

Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix (Review)

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[Intervention Review]

Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix

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ABSTRACT

Background

The National Cancer Institute (USA) alert in February 1999 stated that concomitant chemoradiotherapy should be considered for all patients with cervical cancer, based on evidence from five randomised controlled trials (RCTs).

Objectives

To review all known RCTs comparing concomitant chemotherapy and radiation therapy with radiotherapy for locally advanced cervical cancer.

Search strategy

We searched electronic databases, trials registers and reference lists of published trial reports and review articles were also searched.

Selection criteria

This review includes RCTs in cervical cancer comparing concomitant chemoradiation with radiotherapy in the experimental arm. Trials allowing further adjuvant chemotherapy or hydroxyurea were included. Trials using radiosensitisers or radioprotectors in the experimental arm were excluded.

Data collection and analysis

Two authors reviewed trials for inclusion and extracted data. For meta-analyses of time-to-event outcomes (survival, progression-free survival), a hazard ratio (HR) was extracted or estimated from trial reports, where possible. Only overall rates of local and distant recurrence were presented in many reports so only odds ratios (OR) of recurrence rates could be calculated, which takes no account of time to recurrence or censoring. Few trials reported acute toxicity adequately, but where possible ORs were calculated for the main types and severities of acute toxicity. The HRs and ORs for individual trials were combined across all trials, using the fixed effect model. Late toxicity was rarely described in sufficient detail so could only be reviewed qualitatively.

Main results

The original review was based on nineteen trials (17 published and two unpublished) including 4580 patients. This update includes twenty four trials (21 published, 3 unpublished) and 4921 patients, although due to patient exclusion and differential reporting 61% to 75% were available for the analyses. The review strongly suggests chemoradiation improves overall survival and progression free survival, whether or not platinum was used with absolute benefits of 10% and 13% respectively. There was, however, statistical heterogeneity for these outcomes. There was some evidence that the effect was greater in trials including a high proportion of stage I and II patients. Chemoradiation also showed significant benefit for local recurrence and a suggestion of a benefit for distant recurrence. Acute haematological and gastrointestinal toxicity was significantly greater in the concomitant chemoradiation group. Late effects of treatment were not well reported and so the impact of chemoradiation on these effects could not be determined adequately. Treatment-related deaths were rare.

Authors' conclusions

Concomitant chemoradiation appears to improve overall survival and progression-free survival in locally advanced cervical cancer. It also appears to reduce local and distant recurrence suggesting concomitant chemotherapy may afford radiosensitisation and systemic cytotoxic effects. Some acute toxicity is increased, but the long-term side effects are still not clear.

PLAIN LANGUAGE SUMMARY

Better survival and reduced distant recurrence rate with combined chemotherapy and radiotherapy for cervical cancer

Evidence suggests giving chemotherapy and radiotherapy together improves overall survival, whether or not cisplatin was used. The effect appeared to be greater in trials including a high proportion of patients with early stage disease. Combined chemotherapy/radiotherapy also delayed tumour recurrence and reduced the risk of re-growth near the original cancer site as well as in other parts of the body. There was an increase in side-effects, principally affecting the blood and bowel, but these generally only lasted a short time. Long-term effects were poorly reported.

BACKGROUND

Cancer of the uterine cervix appears to be preventable if pre-malignant changes are detected and treated. Indeed, cervical screening in parts of Europe and North America seems to have been effective in reducing the incidence of cervical cancer and associated mortality (Cook 1984; Day 1984; Devesa 1995). However, on a global scale, it is the second commonest cancer in women and is the most prevalent malignancy in some low-income countries (Parkin 1999) where the disease frequently presents as large tumours of advanced stage (Pisani 1999). Over 80% of patients reported to FIGO (International Federation of Gynaecological Oncology) with invasive cancer were treated by radiotherapy (Benedet 1998).

Management of microscopic, but invasive disease confined to the cervix (FIGO stage IA) is very effective, with simple hysterectomy for giving greater than 95% five-year survival (Cannistra 1996). Most patients with early disease, however, present as stage IB or IIA, and are treated by radical radiotherapy or radical surgery. These are thought to be equally effective, but there is only one recently published randomised trial to support this equivalence (Landoni 1997). For such patients, five-year survival is between 80% and 90% (Eifel 1997).

Radical hysterectomy (removal of the uterus with draining lymph nodes) has become standard management for the majority of early cervical cancers, but radiation therapy was increasingly employed for bulky FIGO Stage I and II tumours (more than four centimetres), which account for one third of the incidence but half the relapses, as tumour size has been shown to be an important prognostic variable. By targeting the cervix, paracervix and sites of potential regional spread, radiotherapy using external beam irradiation with a vaginal application of a radioactive source to the cervix (brachytherapy) provides a good chance of cure even in advanced disease, with five-year survival rates of 50% to 80% for FIGO stage IIB and 25% to 50% for Stage III (Coia 1990). There are different brachytherapy techniques that apply the radioactive source for short periods of time or for several days.

Cytotoxic chemotherapy, has been shown to give good response rates in patients with good kidney function and no prior radiation therapy. Cisplatin is the most effective single agent (Omura 1996), and has been shown in cell lines to be synergistic with radiotherapy. Mechanisms underlying the interaction between drugs and radiation may include inhibition of potentially lethal or sublethal

damage repair, and increasing radiosensitivity of hypoxic cells (Wallner 1987). It has been widely used prior to surgery or radiotherapy with the aim of reducing tumour volume and facilitating local treatment. It may have the additional benefit of controlling micrometastatic disease. A systematic review and meta-analysis of individual patient data from randomised controlled trials (RCTs) that used cytotoxic chemotherapy prior to radiotherapy, however, found that less intensive chemotherapy given in greater than two weekly cycles may actually reduce metastases-free survival and overall survival. Only more intensive chemotherapy given in less than two weekly cycles may improve metastases rates and survival (NACCCMA 2003).

The early side effects of radiotherapy to the pelvis such as fatigue, bowel and bladder irritation and of chemotherapy such bone marrow suppression and bowel toxicity are well known and usually reversible. However, late chronic effects of radiotherapy on the rectum, urinary tract and vagina, such as fistulae, whilst uncommon, can be devastating for the women concerned. The addition of chemotherapy to radiotherapy may increase the incidence of such late chronic toxicities.

Between 1998 and 2000, the initial results of nine RCTs (Eifel 2004; Keys 1999; Pearcey 2002; Peters 2000; Roberts 2000; Rose 1999; Thomas 1998; Whitney 1999; Wong 1999) were published, six of which showed benefit for concomitant cytotoxic chemotherapy with radiation (chemoradiotherapy) (Eifel 2004; Keys 1999; Peters 2000; Rose 1999; Whitney 1999; Wong 1999). In February 1999, the National Cancer Institute (USA) issued an alert that this management should be considered for all patients with cervical cancer. However, the five trials discussed by the NCI differed in terms of the local and experimental treatments and the selected patient populations. Moreover, they formed only a subset of all trials of concomitant chemotherapy and radiotherapy for cervix cancer.

This systematic review and meta-analysis includes all available studies and examines the effects of chemoradiotherapy in terms of survival, progression-free survival, local and distant control, and acute and late toxicity. This is the only known systematic review of all concomitant chemoradiation trials and updates the original Cochrane review by the same authors first published in 2001.

OBJECTIVES

This systematic review aims to compare the effectiveness of concomitant chemotherapy and radiation therapy with radiotherapy in the treatment of locally advanced carcinoma of the cervix.

METHODS

Criteria for considering studies for this review

Types of studies

The review was restricted to:

- RCTs in cancer of the uterine cervix
- Trials accruing patients from January 1980

Types of participants

Patients with locally advanced cancer of the uterine cervix (FIGO stage IB-IVA).

Types of interventions

Inclusion criteria were:

- Trials comparing concomitant cytotoxic chemotherapy plus radiotherapy (with or without surgery)* with radiotherapy (with or without surgery)* alone
- In the experimental arm, further adjuvant chemotherapy in addition to concomitant chemotherapy was an allowable option

*For the purposes of this review, hydroxyurea was considered an inactive agent and therefore allowable with local treatment. The efficacy of hydroxyurea has since been considered in two separate reviews (Symonds 2003; Symonds 2004). The authors found no evidence to support the use of hydroxyurea in addition to radiotherapy in the routine treatment of cervix cancer.

Exclusion criteria were:

- Trials that used radiosensitisers or radioprotectors in the experimental arm
- Cytotoxic chemotherapy is defined as a drug given with the intent of producing tumour regression as defined by World Health Organisation (WHO) criteria.
- A radiosensitiser is defined as a drug that has no cytotoxic activity at the dose and schedule employed, but when combined with ionising radiation produces increased cell killing.
- A radiation protector is a drug which when given with ionising radiation reduces the effect of that radiation.

Types of outcome measures

Survival and progression-free survival were considered the primary endpoints, while rates of local and distant recurrence were analysed as secondary endpoints. We collected and analysed additional data on the type and severity of acute and late toxicity.

Search methods for identification of studies

There is evidence that trials with statistically significant results are more likely to be published than those with inconclusive or negative results (Dickersin 1990; Dickersin 1992; Easterbrook 1991). To avoid publication bias, both published and unpublished trials were included in the meta-analysis. To identify as many relevant trials as possible, systematic searches of a number of sources of reports of trials including ongoing trials were carried out.

Electronic searches

The Cochrane Gynaecological Cancer Collaborative Review Group's specialised register of trials

MEDLINE (date of last search May 2004)

CancerLit (date of last search 2003. NB Cancerlit is no longer updated)

The Cochrane Central Register of Controlled Trials CENTRAL (2004, Issue 2)

LILACS (date of last search June 2004)

The following trial registers were searched for open and closed trials:

Physicians Data Query Protocols (Open and Closed Protocols) (date of last search June 2004)

United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) Register of Cancer Trials (Open and Closed Protocols) (date of last search June 2004)

MetaRegister (June 2004)

For MEDLINE search strategy see Appendix 1.

Searching other resources

The references lists of all published trial reports and review articles were searched for further trial reports.

Data collection and analysis

Data extraction and management

At least two authors reviewed potential trials for inclusion and also extracted data. Where there was disagreement this was settled by discussion, including a third party where necessary. For each trial, the method of randomisation and allocation concealment was recorded, as was the level of follow-up. In addition, data on surgery, radiotherapy, chemotherapy and patient characteristics were collected. This included the dose, schedule and treatment time of both radiotherapy and chemotherapy. Updated data, as yet unpublished, were obtained in two cases from the trial investigators.

Participants

For each trial, data on the number of patients randomised, analysed and excluded from the investigator's analyses was extracted.

The distribution of patients by age, stage, histology, grade and performance status was also assessed. A significant proportion of the studies restricted patients entered to those with negative para-aortic nodes assessed by imaging or surgical techniques.

Interventions

Data on whether surgery was performed and the type of surgery was collected. Details of dose and fractionation of external beam radiotherapy and details of the brachytherapy dose, insertions and dose rate were collected. Data on the proportion of patients in the research treatment and control arms who completed radiotherapy as planned, did not start radiotherapy, and who experienced delay was also extracted. The mode and sequence of delivery of chemotherapy, as well as the dose, number of cycles and cycle length for each drug was obtained.

Outcomes

Survival and progression-free survival were considered the primary outcomes, while patterns of local and distant recurrence, and acute and late toxicity, were secondary outcomes. For meta-analyses of the time-to-event outcomes (survival and progression-free survival), the most appropriate statistic is the hazard ratio (HR). If provided in a trial report, the HR and associated variances were used directly in the meta-analysis. Alternatively, using the methods described in Parmar 1998 they were estimated indirectly from other summary statistics (95% confidence intervals {CIs}, P-values, total number of events) or from data extracted from published Kaplan-Meier curves (Parmar 1998). In the latter method, the numbers at risk are adjusted (reduced), where appropriate, to allow for immature follow-up (Parmar 1998). Where it was feasible, a number of methods were used to indirectly estimate the trial HR, to check its reliability. The estimated log HR and variance were then combined across all trials using the fixed effect model to give a pooled HR (Yusuf 1985). This represents the overall risk of an event on concomitant chemotherapy and radiotherapy versus control.

Only the overall rates of local and distant recurrence were presented in many of the published reports rather than a time-to-event analysis of these events. Therefore, only an odds ratio (OR) of the rates of recurrence could be calculated, with no account being taken of the time to recurrence or any censoring. Figures for recurrence were extracted from the text and the OR was calculated from the total number of patients and the observed number of patients with recurrences on each arm. The ORs for individual trials were combined across all trials, using the fixed effect model (Yusuf 1985). These ORs indicate the odds of a local or distant recurrence in the concomitant chemotherapy and radiotherapy arm versus the control arm. For three studies (Hernandez 1991; Rose 1999; Wong 1989) with multiple arms, the treatment arms were combined and compared with the control arm.

Absolute effects on survival, disease-free survival and recurrence rates were calculated from estimated the proportion event-free in

the control group and the HR or OR for the particular outcome ($\exp[\ln(\text{proportion event free}) \times \text{HR}]$).

The scales, grades and sites of any acute and late toxicity information were extracted from the text. Some trials reported acute toxicity in detail, with several different scales of measurement being used. Information was frequently already combined by site or grade. Extracted data were therefore grouped as mild-moderate toxicity (grades I & II combined) and severe toxicity (grades III & IV combined) for haematological (categorised as white cell count, haemoglobin level, platelet count or grouped), gastrointestinal, genitourinary, skin or neurological for each trial. In this update, it was also possible to include nausea and vomiting. Where more than one type of toxicity was reported in a category (for example nausea reported separately from vomiting), the most frequent was used. Where percentages were supplied, they were used to estimate the numbers of events on each arm. For each trial, ORs were calculated using the total number of toxic events for each type and severity category. These ORs were combined across all trials, using the fixed effect model (Yusuf 1985). These ORs indicate the odds of a mild-moderate or severe toxic event for each type of toxicity in the concomitant chemotherapy and radiotherapy arm versus the control arm.

Late toxicity was mentioned in 12 studies (Chen 1997; Eifel 2004; Fernandez 1995; Leborgne 2000; Lorvidhaya 2003; Onishi 1999; Pearcey 2002; Singh 2003; Thomas 1998; Tseng 1997; Whitney 1999; Wong 1999), but generally was reported with insufficient detail and so was only reviewed qualitatively.

Assessment of heterogeneity

Chi-square tests for heterogeneity and the I^2 statistic were used to test for statistical heterogeneity and inconsistency in results across all trials, irrespective of whether HRs or ORs were calculated. The overall and within group chi-square tests for heterogeneity were also used to assess the consistency of effect between different subsets of trials ($Q_{\text{between}} = Q_{\text{overall}} - Q_{\text{within}}$) and are referred to as chi-square tests for interaction. These tests were aimed primarily at detecting differences in size of effect, rather than direction. Thus, to explore variation in the chemotherapy treatments used between trials, which can introduce statistical heterogeneity, supplementary analyses were performed on pre-specified trial groups. These groupings were by chemotherapy regimen (cisplatin-based versus non-cisplatin based), the chemotherapy scheduling (entirely concomitant versus concomitant plus sequential), the chemotherapy frequency (platinum once per week versus longer cycle times) and the use of hydroxyurea in the control arm (no hydroxyurea versus hydroxyurea in the control arm).

In all tests of significance a two-sided p-value is given.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Searches identified 29 randomised trials that were potentially eligible for inclusion. Five of these were subsequently found to be ineligible, one because it was a review of other studies (Lukas 1998), one because it was confounded by the use of immunotherapy in the treatment arm (Vishnevskaya 1999), one because the radiotherapy on the control arm differed to that on the treatment arm (Mohan Segal 2002) and the fourth was found to be a non-randomised controlled trial (Li 1997). One trial, reported in Polish, was found to be trial of radiotherapy versus combined surgery and radiotherapy (Keitlinska 1984). Therefore, this update is based on 24 eligible trials (see [Characteristics of included studies](#)) comprising a total of 4921 randomised patients of which 301 were excluded from analysis in the published papers or abstracts. No useful data to estimate the effect on the outcomes of interest could be obtained for a further seven trials (638 patients), five of which were published (Bulnes 1986; Fernandez 1995; Kantardzic 2004; Lira Puerto 1990; Singh 1985) and two unpublished (Lanciano 1998; Pras 2000). Sixty patients from another trial were excluded from the meta-analysis on account of the concurrent use of hyperthermia (Chen 1997), as well as 221 from a further trial where maintenance chemotherapy was given in the control arm (Lorvidhaya 2003). This left potentially 3702 patients (75%) who could be included in the analysis. However, the differential availability of data to generate HRs and ORs for the various outcomes restricted the analyses to a maximum of 3578 of these 3702 patients (97%) for survival and progression-free survival, and 3694 (99%) and 3006 (81%) for rates of local and distant recurrence respectively. Substantially less data were available for acute and particularly late toxicity.

The RCTs in this review were carried out in the 1980s and 1990s, and the number of randomised patients ranged from 33 to 705. The trials used markedly different designs and a variety of chemotherapy regimens and radiotherapy schedules. Fifteen trials used concomitant cisplatin-based chemoradiation. Nine of these trials used radiation alone in the control arm and three included surgery in both the chemoradiation and the control arms. Two trials compared radiation plus hydroxyurea with cisplatin-based chemoradiation alone (Whitney 1999) and cisplatin-based chemoradiation with or without hydroxyurea (Rose 1999). One further trial of cisplatin-based chemoradiotherapy used different radiotherapy on the control and treatment arms (Eifel 2004). Eight trials compared radiation alone with non-cisplatin based chemoradiation, using 5-fluorouracil, mitomycin-C, bleomycin, epirubicin, adriamycin and cyclophosphamide, either as single agents or in combined regimens. Two of these trials gave further adjuvant chemotherapy in the chemoradiation arm (Lorvidhaya 2003; Wong 1999). One unpublished study (Lanciano 1998) which had three treatment arms compared radiation alone with cisplatin-based chemoradiation and non-cisplatin based chemoradiation.

The studies included patients with FIGO stages IB to IVA. One large trial (Keys 1999) comprised exclusively bulky Stage IB patients (more than or equal to four centimetres). Five further trials included between 3% and 27% bulky stage IB patients (Eifel 2004; Pearcey 2002; Pras 2000; Roberts 2000; Thomas 1998) whilst four other trials included patients with stage I or Ib tumours but did not specify the tumour size (Leborgne 2000; Peters 2000; Singh 1985; Wong 1999). Further details are given in the Characteristics of included studies.

Searches for phase I and II studies of concomitant chemotherapy and radiation therapy have not been updated in this version of the review. Forty-five phase I and II studies were identified in the previous version and in general, the numbers of patients were small, but two larger studies have been conducted as feasibility studies prior to phase III protocols (Malfetano 1993; Stehman 1997) and useful toxicity data have been provided. These three trials and seven others that included more than 10 patients are summarised in Table 1.

Table 1. Concomitant chemotherapy & radiotherapy - Phase I & II studies of >10 patients

| Author | Regime | Stage | Number of Patients | Toxicity: early/late | Response | Comments |
|-------------|--|------------------|--------------------|---|--|---------------------------|
| Clarke 1994 | 46Gy EBRT +3xICRT 30Gy + Cis 30/weekly | Locally advanced | 43 | 46% late G3/4 14% G3/4 rectal toxicities | 13/13 survivors 72% survivors | May be same Group of Px's |
| Gerson 1993 | Carb40,50,60,70+ To 70-80Gy Carb40,50,60,70+ To 70-80Gy | IIB-IIIB | 19 | G1 diarrhoea | 10px's had surgery,7 CR | |
| Grisby 1996 | 3xCis50+5FU750/ or Cis75+5FU 1000/dx4days +EBRT+2xICRT | IIA-IVB | 67 | G4 23%,3 recto-vaginal fistulae,1 vesicovaginal | 5 yr surv. IB(bulky)/IIB 70%, IIIA-IVA 25%, 39% for recurrent cervical ca. | |
| Grisby 1998 | b.d.EBRT+2xICRT Cis 75 D1&22 | I-IV | 29 | G3/4 chemo tox.48%,28% RT tox.G3/4,21%,28% | 59%alive 1yr, 49% 2 yrs | Hyper-fractionation |

Table 1. Concomitant chemotherapy & radiotherapy - Phase I & II studies of >10 patients (Continued)

| | | | | | | |
|--------------|--|-------------------------|----|--|----------------------------------|--|
| John 1996 | EBRT+ICRT to 70-75Gy to point A+ 1x5FU&MitC+ 1x5FU+Cis | IIB-IVA | 60 | G3/4 RT tox. 15%,3% G3/4 chemo tox. 9%,2% | 5yr surv. IIB 48%,IVA 39% | |
| Ngyuen 1991 | MitC 10, D1&30,+ 5FU 1000 D1-4 & D30-33,+ 50Gy EBRT + ICRT | IB-IVA | 38 | | | ICRT dose unspecified |
| Souhami 1993 | 46Gy EBRT +3xICRT 30Gy +Cis30 weekly | IIA-IVA | 50 | 20% G3/4 rectal tox | 65% survival | 3x10Gy IC insertions 3x10Gy IC insertions |
| Verma 1994 | Carb 300 x4weekly to Carb 450 IA PostDXT | Recurrent intrapelvic d | 12 | 1 death, haem tox. 2x G3 paraesthesia | No objective response | Not useful |
| Wadler 1993 | Cis20x5+EBRT+V | IB to IIIB | 20 | G3/4 nephrotoxic,haem,infecti Vomiting, neurotoxicity,hypocalcaemia | 15/19 alive at 13 months. 9CR | Radio-protector: Amifostine |

Risk of bias in included studies

Although all trials were described as randomised trials or described random assignment of patients, there was only sufficient detail in reports to say that the randomisation procedure was adequate for seven of the 24 trials. Adequacy of concealment could not be assessed for any of the trials. Seven trials excluded between 1 and 5% of randomised patients and six trials excluded between 6 and 24% of patients, mainly because they were found to be ineligible or treatment was not given as per protocol and less frequently, because of short follow-up, missing data or patients being lost to follow-up. Thus, the analyses of these trials were not, strictly speaking, on an intention-to-treat basis and may be prone to bias. Lack of detailed data on survival and progression-free survival meant that the data included in the review had to be estimated in some instances or that no data could be included.

Effects of interventions

Survival

Sufficient data were available in 13 trials to obtain a HR for survival directly (Keys 1999; Leborgne 2000; Pearcey 2002; Peters 2000; Rose 1999; Whitney 1999) or indirectly via the p-value and number of events (Tseng 1997) or Kaplan-Meier curves (Hernandez 1991; Lorvidhaya 2003; Onishi 1999; Roberts 2000; Wong 1999). Together, these trials demonstrated a highly significant overall survival benefit for chemoradiation. The HR of 0.69 across all trials (95% CI = 0.61 to 0.77, $p < 0.00001$) represents a 31% reduction in the risk of death or an absolute improvement in survival of 10% (95% CI = 7 to 13%) from 60% to 70%. There is evidence of a high level of statistical heterogeneity associated with these results (heterogeneity chi-square = 27.71, degrees of freedom (df) = 12, $p = 0.006$, $I^2 = 56.7\%$). However, there is no good

reason to single out any particular trial on the basis of design. None of the planned subset analyses by types of treatment entirely explained the observed heterogeneity. There was evidence of an effect in both the trials using platinum-based chemotherapy (HR = 0.68 95% CI = 0.60 to 0.78, $p < 0.00001$) and in the group of trials using other drugs (HR = 0.72, 95%CI = 0.56 to 0.92, $P = 0.008$), although heterogeneity was confined to the platinum group. There was no evidence that the effect of chemoradiation differed between the two groups (interaction chi-square = 0.13, $p = 0.72$). Similarly, there was no suggestion that the scheduling of chemotherapy (interaction chi-square = 0.99, $p = 0.32$), the use of hydroxyurea in the control arm (interaction chi-square = 0.15, $p = 0.70$), or the frequency of chemotherapy (interaction chi-square = 0.30, $p = 0.58$) altered the effect of chemoradiation. An exploratory, post hoc analysis by the proportion of early stage patients included in the trials ($> = 70\%$ stage I and II versus $< 70\%$ stage I and II), suggested that the effect was larger in the trials randomising a higher proportion of stage I and II patients (interaction chi-square = 7.54 $p = 0.006$). However, the interpretation of this result is complicated by the remaining heterogeneity in the trials of more advanced stage patients ($p = 0.02$).

Progression-free survival

Data from 14 trials were available to directly (Eifel 2004; Keys 1999; Leborgne 2000; Peters 2000; Rose 1999; Whitney 1999), or indirectly (via the Kaplan-Meier curve, Lorvidhaya 2003; Onishi 1999; Pearcey 2002; Roberts 2000; Thomas 1998; Tseng 1997; Wong 1989; Wong 1999) calculate a HR for progression-free survival. Again the overall results are strongly in favour of chemoradiotherapy with a HR of 0.66 (95% CI=0.59-0.73). This translates into an absolute improvement in progression-free survival of 13% (95% CI =10-16%) from 50% to 63%. However, there is a wide range in the size of the effect seen in individual trials (heterogeneity chi-square = 29.17, $df = 13$, $p = 0.006$, $I^2 = 55.4\%$) with HRs from 0.49 to 1.98, which corresponds to between a 25% absolute reduction in survival to a 21% absolute increase in survival. Please note that the plots for survival and progression free survival are HR plots, although labelled as (Peto) OR plots because this is the default mode of the IPD outcome type in RevMan Analysis.

Recurrence

The rate of local recurrence based on 14 trials was significantly reduced by the use of chemoradiation (OR = 0.59, 95% CI = 0.50-0.69, $p < 0.00001$). However, there was statistical heterogeneity across trials (heterogeneity chi-square = 27.15, $df=13$, $p = 0.01$, $I^2 = 52.1\%$), with a wide range of individual effects being recorded. This could not be explained by whether trials used platinum or non-platinum based chemotherapy (interaction chi-square = 0.34, $p = 0.56$).

Rates of distant recurrence alone were available from 13 trials. There was a trend towards a reduction in the occurrence of distant

metastases with chemoradiation overall (OR =0.81, 95% CI 0.65 to 1.01, $p = 0.06$) and separately, in each of the platinum (OR = 0.84, 95% CI 0.67 to 1.06, $p = 0.14$) and non-platinum groups (OR = 0.59, 95% CI 0.31 to 1.14, $p = 0.12$), without any evidence of statistical heterogeneity. Rates of distant recurrence including combined local and distant recurrence were available for another large trial. When this trial is included, there is clearer evidence of an impact of chemoradiation for both the platinum (OR=0.74, 95% CI 0.6 to 0.91, $p = 0.004$) and the non-platinum (OR = 0.59, 95%CI 0.43 to 0.81, $p = 0.001$) trials.

Toxicity

Acute toxicity was described in detail in ten published trials (Eifel 2004; Keys 1999; Pearcey 2002; Peters 2000; Roberts 2000; Rose 1999; Tseng 1997; Whitney 1999; Wong 1989; Wong 1999). For seven other trials, five published (Chen 1997; Lira Puerto 1990; Lorvidhaya 2003; Onishi 1999; Singh 2003) and two unpublished (Leborgne 2000; Pras 2000), some information was available. Across all of the trials, the reported number of deaths attributable to acute treatment-related toxicity was seven. Six of these occurred in the chemoradiation arm; one because of neutropenic sepsis and five due to unspecified treatment-related causes. Four deaths were from one unpublished trial, following which the dose of chemotherapy was modified (Leborgne 2000). One additional patient was reported to have died of complications, but it is not clear which treatment they were allocated (Thomas 1998).

There were statistically significant increases in the rate of grade 1 to 2 haematological (unspecified), white blood cell, haemoglobin, platelet, gastrointestinal, skin and neurological toxicities with chemoradiation and grade 1 to 2 nausea and vomiting. These ranged from a 29% increase in the risk of white blood cell toxicity (OR = 1.29, 95% CI 1.08 to 1.53, $p = 0.004$) up to a greater than three-fold increase in the risk of nausea and vomiting (OR = 3.09, 95% CI 2.27 to 4.21 $p < 0.00001$) on the chemoradiation arm compared with that on control. Rates of grade 3 to 4 haematological, white blood cell, haemoglobin, platelet and gastrointestinal toxicity and nausea and vomiting toxicity were also significantly increased with chemoradiation. These ranged from around a two-fold increase in gastrointestinal toxicity (OR = 1.98 95% CI 1.49 to 2.63 $p < 0.00001$) up to more than four times the risk of nausea and vomiting (OR = 4.09 95% CI 2.34 to 7.16 $p < 0.00001$).

The statistical heterogeneity and inconsistency across trials was high for the analyses of haematological, white blood cell, haemoglobin (grade 1 to 2 only), platelet (grade 1 to 2 only), gastrointestinal, skin (grade 3 to 4 only) and neurological toxicity and nausea and vomiting (grade 1 to 2 only). This is not too surprising given the variation in the drugs, doses and schedules of chemotherapy and range of radiotherapy doses and schedules across trials.

In this update, we conducted additional post hoc sensitivity analyses of the acute toxicity categories, excluding the two trials that had used hydroxyurea on the control arm (Rose 1999; Whitney 1999),

since this cytotoxic agent may impact on the level of toxicity on that arm. Clearly this means that there are fewer trials and fewer events on which to base the estimates. There was little impact of excluding these trials on most of the acute toxicity results. However, exclusion of these trials did lead to greater differences in the risk of grade 1 to 2 (OR = 4.57 95% CI 3.08 to 6.79 $p < 0.00001$) and grade 3 to 4 (OR = 8.97 95% CI 6.11 to 13.15 $p < 0.00001$) haematological toxicity; grade 1 to 2 (OR = 2.40 95% CI 1.91 to 3.00 $p < 0.00001$) and grade 3 to 4 (OR = 6.32 95% CI 4.39 to 9.07 $p < 0.00001$) white blood cell toxicity; grade 3 to 4 gastrointestinal toxicity (OR = 2.77 95% CI 1.90 to 4.02 $p < 0.00001$) and grade 1 to 2 neurological toxicity (OR = 6.04 95% CI 2.35 to 15.55 $p = 0.0002$) between the chemoradiation and control arms. This suggests that hydroxyurea does indeed contribute toxicity on the control arm.

Information on late toxicity was provided for 12 of the 24 trials. The two trials that provided a definition of late toxicity defined it as toxicity that occurred or persisted 3 months (90 days) after the start of radiation treatment. The data provided was used to calculate overall rates of late effects for each of the 12 trials (Table 2). Details of these late events were not provided for all trials, however the most commonly reported late toxicities affected either the gastrointestinal or genitourinary systems (Table 2). In addition, eight deaths were reported due to late toxic effects; four in the control arm (1 radiotherapy-related fistula and 3 bowel / rectum late events) and four in the chemoradiation arm (1 unspecified; 1 small bowel obstruction and perforation; 1 late GI event and 1 bilateral ureteral obstruction with fibrosis and renal failure).

Six of the phase I/II studies provided detailed toxicity data (Table 1). The incidence of serious side effects was variable, with one study reporting acute grade III and IV toxicity in 49% of patients. Chronic toxicity was also common with a fistula rate of 11% in one trial (Grigsby 1996).

Table 2. Late toxicity rates across trials

| Trial | Scale used | Treatment Arm | Control Arm | Comments |
|---------|------------------|----------------------------------|----------------------------------|------------------------------------|
| Whitney | GOG | 16.2% | 16.5% | Grades 3-4 reported. Types unknown |
| Tseng | GOG | 23.3% (GU: 3, GI: 8, Fistula: 3) | 12.9% (GU: 2, GI: 4, Fistula: 2) | Grades not supplied |
| Morris | RTOG/EORTC LRMSC | 13% (GU: 5, GI: 9, Fistula: 10) | 12% (GU: 3, GI: 5, Fistula: 14) | Grades 3-4 reported |

Table 2. Late toxicity rates across trials (Continued)

| | | | | |
|---|----------|--|--|---|
| Hongwei | Unknown | 55% (GU: 1, GI: 10) | 38% (GU: 1, GI: 7) | Grade not supplied |
| Pearcey | NCIC CTC | 20% (GU: 13, GI: 5, Haematological: 5) | 18% (GU: 8, GI: 11, Haematological: 1) | Grades 3-4 reported |
| Thomas | Unknown | 12% | 12% | Grades not supplied. Types unknown |
| Leborgne | WHO | 1% | 1% | Grade 3 reported. Types unknown |
| Lorvidhaya | RTOG | 4.5%* | 3.7% | Grades 3-4 reported. Types unknown |
| Wong 1999 | WHO | 32% (GU: 3, GI: 25, CV: 7) | 51% (GU: 4, GI : 52, CV: 0) | Grade only supplied for GI toxicity (all Grade 1-2 proctitis) |
| Fernandez | RTOG | 10% | 12% | Grade 3 |
| Singh 2003 | Unknown | 21% (GU: 2, GI: 7) | 20% (GU: 2, GI: 6) | Grades 1-2 |
| Onishi | RTOG | 89% (GI: 16) | 20% (GI: 3) | Grades 3-4 reported |
| *Average event rate for the two treatment arms (3.1%, 5.8%) | | | | |
| GU - genitourinary; GI - gastrointestinal; CV - cardiovascular | | | | |
| Event rates are shown as percentages with the numbers of events for each type of late toxicity shown per arm. | | | | |

DISCUSSION

The analysed data are consistent with a benefit in progression-free and overall survival with concomitant chemotherapy and radiotherapy. Progression-free survival was significantly improved for both the platinum and non-platinum group and overall survival for the platinum group. In addition to the expected improvement in local control, there was a suggested reduction in the rate of dis-

tant metastases in both patients treated with platinum and non-platinum based chemotherapy, an effect that was not apparent in the individual trials. This reduction was achieved with a relatively short course of chemotherapy combined with local treatment and a similar effect has been suggested with short course intense chemotherapy given before radiotherapy (NACCCMA 2003). The effect on metastases is somewhat less persuasive in this update, which included more trials and patients, than in the original version of the review. Of particular note is that the rate of metastases in the update of the RTOG trial (Eifel 2004l) differs considerably

from that in the original report (11% versus 14% on the chemoradiation arm and 15% versus 33% on control arm) and may reflect typographical or other errors in the original report. In addition, the update of the Lorvidhaya trial (Lorvidhaya 2003) did not provide distant metastases only rates and so could not be included in the primary analysis of this outcome.

Heterogeneity is evident in the results for survival, progression-free survival and local recurrence. In the platinum group, there are certainly broad differences in trial design, particularly with regard to type and timing of both local and systemic treatments. Furthermore, stringent eligibility criteria in the five studies comprising the NCI alert excluded patients with para-aortic node involvement, leading to a highly selected patient group. The other trials selected patients primarily on the basis of stage, and may have included patients with larger tumour volumes. Nevertheless, with the data available, we have not been able to adequately explain the heterogeneity on the basis of these trial or patient characteristics. Also, not all data from all trials were available for this analysis, trials did not always report on data from all randomised patients, the level of follow-up was variable, and the analyses of the various outcomes are based on different sets of trials. Therefore, while this systematic review considers more of the randomised evidence than any previous article, there may still be sources of bias. A meta-analysis of individual patient data would be required to explain the observed heterogeneity and would enable a more consistent definition of progression-free survival across trials, a proper time-to-event analysis of local and distant recurrence and a more reliable estimate of effect in patient subgroups, as well as better attribution of toxicity. Such a systematic review and meta-analysis of individual patient data is being conducted by two of the authors (CV and JT) as part of the Meta-analysis Group of the MRC Clinical Trials Unit London. Results of this meta-analysis will supersede future updates of this Cochrane review and should be available in 2006.

In the present review, many patients had Stage I and II tumours, but most of the Stage IB patients had other adverse prognostic features, with tumours greater than five centimetres in diameter (Keys 1999), or positive pelvic lymph nodes (Peters 2000). For most of the trials, patients with Stage IA1 or IA2 disease were not included, and radical surgery remains the established treatment for the majority of this group, and the majority of Stage IB tumours of diameter less than four centimetres. An editorial in 1999 (Thomas 1999) reviewed the available data from the five studies comprising the NCI alert (Eifel 2004; Keys 1999; Peters 2000; Rose 1999; Whitney 1999). One further study in which subset analysis did show a five year disease free survival benefit in stages IB, IIA and IIB was discussed (Thomas 1998). While showing an overall reduction in the risk of death with chemoradiotherapy, Thomas suggested caution in extrapolation of the results to advanced stages. One trial has since been reported with updated follow-up (Eifel 2004) and a significant progression-free survival benefit is evident for stages 1B to II and III to IVA and significant survival benefit was seen

for stages IB to II with trend toward improved survival in the later stages. The authors comment that their study was not powered for formal subgroup analyses. The exploratory analysis presented here demonstrates lesser benefit and more heterogeneity in those studies with a high proportion of advanced stage. Therefore, the overall conclusions should take into account that there are both selected and unselected populations of women in the trials on which this review is based. The overall benefit demonstrated in this meta-analysis suggests these results may be cautiously extrapolated to all women with locally advanced disease, which we would define as those with adverse factors such as large tumour size and pelvic lymph node involvement, but absence of extra-pelvic involvement and residual disease after surgery.

Combined chemoradiotherapy seems to offer substantial benefit for women with cervical cancer. However, acute toxicity, predominantly haematological and gastrointestinal, was increased with chemoradiation. Chemotherapy toxicity may be harmful if this leads to prolongation of radiotherapy, as control of local disease has been shown to fall by up to 1% per day if treatment is prolonged beyond seven weeks (Perez 1995). Acute side effects are generally of short duration and resolve with medical management, while the late complications of radiotherapy lead to damage which can be difficult to reverse, and may permanently impair quality of life. Details of late morbidity are more poorly documented, but with the exception of one trial (Leborgne 2000) where the regimen has now been modified, there is insufficient evidence to say whether it increased with combined therapy. Data on late toxicity have matured and more trials have become available. The highest rate of grade 3 to 4 toxicity (58%) was in one trial of 33 patients treated with interarterial chemotherapy (Onishi 1999). The treatment arm in this trial had a late grade 3 to 4 toxicity rate of 89%. For the remaining 7 trials that reported serious late effects, the overall rates ranged from 1% to 19%. This probably reflects differences in the radiotherapy dose and scheduling between the trials.

This review may give some clues to the mechanism of interaction of combined treatment. The most striking finding in this meta-analysis is the highly significant reduction in distant metastases in the combined therapy group. This suggests the drugs at the doses and schedules employed are acting as systemic cytotoxic agents. By inference, the observed increase in local control may be due to independent cell killing by radiation and drug(s). Some agents, particularly cisplatin and mitomycin C may be synergistic with radiation leading to supra-additive effects, but we are unable to quantify the relative degree of cytotoxicity of either modality.

AUTHORS' CONCLUSIONS

Implications for practice

The majority of these studies employed some form of patient selection, but in a trial-level analysis of published (or other) summary data, it is difficult to distinguish any interaction between the treatment effect and patient characteristics. In some trials, only patients with negative para-aortic nodes were included, and less frequently there were exclusions based on disease volume or stage. This degree of selection is likely to have contributed to the long duration of accrual of many of the studies, and an accurate assessment of their effect would require an individual patient meta-analysis. However, based on the data analysed, a potential absolute survival benefit of 12% is attributable to the use of chemoradiotherapy, a figure which could not have been appreciated from the individual phase II or III trial data. Despite the above limitations, we believe that the weight of evidence favours the use of chemoradiotherapy and, because the results are derived from trials of different populations, using different treatment regimens and supportive care facilities, they are potentially generalisable. Application to the developing world requires the regimen to be cheap, and simple to administer, and we suggest that weekly cisplatin may fit these criteria.

Implications for research

Issues to be considered for future research include exploration of the sources of heterogeneity and bias between trials; whether early stage patients benefit more than later stage, the impact of radiation dose and treatment duration, and the addition of other cytotoxics to cisplatin and drug scheduling. Haemoglobin levels before and during treatment may also influence outcome (Grogan 1999). In future trials, more information on quality of life and toxicity is imperative if we are to place the results in a proper context.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bulnes 1986

| | | |
|-------------------------|---|--------------------|
| Methods | RCT, ? - 1983 | |
| Participants | 100 randomised (24 excluded). 37% stage I & II. Unknown if those with involved nodes were not eligible. | |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + concomitant Adriamycin (50mg IV days 1, 30 and 60) Arm 3: Optimal RT + concomitant cyclophosphamide (500mg IV days 1, 30 and 60) Arm 4: Optimal RT + concomitant cyclophosphamide (2 x 50mg/day (oral) days 1-10; 30-40 and 60-70) | |
| Outcomes | | |
| Notes | Optimal RT | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Chen 1997

| | | |
|---------------------|---|--|
| Methods | RCT, 1992-93 | |
| Participants | 120 randomised (0 excluded). Unknown % stage I & II. Those with involved nodes were not eligible. | |
| Interventions | Arm 1: RT* Arm 2: RT* + concomitant cisplatin (30mg IV days 1-3), 5-FU (500mg days 1-3) and vincristine (1mg IV days 8 and 15) Arm 3: RT* + hyperthermia Arm 4: RT* + hyperthermia + concomitant CT (as for arm 2) | |
| Outcomes | Survival (at 5 years) Acute toxicity | |
| Notes | *Unclear whether RT was optimal or not. Hyperthermic RT arms excluded | |
| <i>Risk of bias</i> | | |

Chen 1997 (Continued)

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Eifel 2004

| | | |
|---------------|--|--|
| Methods | RCT, 1990-97 | |
| Participants | 403 randomised (14 excluded). 70% stage I & II. Those with involved nodes were eligible. | |
| Interventions | Arm 1: Sub-optimal RT Arm 2: Sub-optimal RT + concomitant cisplatin (75mg/m2 IV day 1), 5-FU (4000 mg/m2 days 1-4) 3 cycles at 3 weekly intervals | |
| Outcomes | Survival PFS Local recurrence Metastases Acute, late toxicity | |
| Notes | Sub-optimal RT | |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Fernandez 1995

| | | |
|---------------|---|--|
| Methods | RCT, 1990-92 | |
| Participants | 82 randomised (0 excluded). 70% stage I & II. Unknown if those with involved nodes were eligible. | |
| Interventions | Arm 1: RT* Arm 2: RT* + concomitant 5-FU + Mitomycin-C (details of doses and schedules not provided) | |
| Outcomes | PFS(at 4 years) Acute toxicity | |
| Notes | *Unclear whether RT was optimal or not | |

Risk of bias

Fernandez 1995 (Continued)

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Hernandez 1991

| | | |
|---------------|--|--|
| Methods | RCT, 1986-87 | |
| Participants | 55 randomised (0 excluded). 0 % stage I & II. Those with involved nodes were not eligible. | |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + concomitant bleomycin (15mg twice-weekly for 5 weeks) | |
| Outcomes | Survival Local recurrence Metastases | |
| Notes | Optimal RT | |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Kantardzic 2004

| | | |
|---------------|--|--|
| Methods | RCT, 1997-1999 | |
| Participants | 80 randomised (0 excluded). ?% stage I & II. Unknown if those with involved nodes were not eligible. | |
| Interventions | Arm 1: RT* Arm 2: RT* + concomitant cisplatin (40mg/m2) and bleomycin (15mg/m2) | |
| Outcomes | Acute toxicity | |
| Notes | *Unclear whether RT was optimal or not | |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Keys 1999

| | |
|---------------|---|
| Methods | RCT, 1992-93 |
| Participants | 374 randomised (5 excluded). 100% stage I & II. Those with involved nodes were eligible. |
| Interventions | Arm 1: Sub-optimal RT Arm 2: Sub-optimal RT + concomitant cisplatin (40mg/m ² per week up to a maximum of 6 cycles) |
| Outcomes | Survival PFS Acute, late toxicity |
| Notes | Sub-optimal RT |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Lanciano 1998

| | |
|---------------|--|
| Methods | RCT, unknown recruitment period |
| Participants | Unknown randomised (0 excluded). ?% stage I & II. Those with involved nodes were not eligible. |
| Interventions | Arm 1: RT* Arm 2: RT* + concomitant cisplatin (IV weekly for 5 weeks + once during parametrial boost) Arm 3: RT* + concomitant 5-FU (PVI weekly for 5 weeks + once during parametrial boost) |
| Outcomes | Survival; PFS Acute, late toxicity |
| Notes | Unpublished study. *Unclear whether RT was optimal or not. |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Leborgne 2000

| | |
|---------------|---|
| Methods | RCT, 1995-99 |
| Participants | 153 randomised (0 excluded). 28 % stage I & II. Those with involved nodes were not eligible. |
| Interventions | Arm 1: Optimal RT* Arm 2: Optimal RT* + concomitant cisplatin (80mg/m2 day 1) and 5-FU (600mg/m2 days 1 and 2-4) 2cycles at 4-weekly intervals (NB. 20% dose reduction due to high levels of acute toxicity) |
| Outcomes | Survival PFS Local recurrence Metastases Acute toxicity |
| Notes | * Different doses of external RT and brachytherapy given by stage Stage I-II - sub-optimal Stage III-IVa - optimal |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Lira Puerto 1990

| | |
|---------------|--|
| Methods | RCT, 1988-88 |
| Participants | 24 randomised (0 excluded) 0% stage I & II. Those with involved nodes were not eligible. |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + concomitant cisplatin (20mg/m2) |
| Outcomes | Acute toxicity |
| Notes | Optimal RT |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Lorvidhaya 2003

| | | |
|----------------------------|---|--------------------|
| Methods | RCT, 1988-92 | |
| Participants | 705 randomised (17 excluded). 48% stage I & II. Those with involved nodes are not eligible. | |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + maintenance chemotherapy Arm 3: Optimal RT + concomitant mitomycin-C (10mg/m ² days 1, 29) and 5-FU (300mg days 1-14 and 29-42) Arm 4: Optimal RT + concomitant mitomycin-C (10mg/m ² days 1, 29) and 5-FU (300mg days 1-14 and 29-42) plus maintenance chemotherapy | |
| Outcomes | Survival, PFS Local recurrence, Metastases Acute, late toxicity | |
| Notes | Optimal RT. Arm 2: RT and maintenance CT only arm excluded (221 patients) Arms 3 and 4 combined. | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Onishi 1999

| | | |
|----------------------------|---|--------------------|
| Methods | RCT; 1988-1998 | |
| Participants | 33 randomised (0 excluded). 0% stage I & II. Unknown whether those with involved nodes are eligible. | |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + concomitant cisplatin (100mg/m ² , 2 cycles 2-3 weekly) OR carboplatin (100mg/m ² weekly for 5-6 cycles) OR cisplatin (10mg/day for 21 days) | |
| Outcomes | Survival, PFS Acute, late toxicity | |
| Notes | Optimal RT | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Pearcey 2002

| | | |
|----------------------------|---|--------------------|
| Methods | RCT | |
| Participants | 259 randomised (6 excluded). 68% stage I & II. Those with involved nodes are eligible. | |
| Interventions | Arm 1: Sub-optimal RT Arm 2: Sub-optimal RT + concomitant cisplatin (40mg/m ² days 1,8,15,22, 29) | |
| Outcomes | Survival PFS Local recurrence Metastases Acute toxicity | |
| Notes | Sub-optimal RT | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Peters 2000

| | | |
|----------------------------|--|--------------------|
| Methods | RCT, 1991-96 | |
| Participants | 268 randomised (25 excluded). 100% stage I & II. Those with involved nodes are eligible. | |
| Interventions | Arm 1: Radical hysterectomy + sub-optimal RT Arm 2: Radical hysterectomy + sub-optimal RT + concomitant cisplatin (70mg/m ² day 1) and 5-FU (1000mg/m ² /day day 1-4) 3-weekly for 4 cycles | |
| Outcomes | Survival PFS Local recurrence Metastases Acute, late toxicity | |
| Notes | Sub-optimal RT. All patients had prior hysterectomy and pelvic lymphadenectomy | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Pras 2000

| | |
|---------------|--|
| Methods | RCT, 1998-99 |
| Participants | 52 randomised (0 excluded). Unknown % stage I & II. Unknown if those with involved nodes were eligible. |
| Interventions | Arm 1: Sub-optimal RT +/- hysterectomy Arm 2: Sub-optimal RT +/- hysterectomy + concomitant carboplatin (300mg/m2 IV days 1, 29 and 57) and 5-FU (600mg/m2 days 1-4, 29-32 and 57-60) |
| Outcomes | Survival (at 1 year) Acute toxicity |
| Notes | Sub-optimal RT |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Roberts 2000

| | |
|---------------|--|
| Methods | RCT, 1994-97 |
| Participants | 212 randomised (52 excluded). 62% stage I & II. Those with involved nodes were not eligible. |
| Interventions | Arm 1: Optimal RT* Arm 2: Optimal RT* + concomitant mitomycin-c (15mg/m2, weeks 1 and 7) |
| Outcomes | Survival PFS Local recurrence Metastases |
| Notes | * Different doses of external RT and brachytherapy given by stage |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Rose 1999

| | | |
|----------------------------|---|--------------------|
| Methods | RCT, 1992-97 | |
| Participants | 575 randomised (49 excluded). 53% stage I & II. Those with involved nodes were eligible. | |
| Interventions | Arm 1: Sub-optimal RT + hydroxyurea (3000mg/m ² oral twice weekly, weeks 1-6) Arm 2: Sub-optimal RT + concomitant cisplatin (40mg/m ² weekly, weeks 1-6) Arm 3: Sub-optimal RT + concomitant cisplatin (50mg/m ² IV days 1, 29) 5-FU (4000mg/m ² days 1-4 and 29-33) and hydroxyurea (2000mg/m ² orally, twice weekly weeks 1-6) | |
| Outcomes | Survival PFS Local recurrence Metastases Acute toxicity | |
| Notes | Sub-optimal RT. Cisplatin CT arms combined. Hydroxyurea in control arm. | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Singh 1985

| | | |
|----------------------------|---|--------------------|
| Methods | RCT, 1981-83 | |
| Participants | 300 randomised (62 excluded). 62% stage I & II. Those with involved nodes were not eligible. | |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + concomitant bleomycin (15mg day 1 then every 6 days during RT) and mitomycin-C (4mg day 1 then every 6 days during RT) | |
| Outcomes | Survival (at 1 year) | |
| Notes | Optimal RT | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Singh 2003

| | | |
|----------------------------|---|--------------------|
| Methods | RCT; 1996-1999 | |
| Participants | 96 randomised (12 excluded). 63% stage I & II. Unknown whether those with involved nodes were not eligible. | |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + concomitant cisplatin (16mg/m ² IV days 1-5) 3-weekly for 2 cycles plus 40mg/m ² cisplatin during intracavitary RT | |
| Outcomes | Local Recurrence Metastases Acute, late toxicity | |
| Notes | Optimal RT | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Thomas 1998

| | | |
|----------------------------|--|--------------------|
| Methods | RCT, 1987-95 | |
| Participants | 234 randomised (13 excluded). ? stage I & II. Those with involved nodes were not eligible. | |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + concomitant 5-FU 1000mg/m ² (First 4 days of RT and last 4 days of RT) Arm 3: Optimal RT2 Arm 4: Optimal RT2 + concomitant 5-FU 1000mg/m ² (First 4 days of RT and last 4 days of RT) | |
| Outcomes | PFS Late toxicity | |
| Notes | Optimal RT RT1 - standard radiotherapy RT2 - hyperfractionated radiotherapy | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Tseng 1997

| | |
|---------------|--|
| Methods | RCT, 1990-95 |
| Participants | 122 randomised (0 excluded). 48% stage I & II. Those with involved nodes were eligible. |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + concomitant cisplatin (50mg/m ² IV day 1), vincristine (1mg/m ² IV day 2) and bleomycin 25mg/m ² IV day 2-4) 3-weekly for 4 cycles |
| Outcomes | Survival PFS Local recurrence Metastases Acute, late toxicity |
| Notes | Optimal RT |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Whitney 1999

| | |
|---------------|--|
| Methods | RCT, 1986-90 |
| Participants | 388 randomised (20 excluded). 64% stage I & II. Those with involved nodes were eligible. |
| Interventions | Arm 1: Optimal RT + hydroxyurea (80mg/m ² twice-weekly for each week of external beam RT) Arm 2: Optimal RT + concomitant cisplatin (50mg/m ² IV days 1 and 29) and 5-FU (1000mg/m ² IV per day, days 2-5 and 30-33) |
| Outcomes | Survival, PFS Acute and late toxicity |
| Notes | Optimal RT (NB. Stage IIB patients received sub-optimal RT) Hydroxyurea in control arm. |

Risk of bias

| Item | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear | B - Unclear |

Wong 1989

| | | |
|----------------------------|---|--------------------|
| Methods | RCT, 1982-83 | |
| Participants | 64 randomised (0 excluded). 70% stage I & II. Those with involved nodes were eligible. | |
| Interventions | Arm 1: Sub-optimal RT Arm 2: Sub-optimal RT + concomitant cisplatin (25mg/m ² IV day 1, 8, 15 and 22 Arm 3: Optimal RT + concomitant cisplatin (25mg/m ² IV days 1,3, 8, 10, 15, 17, 22 and 24) | |
| Outcomes | Survival PFS Local recurrence Metastases Acute toxicity | |
| Notes | Sub-optimal RT. Arms 2 and 3 (CT arms) combined. | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |
| Allocation concealment? | Unclear | B - Unclear |

Wong 1999

| | | |
|----------------------------|---|--------------------|
| Methods | RCT, 1989-92 | |
| Participants | 222 randomised (2 excluded). 80% stage I & II. Those with involved nodes were not eligible. | |
| Interventions | Arm 1: Optimal RT Arm 2: Optimal RT + concomitant epirubicin (60mg/m ² day 1) + adjuvant epirubicin (90mg/m ² every 4 weeks for 5 courses) | |
| Outcomes | Survival PFS Local recurrence Metastases Acute, late toxicity | |
| Notes | Optimal RT | |
| <i>Risk of bias</i> | | |
| Item | Authors' judgement | Description |

Wong 1999 (Continued)

| | | |
|-------------------------|---------|-------------|
| Allocation concealment? | Unclear | B - Unclear |
|-------------------------|---------|-------------|

RCT - randomised controlled trial

PFS - progression-free survival

RT - radiotherapy/radiation therapy

CT - chemotherapy

*Optimal RT defined as external beam dose greater than 40Gy in 20# (i.e. 2Gy per fraction) plus brachytherapy

Characteristics of excluded studies [ordered by study ID]

| | |
|-------------------|--|
| Keitlinska 1984 | Trial of surgery plus radiotherapy versus radiotherapy |
| Li 1997 | Not a RCT |
| Lukas 1998 | Review of three studies |
| Mohan Segal 2002 | Different radiotherapy regimens on treatment and control |
| Vishnevskaya 1999 | Immunotherapy given on the treatment arm |

DATA AND ANALYSES

Comparison 1. Concomitant chemoradiotherapy versus radiotherapy

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--|----------------|---------------------|---------------------------------------|-------------------|
| 1 Survival by type of chemotherapy | 13 | 3578 | Peto Odds Ratio (99% CI) | 0.69 [0.61, 0.77] |
| 1.1 Platinum chemotherapy | 9 | 2456 | Peto Odds Ratio (99% CI) | 0.68 [0.60, 0.78] |
| 1.2 Non-platinum chemotherapy | 4 | 1122 | Peto Odds Ratio (99% CI) | 0.72 [0.56, 0.92] |
| 2 Survival by scheduling of chemotherapy | 13 | 3578 | Peto Odds Ratio (99% CI) | 0.69 [0.61, 0.77] |
| 2.1 Concomitant CT | 10 | 2427 | Peto Odds Ratio (99% CI) | 0.71 [0.62, 0.81] |
| 2.2 Concomitant and sequential | 3 | 1151 | Peto Odds Ratio (99% CI) | 0.61 [0.47, 0.79] |
| 3 Survival by hydroxyurea on control | 13 | 3578 | Peto Odds Ratio (99% CI) | 0.69 [0.61, 0.77] |
| 3.1 No hydroxyurea on control | 11 | 2684 | Peto Odds Ratio (99% CI) | 0.70 [0.61, 0.81] |
| 3.2 Hydroxyurea on control | 2 | 894 | Peto Odds Ratio (99% CI) | 0.67 [0.54, 0.82] |
| 4 Survival by timing of chemotherapy | 13 | 3578 | Peto Odds Ratio (99% CI) | 0.69 [0.61, 0.77] |
| 4.1 Weekly | 3 | 1148 | Peto Odds Ratio (99% CI) | 0.66 [0.53, 0.81] |
| 4.2 > Weekly | 10 | 2430 | Peto Odds Ratio (99% CI) | 0.70 [0.61, 0.81] |
| 5 Survival by stage | 13 | 3578 | Peto Odds Ratio (99% CI) | 0.69 [0.61, 0.77] |
| 5.1 ≥ 70% Stage I & II | 5 | 1254 | Peto Odds Ratio (99% CI) | 0.54 [0.44, 0.66] |
| 5.2 <70 % Stage I & II | 8 | 2324 | Peto Odds Ratio (99% CI) | 0.77 [0.67, 0.89] |
| 6 Progression-free survival by type of chemotherapy | 14 | 3805 | Peto Odds Ratio (99% CI) | 0.66 [0.59, 0.73] |
| 6.1 Platinum chemotherapy | 10 | 2514 | Peto Odds Ratio (99% CI) | 0.66 [0.59, 0.75] |
| 6.2 Non-platinum chemotherapy | 4 | 1291 | Peto Odds Ratio (99% CI) | 0.65 [0.54, 0.78] |
| 7 Rate of local recurrence by type of chemotherapy | 14 | 3694 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.59 [0.50, 0.69] |
| 7.1 Platinum chemotherapy | 10 | 2571 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.57 [0.48, 0.69] |
| 7.2 Non-platinum chemotherapy | 4 | 1123 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.64 [0.47, 0.88] |
| 8 Rate of distant recurrence by type of chemotherapy | 13 | 3006 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.81 [0.65, 1.01] |
| 8.1 Platinum chemotherapy | 10 | 2571 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.84 [0.67, 1.06] |
| 8.2 Non-platinum chemotherapy | 3 | 435 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.59 [0.31, 1.14] |
| 9 Rate of distant +/- local recurrence by type of chemotherapy | 14 | 3694 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.69 [0.58, 0.82] |
| 9.1 Platinum chemotherapy | 10 | 2571 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.74 [0.60, 0.91] |
| 9.2 Non-platinum chemotherapy | 4 | 1123 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.59 [0.43, 0.81] |

| | | | | |
|--|----|------|---------------------------------------|-------------------|
| 10 Acute haematological toxicity (non-specified) | 7 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 10.1 Grade 1/2 | 5 | 1360 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.60 [1.26, 2.03] |
| 10.2 Grade 3/4 | 7 | 1998 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 3.42 [2.59, 4.51] |
| 11 Acute white blood cell toxicity | 11 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 11.1 Grade 1/2 | 8 | 2267 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.29 [1.08, 1.53] |
| 11.2 Grade 3/4 | 11 | 2575 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.20 [1.72, 2.80] |
| 12 Acute haemoglobin toxicity | 5 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 12.1 Grade 1/2 | 4 | 1164 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.71 [1.33, 2.21] |
| 12.2 Grade 3/4 | 5 | 1286 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 3.66 [1.72, 7.77] |
| 13 Acute platelet toxicity | 8 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 13.1 Grade 1/2 | 7 | 2207 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.30 [1.81, 2.94] |
| 13.2 Grade 3/4 | 8 | 2329 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.44 [1.18, 5.06] |
| 14 Acute GI toxicity | 14 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 14.1 Grade 1/2 | 10 | 2126 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.33 [1.11, 1.58] |
| 14.2 Grade 3/4 | 13 | 2859 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.98 [1.49, 2.63] |
| 15 Acute nausea / vomiting | 7 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 15.1 Grade 1/2 | 5 | 738 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 3.09 [2.27, 4.21] |
| 15.2 Grade 3/4 | 7 | 1245 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 4.09 [2.34, 7.16] |
| 16 Acute GU toxicity | 9 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 16.1 Grade 1/2 | 7 | 1744 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.14 [0.90, 1.45] |
| 16.2 Grade 3/4 | 9 | 2382 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.08 [0.57, 2.04] |
| 17 Acute skin toxicity | 8 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 17.1 Grade 1/2 | 6 | 1866 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.37 [1.05, 1.78] |
| 17.2 Grade 3/4 | 8 | 2504 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.36 [0.74, 2.50] |
| 18 Acute neurologic toxicity | 5 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 18.1 Grade 1/2 | 4 | 1316 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.82 [1.16, 2.85] |
| 18.2 Grade 3/4 | 5 | 1569 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.95 [0.29, 3.08] |

FEEDBACK

Analysis tables and graphs

Summary

I am currently updating our clinical practice guideline and so while checking through the data you have extracted I noticed that you have analysed the mortality rate not the survival rate. Also in some trials the outcome used is disease-free survival and in others it is progression-free survival - since these are not the same outcome I don't think they should be combined. Also for this outcome you have analysed the number of patients in progression, not the number that are progression-free.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

1. We have analysed neither the mortality rate nor the survival rate, but rather the relative survival experience of the treatment and control groups, which is represented by the hazard ratio.
2. Some trials have analysed 'progression-free survival' and others 'disease-free survival'. However, where these have been defined, they each usually refer to the time free from local disease progression, local recurrence or metastases. In fact two trials used both terms interchangeably. Thus, in cervical cancer it is reasonable to combine these apparently different outcomes.
3. We have not analysed the number of patients in progression, but rather the relative progression-free survival experience of the treatment and control groups, which is again represented by the hazard ratio.

[Response from Jayne Tierney, August 2003]

Contributors

[Comment from Margaret Haugh, August 2003]

WHAT'S NEW

Last assessed as up-to-date: 22 May 2005.

| | | |
|-----------------|---------|---------------------------------|
| 13 October 2008 | Amended | Converted to new review format. |
|-----------------|---------|---------------------------------|

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 4, 2001

| | | |
|---------------|--|--|
| 12 May 2005 | New citation required and conclusions have changed | New studies found Conclusions changed |
| 1 August 2003 | Feedback has been incorporated | Feedback added and incorporated |
| 1 May 2003 | Amended | New studies found but not yet included or excluded |

CONTRIBUTIONS OF AUTHORS

All reviewers met regularly to discuss and work on all aspects of the review process, with the exception of the search strategy design and the statistical analysis which was carried out by Jayne Tierney.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Medical Research Council, UK.
- NHS R&D, UK.
- Macmillan Cancer Relief, UK.
- University of Liverpool, UK.
- University of Leicester, UK.

External sources

- No sources of support supplied

NOTES

An additional paper on the toxicity relating to the use of concomitant chemotherapy and radiation therapy for carcinoma of the uterine cervix is currently being prepared, and will be incorporated in this review on completion.

May 2003 - searches have been carried out in preparation for the update of this review. The results have been entered into 'Studies awaiting assessment'.

INDEX TERMS

Medical Subject Headings (MeSH)

Combined Modality Therapy; Randomized Controlled Trials as Topic; Uterine Cervical Neoplasms [*drug therapy; *radiotherapy]

MeSH check words

Female; Humans