) OS
Notes	3 patients ineligible (did not receive chemotherapy owing to rapid progression). ITT analysis performed. Trial stopped early owing to poor accrual

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias)	Unclear risk	Not documented but OS unlikely to be affected by blinding

Cadron 2005 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Edmonson 1988

Methods	Randomised Phase II trial 1980 to 1985
Participants	91 women with advanced cervical carcinoma
Interventions	Arm 1: bleomycin 20 U/m^2 iv 3-d infusion, cisplatin 60 mg/m^2 d1 iv, doxorubicin 40 mg/m^2 iv D1, cyclophosphamide 400 mg/m^2 iv d1 q28 Arm 2: bleomycin 20 U/m^2 iv 3-d infusion, cisplatin 60 mg/m^2 d1 iv q21 Bleomycin omitted after 4 cycles in both arms
Outcomes	Response rates OS
Notes	1 patient excluded as ineligible owing to second primary cancer. No ITT analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Dynamic allocation system
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Freedman 1980

Methods	Randomised Phase II trial 1975
Participants	59 women with recurrent squamous cell cervical cancer
Interventions	Arm 1: sequential cyclophosphamide 8 mg/kg iv d1-5 q28 then adriamycin 80 mg/m^2 iv d1 q28 then hexamethylmelamine 8 mg/kg po daily continuously Arm 2: sequential adriamycin 80 mg/m^2 iv d1 q28 then cyclophosphamide 8 mg/kg iv d1-5 q28 then hexamethylmelamine 8 mg/kg po daily continuously Arm 3: sequential hexamethylmelamine 8 mg/kg po daily continuously then cyclophosphamide 8 mg/kg iv d1-5 q28 then adriamycin 80 mg/m^2 iv d1 q28 Not stated prospectively what criteria would be for switching treatment (i.e. number of cycles versus progressive disease)
Outcomes	Response rates Survival time after chemotherapy start Survival from time of treatment change
Notes	1 patient excluded (died prior to starting chemotherapy). No ITT analysis performed. Cross-over between arms allowed. Reasons for switching chemotherapy agents varied and included disease progression, toxicity and cumulative doxorubicin dose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified by ease of disease evaluation then randomised
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Low risk	Not documented, but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	High risk	Patients allowed to switch between arms for variety of reasons including toxicity, cumulative doxorubicin dose and disease progression

Greenberg 1977

Methods	Randomised Phase II trial

Greenberg 1977 *(Continued)*

Participants	20 women with recurrent or metastatic epidermoid cervical cancer
Interventions	Arm 1: adriamycin 30 mg/m^2 iv cycle 1 then 45 mg/m^2 iv cycle 2; 3rd and subsequent cycles 60 mg/m^2 iv q21 Arm 2: bleomycin 10 U/m^2 weekly plus adriamycin 30 mg/m^2 iv cycle 1 then 45 mg/m^2 iv cycle 2; 3rd and subsequent cycles 60 mg/m^2 iv q21
Outcomes	Response rates Toxicity OS
Notes	No patients excluded. ITT analysis performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not documented
Allocation concealment (selection bias)	Low risk	Randomisation performed by Statistical Office of Western Cancer Study Group
Blinding (performance bias and detection bias) All outcomes	Low risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Lira-Puerto 1991

Methods	Randomised Phase II trial 1984 to 1987
Participants	89 women with recurrent measurable squamous cell cervical cancer
Interventions	Arm 1: carboplatin 400 mg/m^2 iv d1, 1 dose escalation if haematological toxicity ≤ grade 1 Arm 2: iproplatin 300 mg/m^2 iv d1, 1 dose escalation if haematological toxicity ≤ grade 1 Cycle length not stated
Outcomes	Response rates Toxicity

Lira-Puerto 1991 *(Continued)*

	OS
Notes	3 patients excluded (1 patient refused treatment after randomisation, 2 patients excluded as recurrence subsequently deemed to be benign fibrosis). ITT analysis not performed but excluded patients eligible for toxicity evaluation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Long 2005

Methods	Randomised Phase III trial 1999 to 2002
Participants	294 women with histologically confirmed advanced (Stage IVb), recurrent or persistent squamous cell, adenocarcinoma or adenosquamous cervical cancer unsuitable for curative treatment with surgery or radiotherapy, or both
Interventions	Arm 1: cisplatin 50 mg/m^2 iv d1 q21 Arm 2: cisplatin 50 mg/m^2 iv d1 and topotecan 0.75 mg/m^2 iv d1-3 q21
Outcomes	Response rates Toxicity OS
Notes	8 patients excluded (1 institutional review board approval error, 2 second active malignancy present, 2 wrong histological type, 1 primary tumour other than cervical cancer, 2 inadequate tissue to confirm metastases). ITT analysis performed Trial originally had 3 arms but third arm (MVAC) was closed early owing to toxicity and is reported in detail in separate papers

Risk of bias

Long 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients assigned with equal probability using a fixed-block design
Allocation concealment (selection bias)	Low risk	GOG Statistical and Data Centre performed randomisation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 patients excluded but balanced across groups. ITT analysis performed
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Unclear risk	MVAC arm closed early owing to toxic deaths

Long 2006

Methods	Randomised Phase III trial 1999 to 2001
Participants	186 women with histologically confirmed advanced (Stage IVb), recurrent or persistent squamous cell, adenocarcinoma or adenosquamous cervical cancer unsuitable for curative treatment with surgery or radiotherapy, or both
Interventions	Arm 1: cisplatin 50 mg/m^2 iv d1 q21 Arm 2: cisplatin 50 mg/m^2 iv d1 and topotecan 0.75 mg/m^2 iv d1-3 q21 Arm 3: methotrexate 30 mg/m^2 iv d1, 15, 22, vinblastine 3 mg/m^2 iv d2, 15, 22, doxorubicin 30 mg/m^2 iv d2, cisplatin 70 mg/m^2 iv d2 q28 Maximum 6 cycles given unless maximum cumulative dose of doxorubicin achieved or progressive disease or unacceptable toxicity
Outcomes	Response rates Toxicity OS
Notes	6 patients ineligible (1 clerical error, 2 wrong cell type, 1 wrong primary, 1 inadequate pathology tissue, 1 second primary tumour. ITT analysis performed This paper reports the third arm of trial reported by Long 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Long 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Patients assigned with equal probability using a fixed-block design
Allocation concealment (selection bias)	Low risk	GOG Statistical and Data Centre randomly assigned patients
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 patients excluded balanced across arms. ITT analysis
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Unclear risk	MVAC arm closed early owing to toxic deaths

Malkasian 1981

Methods	Randomised Phase II trial
Participants	41 women with recurrent and metastatic cervical cancer who had had as much surgery as was possible and radiotherapy where appropriate
Interventions	Arm 1: 5-fluorouracil 450 mg/m^2 iv d1-5 and vincristine 1.5 mg/m^2 d1 and d5 q35 Arm 2: doxorubicin 60 mg/m^2 iv d1 q21
Outcomes	Response rates Toxicity OS Time to treatment failure
Notes	2 patients excluded (1 refused treatment after randomisation, 1 immediately lost to follow-up). ITT analysis was not performed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding

Malkasian 1981 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients excluded. No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

McGuire 1989

Methods	Randomised Phase III trial 1984 to 1987
Participants	394 patients with histologically confirmed squamous carcinoma of the cervix, recurrent disease following primary therapy or metastases. No previous chemotherapy allowed
Interventions	Arm 1: carboplatin 400 mg/m^2 d1 q28 Arm 2: iproplatin 270 mg/m^2 d1 q28
Outcomes	Response rates Response duration Toxicity (GOG) OS
Notes	23 ineligible (7 non-squamous histology, 4 other primaries, 8 previous other malignancy, 3 no pathological documentation of primary tumour, 1 previous chemotherapy). 10 additional patients not evaluable for toxicity or response. 7 did not receive treatment. 3 lost to follow-up. ITT analysis not performed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block design with balanced assignments
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	23 ineligible and 10 additional patients not evaluable for toxicity or response balanced across groups. ITT analysis not performed
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Monk 2008

Methods	Randomised Phase III trial 2003 to 2007
Participants	513 women with advanced, recurrent or persistent squamous cell cervical cancer not suitable for surgery or radiotherapy
Interventions	Arm 1: cisplatin 50 mg/m^2 d2 plus paclitaxel 135 mg/m^2 over 24 h d1 q21 Arm 2: cisplatin 50 mg/m^2 d1 plus vinorelbine 30 mg/m^2 d1, 8 q21 Arm 3: cisplatin 50 mg/m^2 plus gemcitabine 1000 mg/m^2 d1, 8 q21 Arm 4: cisplatin 50 mg/m^2 plus topotecan 0.75 mg/m^2 d1-3 q21
Outcomes	OS PFS Response rates Toxicity (WHO) QoL
Notes	First 41 patients enrolled were excluded from primary analysis. another 38 patients later found to be ineligible. 434 evaluable for efficacy. 9 patients never treated so excluded from toxicity assessment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Low risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	First 41 patients enrolled were excluded from primary analysis. Another 38 patients later found to be ineligible
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Moore 2004

Methods	Randomised Phase III trial

Moore 2004 *(Continued)*

Participants	280 women with squamous cell Stage IVb, recurrent or persistent cervical cancer. No previous chemotherapy allowed
Interventions	Arm 1: cisplatin 50 mg/m^2 iv d1 q21 Arm 2: cisplatin 50 mg/m^2 iv d1 and paclitaxel 135 mg/m^2 iv d1 q21
Outcomes	Response rates OS PFS Toxicity (WHO)
Notes	16 ineligible patients (7 non-squamous histology, 1 incorrect stage, 8 inadequate pathology). A further 5 patients did not receive chemotherapy, but were included in the ITT analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	With equal probability block design balancing sequences of assigned arms within institutions
Allocation concealment (selection bias)	Low risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Low risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 ineligible patients A further 5 patients did not receive chemotherapy, but were included in the ITT analysis
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Moseley 1976

Methods	Randomised Phase II trial
Participants	5 women with squamous cell cervical cancer considered to be unsuitable for surgery. These women were part of a larger trial of 35 patients with squamous cell cancer in a variety of primary sites
Interventions	Arm 1: CCNU (lomustine) 100-130 mg/m^2 po depending on bone marrow reserves d1 plus bleomycin 0.5 mg/kg im or iv d8, 11, 15, 18, 22, 25, 29, 32, 36, 39 q42 days Arm 2: CCNU 100-130 mg/m^2 po depending on bone marrow reserves d1 plus vinblastine 0.1 mg/kg iv d8, 15 plus methotrexate 0.5 mg/kg iv (maximum 25 mg) d8, 15 plus bleomycin 0.5 mg/kg im or iv d8, 15, 18, 22, 25, 29, 32 q56 days Maximum cumulative dose of bleomycin is 300 mg

Moseley 1976 *(Continued)*

Outcomes	Response rates Toxicity
Notes	1 patient dropped out after cycle 1 day 1 treatment (single-dose CCNU) to have treatment elsewhere and was considered unevaluable. No ITT analysis performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Mountzios 2009

Methods	Randomised Phase II clinical trial
Participants	153 women with metastatic, persistent or recurrent cervical cancer. performance status 0 to 2
Interventions	Arm 1: ifosfamide 1.5 g/m^2 d1-3 plus cisplatin 70 mg/m^2 d2 q28 Arm 2: ifosfamide 1.5 g/m^2 d1-3 plus cisplatin 70 mg/m^2 d2 plus paclitaxel 175 mg/m^2 d1 q28
Outcomes	Response rates PFS OS Toxicity
Notes	4 patients excluded (3 had had previous chemotherapy, 1 previous primary cancer)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented

Mountzios 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Omura 1978

Methods	Randomised Phase II trial
Participants	284 women with biopsy-confirmed cancer of the genital tract not amenable to surgery or radiotherapy. 231 of these had cervical cancer. Previous chemotherapy allowed unless contained a nitrosourea
Interventions	Arm 1: CCNU (lomustine) 100 mg/m^2 q6 weeks Arm 2: methyl-CCNU 150 mg/m^2 q6 weeks
Outcomes	Response rates Toxicity
Notes	82 patients with cervical cancer were ineligible or unevaluable. In the whole trial 102 patients were excluded owing to missing data in 77, chemotherapy violation in 22, clerical error in 2, and inadequate pathology material in 3. No ITT analysis was performed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	closed envelope technique
Allocation concealment (selection bias)	Low risk	closed envelope technique
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	82 patients with cervical cancer were ineligible or women not evaluable. Further 102 patients were excluded as not evaluable
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes

Omura 1978 *(Continued)*

Other bias	High risk	102 patients of 284 not evaluable

Omura 1981

Methods	Randomised Phase II trial
Participants	75 women with metastatic or recurrent squamous cell cervical cancer not amenable to surgery or radiotherapy
Interventions	Arm 1: doxorubicin 50 mg/m^2 iv d1, vincristine 1.5 mg/m^2 iv d1, 8, 5-fluorouracil 500 mg/m^2 iv d1, 8 q21 Arm 2: cyclophosphamide 1100 mg/m^2 iv d1 q21
Outcomes	Response rates OS PFS Toxicity
Notes	14 patients excluded (1 incomplete data, 2 ineligible for trial, 3 major protocol violation, 5 lost to follow-up, 1 patient refused treatment after randomisation, 1 inter-current illness preventing chemotherapy administration, 1 only evaluable for toxicity)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	14 patients excluded balanced across groups
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Omura 1997

Methods	Randomised Phase II trial
Participants	454 women with Stage IVb, persistent or recurrent squamous cell cervical cancer not amenable to curative surgery or radiotherapy

Omura 1997 *(Continued)*

Interventions	Arm 1: cisplatin 50 mg/m^2 iv q21 Arm 2: cisplatin 50 mg/m^2 iv, mitolactol 180 mg/m^2 po od d2-6 q21 Arm 3: cisplatin 50 mg/m^2 iv, ifosfamide 5 g/m^2 iv over 24 h with mesna 6 g/m^2 q21 Maximum 6 cycles
Outcomes	Response rates OS PFS Toxicity
Notes	16 patients excluded (ineligible on grounds of: 2 wrong stage, 9 wrong cell type, 2 wrong primary site, 2 previous chemotherapy, 1 second primary cancer). 10 further patients never received chemotherapy but were included in an ITT analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Central randomisation with equal probity
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 patients excluded and 10 further patients never received chemotherapy but were included in an ITT analysis balanced across groups
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Palo 1976

Methods	Randomised Phase II trial
Participants	48 women with cervical cancer
Interventions	Arm 1: adriamycin 75 mg/m^2 d1 + bleomycin 15 mg/m^2 d1, 8 q21 Arm 2: cyclophosphamide 1.2 g/m^2 d1 + vincristine 1.4 mg/m^2 d1, 8 q21
Outcomes	Response rates OS

Palo 1976 *(Continued)*

	PFS
	Toxicity
Notes	14 patients excluded from analysis (3 lack of measurable disease, 11 lost to follow-up). 18 patients also allowed to cross-over between arms

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	14 patients excluded from analysis balanced across group
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Pfeiffer 1998

Methods	Randomised Phase II trial
	March 1990 to May 1994
Participants	28 women with recurrent or advanced cervical cancer
Interventions	Arm 1: carboplatin 400 mg/m^2 iv d1 q28
	Arm 2: teniposide 125 mg/m^2 iv d1-3 q28
Outcomes	Response rates
	OS
	PFS
	Toxicity (WHO)
Notes	2 patients ineligible (1 severe renal impairment, 1 poor performance status). No ITT analysis performed

Risk of bias

Bias	Authors' judgement	Support for judgement

Pfeiffer 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Thigpen 1989

Methods	Randomised Phase II trial April 1982 to July 1985
Participants	331 women with advanced or recurrent squamous cell cervical cancer no longer amenable to control by surgery or radiotherapy
Interventions	Arm 1: cisplatin 50 mg/m^2 iv rate 1 mg/minute q21 days Arm 2: cisplatin 50 mg/m^2 iv rate over 24 h q21 days
Outcomes	Response rates OS PFS Toxicity
Notes	63 patients deemed ineligible (7 other primary site, 4 second primary, 26 wrong histological subtype, 26 no documentation of cervical primary, 1 elevated blood nitrogen urea at entry, 1 GOG performance status 4 at entry). 6 further patients with unevaluable (1 clerical error at entry, 1 never treated, 1 inadequate pathology, 2 inadequate data submitted, 1 not documented reason for unevaluability)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Latin square arrangement balancing the sequence of assigned regimens within and across institutions
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias)	Unclear risk	Not documented but OS unlikely to be affected by blinding

Thigpen 1989 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	63 patients excluded as ineligible and further 6 patients were unevaluable balanced across groups
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

Wallace 1978

Methods	Randomised Phase II trial September 1974 to June 1976
Participants	326 women with advanced, recurrent or persistent squamous cell cervical cancer not suitable for surgery or radiotherapy
Interventions	Arm 1: adriamycin 60 mg/m^2 iv q21 Arm 2: adriamycin 60 mg/m^2 iv, vincristine 1.5 mg/m^2 iv q21 Arm 3: adriamycin 60 mg/m^2 iv, cyclophosphamide 500 mg/m^2 iv q21
Outcomes	OS PFS Response rates Toxicity (WHO)
Notes	65 patients ineligible (more than half for wrong histological subtype, remainder because of wrong primary, 2nd primary, elevated urea or creatinine, poor risk at entry or no evidence of progression after previous treatment; breakdown of numbers not given). Further 69 patients deemed to be not evaluable (inadequate data collection, therapy not initiated, insufficient follow-up after first course, improper randomisation, clerical errors and others; no specific breakdown in numbers)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Low risk	Closed envelope technique
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not documented but OS unlikely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	65 patients ineligible and further 69 patients deemed to be not evaluable balanced across groups

Wallace 1978 *(Continued)*

Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes

Weiss 1992

Methods	Randomised Phase II
Participants	44 women with persistent, recurrent or metastatic Squamous cell cancer cervix 1987 to 1990
Interventions	Arm 1: didemnin B 2.6-3.5 mg/m^2 iv over 30 minutes d1 q28 (subsequent dose escalations if no toxicity) Arm 2: trimetrexate 8 mg/m^2 if previous radiotherapy or 12 mg/m^2 if no radiotherapy iv over 10 minutes d1-5 q21 (dose escalations to 15 mg/m^2 and 18 mg/m^2 respectively permitted on subsequent cycles if no toxicity)
Outcomes	Overall response rate
Notes	0% response rate in either arm at any dose 1 patient ineligible as baseline imaging not done within 14 days of starting treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not documented
Allocation concealment (selection bias)	Unclear risk	Not documented
Blinding (performance bias and detection bias) All outcomes	High risk	Not documented
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all pre-specified outcomes
Other bias	Low risk	No hint at any other possible biases

d: day; h: hour; GOG: Gynecologic Oncology Group; im: intramuscular; ITT: intention to treat; iv: intravenous; OS: overall survival; po: orally; QoL: quality of life; SWOG: Southwest Oncology Group; MVAC: methotrexate/vinblastine/doxorubicin/cisplatin; WHO: World Health Organization.

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

Study	Reason for exclusion
Armstrong 2003	Comparison of 2 Bryostatin-1 schedules, neither active
Baker 1978	Not an RCT
Greggi 2000	Not an RCT
Kumar 1998	No evidence that patients randomised between treatment arms

RCT: randomised controlled trial.

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

Saito 2010

Trial name or title	JCOG0505
Methods	Phase III RCT
Participants	Women with IVB persistent or recurrent cervical cancer not amenable to curative treatment with local therapy
Interventions	Arm 1: paclitaxel 135 mg/m^2 over 24 h d1 plus carboplatin AUC 5 d1 q21 Arm 2: paclitaxel 135 mg/m^2 over 24 h d1 plus cisplatin 50 mg/m^2 2 h d2 q21
Outcomes	OS PFS Toxicity Unplanned hospital admissions (surrogate for QoL)
Starting date	21 February 2006
Contact information	kitagawa.ryo@east.ntt.co.jp
Notes	Planned sample size 250

AUC: area under curve; d: day; h: hour; OS: overall survival; PFS: progression-free survival; QoL: quality of life; RCT: randomised controlled trial.

DATA AND ANALYSES

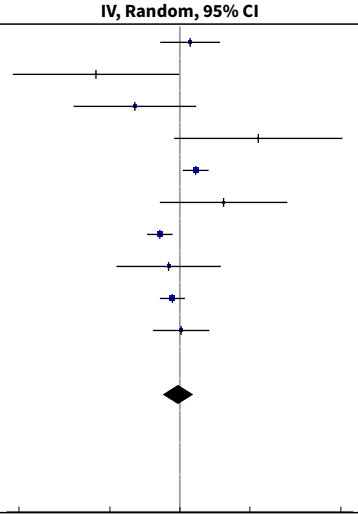
Comparison 1. Response rate (complete response + partial response)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Single agent vs. combination	10	1438	Risk Ratio (IV, Random, 95% CI)	0.94 [0.57, 1.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Single agent vs. combination: sensitivity analysis	8	1368	Risk Ratio (IV, Random, 95% CI)	0.94 [0.59, 1.50]
3 Cisplatin single agent vs. cisplatin doublet	5	1114	Risk Ratio (IV, Random, 95% CI)	0.60 [0.44, 0.81]
4 Platinum-containing regimen vs. non-platinum-containing regimen	3	413	Risk Ratio (IV, Random, 95% CI)	1.33 [0.50, 3.54]
5 Platinum-containing regimen vs. non-platinum-containing regimen: sensitivity analysis	2	363	Risk Ratio (IV, Random, 95% CI)	0.93 [0.58, 1.49]
6 Platinum + paclitaxel vs. platinum combination (non-paclitaxel)	2	587	Risk Ratio (IV, Random, 95% CI)	1.47 [1.01, 2.15]
7 In-field vs. out-field recurrence patients with platinum-containing regimen	6	1062	Risk Ratio (IV, Random, 95% CI)	0.62 [0.46, 0.83]

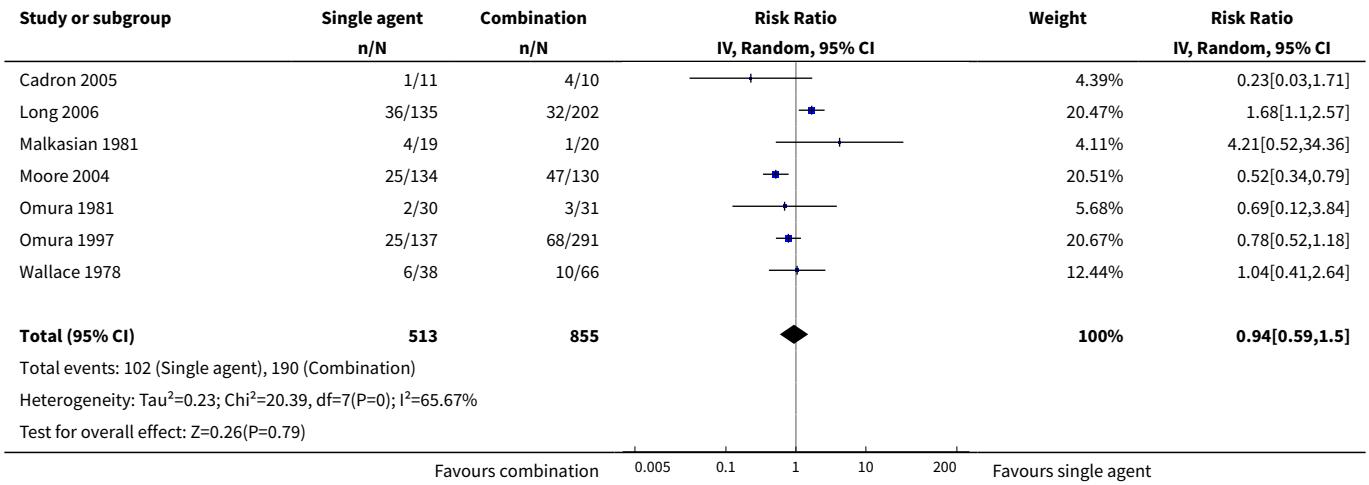
Analysis 1.1. Comparison 1 Response rate (complete response + partial response), Outcome 1 Single agent vs. combination.

Study or subgroup	Single agent n/N	Combination n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Alberts 1987	3/9	25/105		11.63%	1.4[0.52,3.75]
Bezwoda 1986	0/13	21/37		2.91%	0.06[0,0.97]
Cadron 2005	1/11	4/10		4.8%	0.23[0.03,1.71]
Greenberg 1977	5/9	0/11		2.85%	13.2[0.83,210.81]
Long 2006	36/135	32/202		18.28%	1.68[1.1,2.57]
Malkasian 1981	4/19	1/20		4.51%	4.21[0.52,34.36]
Moore 2004	25/134	47/130		18.31%	0.52[0.34,0.79]
Omura 1981	2/30	3/31		6.09%	0.69[0.12,3.84]
Omura 1997	25/137	68/291		18.42%	0.78[0.52,1.18]
Wallace 1978	6/38	10/66		12.22%	1.04[0.41,2.64]
Total (95% CI)	**535**	**903**		**100%**	**0.94[0.57,1.55]**
Total events: 107 (Single agent), 211 (Combination)					
Heterogeneity: Tau^2=0.31; Chi^2=27.62, df=9(P=0); I^2=67.42%					
Test for overall effect: Z=0.25(P=0.81)					

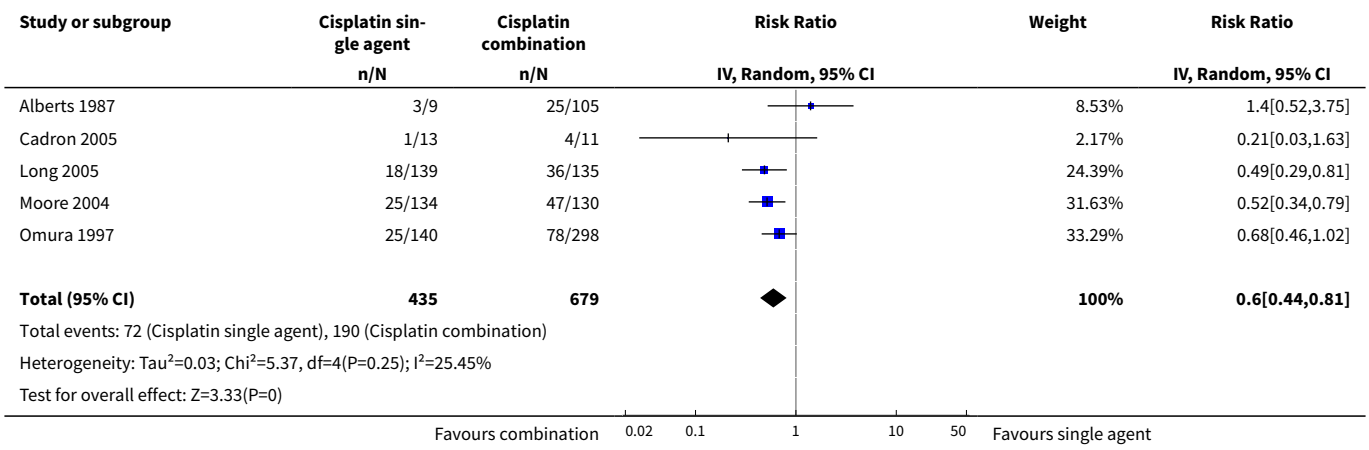


Analysis 1.2. Comparison 1 Response rate (complete response + partial response), Outcome 2 Single agent vs. combination: sensitivity analysis.

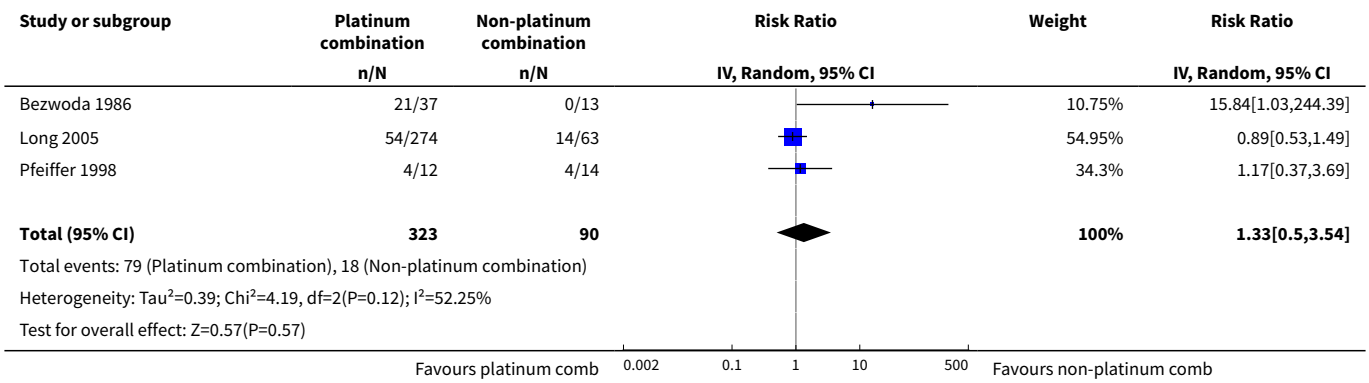
Study or subgroup	Single agent n/N	Combination n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Alberts 1987	3/9	25/105		11.73%	1.4[0.52,3.75]



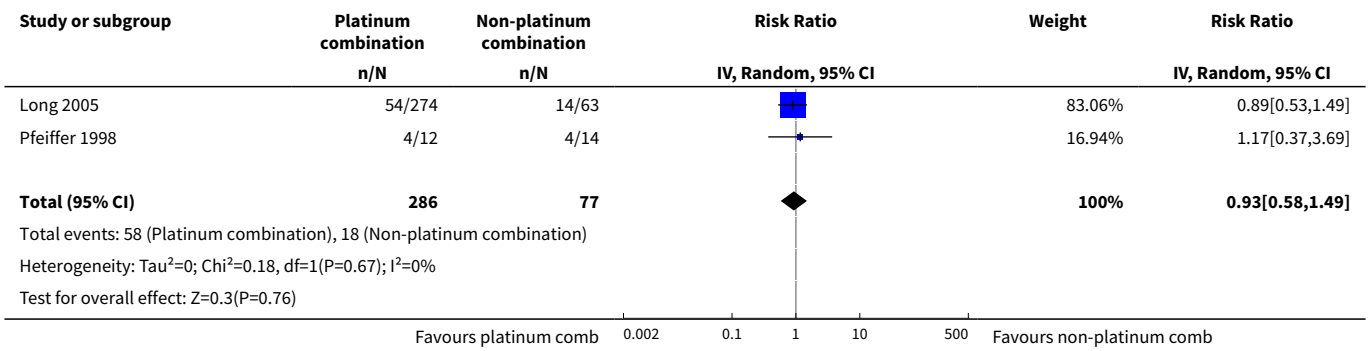
Analysis 1.3. Comparison 1 Response rate (complete response + partial response), Outcome 3 Cisplatin single agent vs. cisplatin doublet.



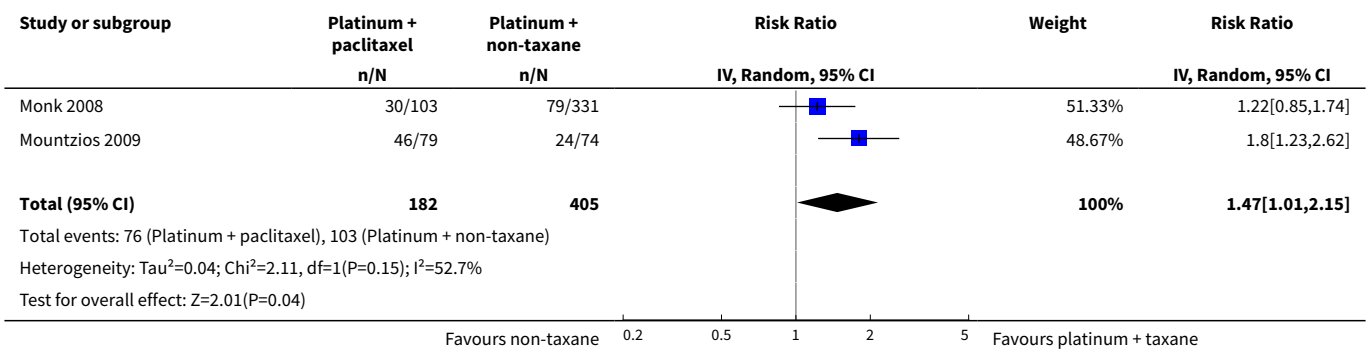
Analysis 1.4. Comparison 1 Response rate (complete response + partial response), Outcome 4 Platinum-containing regimen vs. non-platinum-containing regimen.



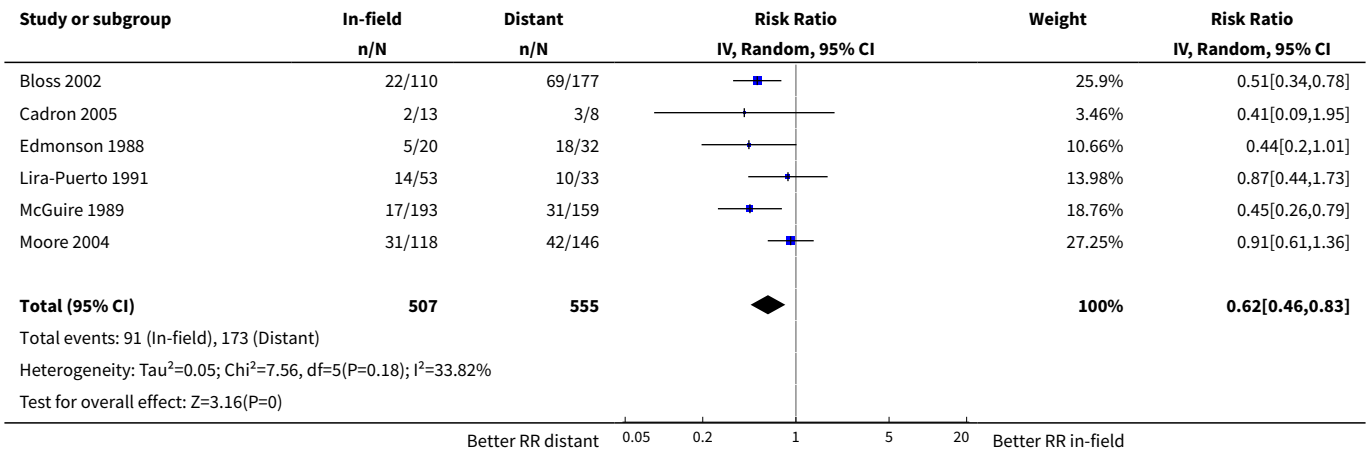
Analysis 1.5. Comparison 1 Response rate (complete response + partial response), Outcome 5 Platinum-containing regimen vs. non-platinum-containing regimen: sensitivity analysis.



Analysis 1.6. Comparison 1 Response rate (complete response + partial response), Outcome 6 Platinum + paclitaxel vs. platinum combination (non-paclitaxel).



Analysis 1.7. Comparison 1 Response rate (complete response + partial response), Outcome 7 In-field vs. out-field recurrence patients with platinum-containing regimen.

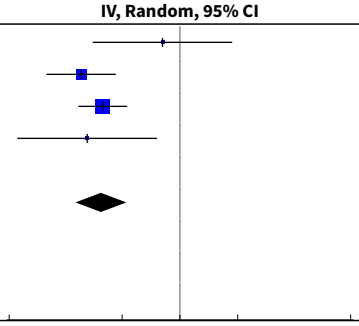


Comparison 2. Toxicity rates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neutropenia G3/G4 in single-agent cisplatin vs. combination	4	1073	Risk Ratio (IV, Random, 95% CI)	0.04 [0.02, 0.12]
2 Thrombocytopenia G3/4 in single-agent cisplatin vs. combination	4	1104	Risk Ratio (IV, Random, 95% CI)	0.16 [0.05, 0.48]
3 Infection G3/4 in single-agent cisplatin vs. combination	2	552	Risk Ratio (IV, Random, 95% CI)	0.42 [0.22, 0.81]
4 Renal dysfunction G3/G4 in single-agent cisplatin vs. combination	3	980	Risk Ratio (IV, Random, 95% CI)	0.81 [0.46, 1.41]
5 Neuropathy G3/G4 in single-agent cisplatin vs. combination	2	552	Risk Ratio (IV, Random, 95% CI)	1.39 [0.45, 4.33]

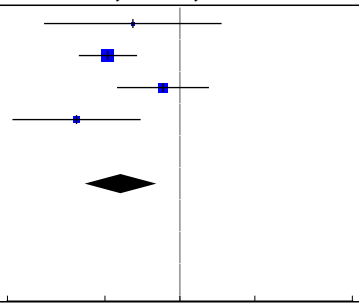
Analysis 2.1. Comparison 2 Toxicity rates, Outcome 1 Neutropenia G3/G4 in single-agent cisplatin vs. combination.

Study or subgroup	Cisplatin n/N	Combination n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Alberts 1987	0/9	8/84		11.38%	0.5[0.03,8.03]
Long 2005	2/146	103/147		31.87%	0.02[0,0.08]
Moore 2004	4/130	86/129		45.39%	0.05[0.02,0.12]
Omura 1997	0/137	42/291		11.35%	0.02[0,0.4]
Total (95% CI)	**422**	**651**		**100%**	**0.04[0.02,0.12]**
Total events: 6 (Cisplatin), 239 (Combination)					
Heterogeneity: Tau^2=0.34; Chi^2=4.4, df=3(P=0.22); I^2=31.89%					
Test for overall effect: Z=6.09(P<0.0001)					

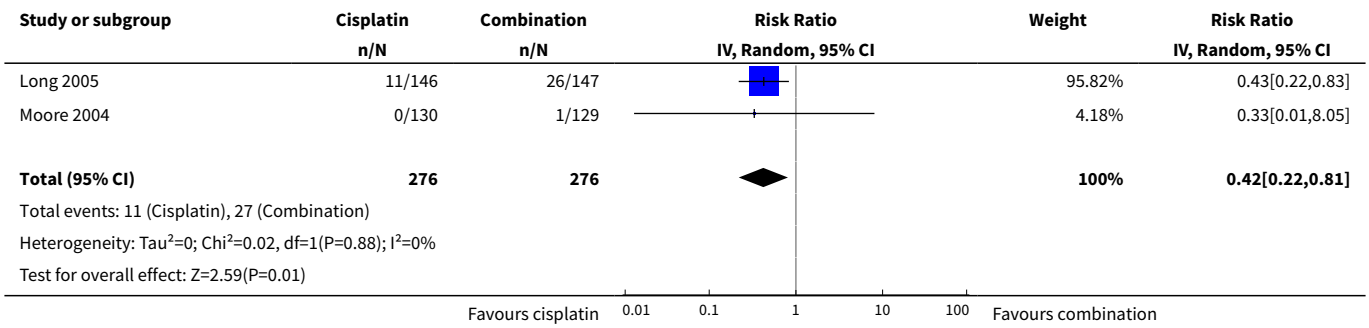


Analysis 2.2. Comparison 2 Toxicity rates, Outcome 2 Thrombocytopenia G3/4 in single-agent cisplatin vs. combination.

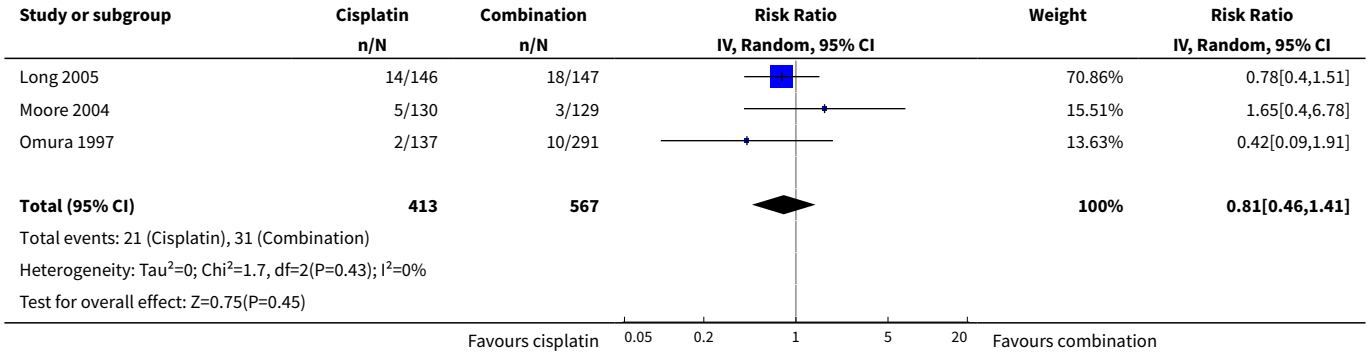
Study or subgroup	Cisplatin n/N	Combination n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Alberts 1987	0/9	22/105		12.49%	0.24[0.02,3.6]
Long 2005	5/146	46/147		39.39%	0.11[0.04,0.27]
Moore 2004	3/130	5/129		28.41%	0.6[0.15,2.44]
Omura 1997	1/140	51/298		19.7%	0.04[0.01,0.3]
Total (95% CI)	**425**	**679**		**100%**	**0.16[0.05,0.48]**
Total events: 9 (Cisplatin), 124 (Combination)					
Heterogeneity: Tau^2=0.59; Chi^2=5.87, df=3(P=0.12); I^2=48.92%					
Test for overall effect: Z=3.25(P=0)					



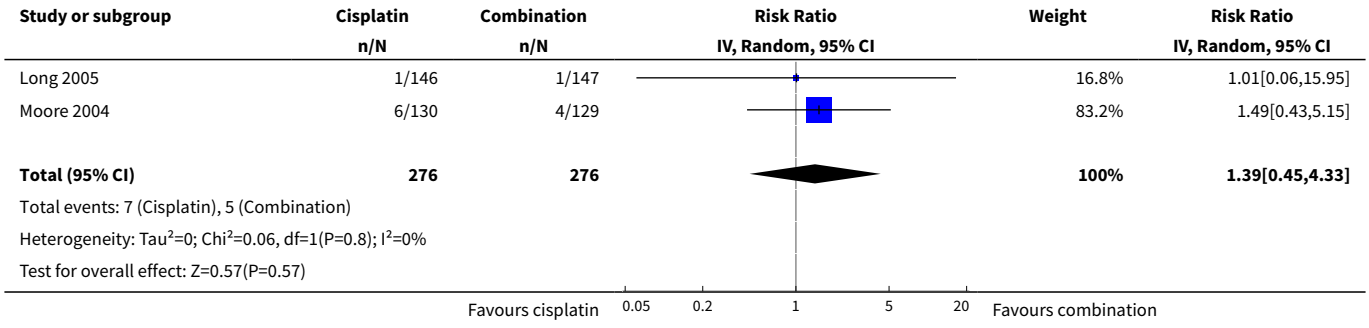
Analysis 2.3. Comparison 2 Toxicity rates, Outcome 3 Infection G3/4 in single-agent cisplatin vs. combination.



Analysis 2.4. Comparison 2 Toxicity rates, Outcome 4 Renal dysfunction G3/G4 in single-agent cisplatin vs. combination.



Analysis 2.5. Comparison 2 Toxicity rates, Outcome 5 Neuropathy G3/G4 in single-agent cisplatin vs. combination.



ADDITIONAL TABLES

Table 1. Comparison of median survival: any single agent vs. any combination

Study	Single agent	Combination

Table 1. Comparison of median survival: any single agent vs. any combination *(Continued)*

	n	Median OS (months)	Median PFS (months)	n	Median OS (months)	Median PFS (months)
Alberts 1987 C vs. MC vs. MVBC	9	17 (C)	nr	54 (MVBC) 51 (MC)	6.9 (MVBC) 7 (MC)	5.4 (MVBC) 7.2 (MC)
Bezwoda 1986 H vs. CMeth	13	4 (H)	nr	37	9 (CMeth)	nr
Cadron 2005 C vs. CIF	11	13 (C)	nr	10	12.3 (CIF)	nr
Greenberg 1977 A vs. AB	9	4 (A)	nr	11	4.3 (AB)	nr
Long 2005 C vs. CTop vs. MVAC	146	6.5 (C)	2.9 (C)	63 (MVAC) 147 (CTop)	9.4 (MVAC) 9.4 (CTop)	4.4 (MVAC) 4.6 (CTop)
Malkasian 1981 A vs. VF	20	5.9 (A)	2.8 (A)	21	9 (VF)	2.9 (VF)
Moore 2004 C vs. CP	134	8.9 (C)	3	130	9.9 (CP)	4.9
Omura 1981 cyclo vs. AFV	30	6.5 (cyclo)	nr	31	7.6 (AFV)	nr
Omura 1997 C vs. CMito vs. CI	140	8 (C)	3.2	147 (CMito) 151 (CI)	7.3 8.3	nr (CMito) 4.6 (CI)
Wallace 1978 A vs. AV vs. Acyclo	63	5.9 (A)	3.3	63 (AV) 52 (Acyclo)	5.5 (AV) 7.3 (Acyclo)	3.4 (AV) 3.9 (Acyclo)

A: adriamycin; AB: adriamycin/bleomycin; Acyclo: adriamycin/cyclophosphamide; AFV: adriamycin/5-fluorouracil/vincristine; AV: adriamycin/vincristine; C: cisplatin; CI: cisplatin/ifosfamide; CIF: cisplatin/ifosfamide/5-fluorouracil; CMeth: cisplatin/methotrexate; CMito: cisplatin/mitolactol; CP: cisplatin/paclitaxel; CTop: cisplatin/topotecan; cyclo: cyclophosphamide; H: hydroxyurea; M: mitomycin; MC: mitomycin/cisplatin; MVAC: methotrexate/vinblastine/doxorubicin/cisplatin; MVBC: mitomycin/vincristine/bleomycin/cisplatin; nr: not reported; OS: overall survival; PFS: progression-free survival; VF: vincristine/5-fluorouracil.

Table 2. Comparison of median survival: cisplatin single agent vs. cisplatin combination

Study	Single-agent cisplatin			Cisplatin combination		
	n	Median OS (months)	Median PFS (months)	n	Median OS (months)	Median PFS (months)
Alberts 1987	9	17	nr	54 (MVBC)	6.9 (MVBC)	5.4 (MVBC)

Table 2. Comparison of median survival: cisplatin single agent vs. cisplatin combination *(Continued)*

C vs. MC vs. MVBC				51 (MC)	7 (MC)	7.2 (MC)
Cadron 2005	11	13	nr	10	12.3	nr
C vs. CIF						
Long 2005	146	6.5	2.9	147	9.4	4.6
C vs. CT						
Moore 2004	134	8.9	3	130	9.9	4.9
C vs. CP						
Omura 1997	140	8	3.2	147 (CMito)	7.3	nr (CMito)
C vs. CMito vs. CI				151 (CI)	8.3	4.6 (CI)

C: cisplatin; CI: cisplatin/ifosfamide; CIF: cisplatin/ifosfamide/5-fluorouracil; CMito: cisplatin/mitolactol; CP: cisplatin/paclitaxel; CT: cisplatin/topotecan; MC: mitomycin/cisplatin; MVBC: mitomycin/vincristine/bleomycin/cisplatin; nr: not reported; OS: overall survival; PFS: progression-free survival.

Table 3. Comparison of median survival: platinum vs. non-platinum-containing regimens

Study	Platinum containing			Non-platinum containing		
	n	Median OS (months)	Median PFS (months)	n	Median OS (months)	Median PFS (months)
Bezwoda 1986	37	11 (CMeth)	nr	13	4 (H)	nr
H vs. CMeth						
Long 2005/Long 2006	146	6.5 (C)	2.9 (C)	63	9.4 (MVAC)	4.4
C vs. CT vs. MVAC	147	9.4 (CT)	4.6 (CT)			
Pfeiffer 1998	12	9.3 (Carbo)	4.6	14	9.6 (Ten)	4.0
Carbo vs. Ten						

C: cisplatin; Carbo: carboplatin; CMeth: cisplatin/methotrexate; CT: cisplatin/topotecan; H: hydroxyurea; MVAC: methotrexate/vinblastine/doxorubicin/cisplatin; nr: not reported; OS: overall survival; PFS: progression-free survival; Ten: teniposide.

Table 4. Comparison of median survival: cisplatin combination including or excluding a taxane

Study	Cisplatin + other			Cisplatin + taxane			P value
	n	Median OS (months)	Median PFS (months)	n	Median OS (months)	Median PFS (months)	
Monk 2008 CV vs. CT vs. CG vs. CP	117 (CV) 118 (CT) 119 (CG)	10-10.3	4.9 (CV) 4.6 (CT) 4.7 (CG)	118 (CP)	12.9	5.8	ns
Mountzios 2009 CI vs. CIP	74 (CI)	13.2	6.3	79 (CIP)	15.4	7.9	0.048 (OS) 0.023 (PFS)

CG: cisplatin/gemcitabine; CI: cisplatin/ifosfamide; CIP: cisplatin/ifosfamide/paclitaxel; CP: cisplatin/paclitaxel; CT: cisplatin/topotecan; CV: cisplatin/vinorelbine; OS: overall survival; PFS: progression-free survival; ns: not significant

Table 5. Comparison of different single-agent cisplatin regimens

Study	Platinum / dose (mg/m2)	n	RR (%)	OS (months)	PFS (months)	TP (months)
Alberts 1987	C 50 d1 q21	9	33	17	nr	nr
Bonomi 1985	C 50 d1 q21	150	20	7.1	nr	3.7
	C 100 d1 q21	166	31.4	7.0		4.6
	C 20 d1-5 q21	128	25	6.1		3.9
Cadron 2005	C 37.5 d1, 2 q28	11	9	13	nr	nr
Lira-Puerto 1991	Carbo 400 d1 q28	48	26	7.5	nr	5.5
	I 300 d1 q 28	41	30	7.6		6
Long 2005	C 50 d1 q21	146	13	6.5	2.9	nr
McGuire 1989	Carbo 400/340 d1 q28	175	15.4	6.5	nr	2.7
	I 270/230 d1 q28	177	10.8	5.6		3.0
Moore 2004	C 50 d1 q21	134	19	8.9	3.0	nr
Omura 1997	C 50 d1 q21	140	17.8	8	nr	nr
Thigpen 1989	C 50 d1 (24 h) q21	163	18	6.4	nr	3.5
	C 50 d1 (1 mg/minute) q21	168	17	6.2		2.9
Pfeiffer 1998	Carbo 400 d1 q28	12	33	9.3	4.6	4

C: cisplatin; Carbo: carboplatin; d: day; h: hour; I: iproplatin; nr: not reported; OS: overall survival; PFS: progression-free survival; RR: risk ratio; TP: time to progression.

Table 6. Comparison of four cisplatin-containing doublets

Regimen	Hazard ratio PFS	Hazard ratio OS
CV vs. CP	1.357	1.147
CG vs. CP	1.394	1.322
CT vs. CP	1.268	1.255

*From Monk 2008. CG: cisplatin/gemcitabine; CP: cisplatin/paclitaxel; CT: cisplatin/topotecan; CV: cisplatin/vinorelbine; OS: overall survival; PFS: progression-free survival.

APPENDICES

Appendix 1. MEDLINE search strategy

1950 to January 2012

1 exp Uterine Cervical Neoplasms/
2 (cervi* adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm* or malignan*)).mp.
3 1 or 2
4 metasta*.mp.
5 recur*.mp.
6 (FIGO and IVB).mp.
7 4 or 5 or 6
8 3 and 7
9 exp Antineoplastic Agents/
10 Antineoplastic Combined Chemotherapy Protocols/
11 chemotherap*.mp.
12 drug therapy.fs.
13 cisplatin.mp.
14 carboplatin.mp.
15 gemcitabine.mp.
16 ifosfamide.mp.
17 paclitaxel.mp.
18 docetaxel.mp.
19 irinotecan.mp.
20 capecitabine.mp.
21 (5-FU or 5-Fluorouracil).mp.
22 topotecan.mp.
23 methotrexate.mp.
24 vinorelbine.mp.
25 doxorubicin.mp.
26 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 8 and 26
28 randomized controlled trial.pt.
29 controlled clinical trial.pt.
30 randomized.ab.
31 placebo.ab.
32 clinical trials as topic.sh.
33 randomly.ab.
34 trial.ti.
35 28 or 29 or 30 or 31 or 32 or 33 or 34
36 27 and 35

key:

mp = title, original title, abstract, name of substance word, subject heading word, unique identifier, fs = floating subheading, pt = publication type, ab = abstract, sh = subject heading, ti = title

Appendix 2. EMBASE search strategy

EMBASE Ovid 1980 to January 2012

1 exp uterine cervix tumor/
2 (cervi* adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm* or malignan*)).mp.
3 1 or 2
4 metasta*.mp.
5 recur*.mp.
6 (FIGO and IVB).mp.
7 4 or 5 or 6
8 exp cancer chemotherapy/
9 exp antineoplastic agent/
10 chemotherap*.mp.
11 dt.fs.
12 cisplatin.mp.
13 carboplatin.mp.
14 gemcitabine.mp.
15 ifosfamide.mp.
16 paclitaxel.mp.
17 docetaxel.mp.

18 irinotecan.mp.
19 capecitabine.mp.
20 (5-FU or 5-Fluorouracil).mp.
21 topotecan.mp.
22 methotrexate.mp.
23 vinorelbine.mp.
24 doxorubicin.mp.
25 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 3 and 7 and 25
27 random*.mp.
28 factorial*.mp.
29 crossover*.mp.
30 cross over*.mp.
31 cross-over*.mp.
32 placebo*.mp.
33 (doubl* adj blind*).mp.
34 (singl* adj blind*).mp.
35 assign*.mp.
36 volunteer*.mp.
37 crossover procedure/
38 double blind procedure/
39 randomized controlled trial/
40 single blind procedure/
41 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42 26 and 41

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

Appendix 3. CENTRAL search strategy

CENTRAL Issue 1, 2012

#1 MeSH descriptor Uterine Cervical Neoplasms explode all trees
#2 cervi* near/5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm* or malignan*)
#3 (#1 OR #2)
#4 metasta*
#5 recur*
#6 FIGO and 1VB
#7 (#4 OR #5 OR #6)
#8 (#3 AND #7)
#9 MeSH descriptor Antineoplastic Agents explode all trees
#10 MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
#11 chemotherap*
#12 Any MeSH descriptor with qualifier: DT
#13 cisplatin
#14 carboplatin
#15 gemcitabine
#16 ifosfamide
#17 paclitaxel
#18 docetaxel
#19 irinotecan
#20 capecitabine
#21 5-FU or 5-Fluorouracil
#22 topotecan
#23 methotrexate
#24 vinorelbine
#25 doxorubicin
#26 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27 (#8 AND #26)

WHAT'S NEW

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2007
Review first published: Issue 10, 2012

Date	Event	Description
27 March 2014	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

KS, JF and MF prepared the protocol, assisted the literature search, analysed the data and wrote the review.

DECLARATIONS OF INTEREST

No declarations of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Gynaecological Cochrane Study Group, UK.

  Helping with running of searches and using Archie.

External sources

- Bristol Royal Infirmary Library, UK.

  Obtaining papers.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- There were no data comparing best supportive care with chemotherapy.
- It was not possible to undertake a meta-analysis of survival data.
- Only three trials reported any QoL data and this was limited.
- Toxicity data was reported using a variety of scales making comparisons difficult to perform.
- A formal meta-analysis could only be performed for response rate and some toxicity outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Age Factors; Antineoplastic Agents [administration & dosage] [adverse effects]; Antineoplastic Combined Chemotherapy Protocols [adverse effects] [*therapeutic use]; Cisplatin [administration & dosage] [adverse effects]; Neoplasm Recurrence, Local [*drug therapy]; Paclitaxel [administration & dosage]; Uterine Cervical Neoplasms [*drug therapy] [pathology]

MeSH check words

Adult; Aged; Female; Humans; Middle Aged; Young Adult