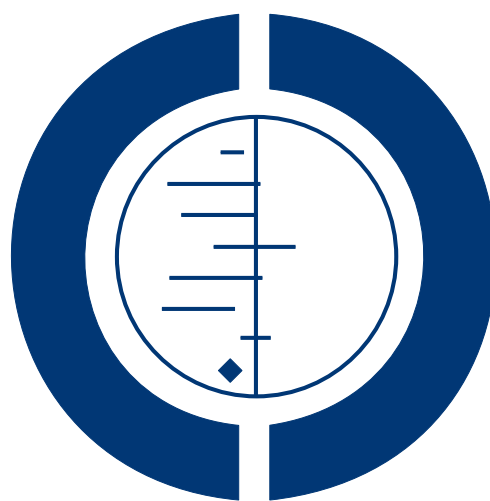


Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis (Review)

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC)



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[Intervention Review]

Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC)¹

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Editorial group: Cochrane Gynaecological Cancer Group.

Publication status and date: New, published in Issue 1, 2010.

Review content assessed as up-to-date: 22 October 2009.

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

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ABSTRACT

Background

After a 1999 National Cancer Institute (NCI) clinical alert was issued, chemoradiotherapy has become widely used in treating women with cervical cancer. Two subsequent systematic reviews found that interpretation of the benefits was complicated and some important clinical questions were unanswered.

Objectives

We initiated a meta-analysis seeking updated individual patient data (IPD) from all randomised controlled trials (RCTs) to assess the effect of chemoradiotherapy on all outcomes. We pre-specified analyses to investigate whether the effect of chemoradiotherapy differed by trial or patient characteristics.

Search strategy

We supplemented MEDLINE, LILACS and CANCELIT searches with information from trial registers, by handsearching relevant meeting proceedings and by discussion with relevant trialists and organisations. Searches were updated until October 2009.

Selection criteria

Both published and unpublished trials were eligible for inclusion provided the patients had been randomised between radiotherapy (with or without surgery) versus concomitant chemoradiotherapy (with or without surgery); that the method of randomisation precluded prior knowledge of the treatment to be assigned; and that the trial had completed patient recruitment before the date of the final analyses.

Data collection and analysis

We carried out a quantitative meta-analysis using updated information from individual patients from all available RCTs. We sought data from all patients randomised in all eligible trials. We obtained updated information on survival, recurrence and date of last follow up. To avoid potential bias, we requested information for all randomised patients, including those who had been excluded from the investigators' original analyses.

Main results

Eighteen trials were identified and 15 of these were eligible for inclusion in the main analysis. On the basis of 13 trials that compared chemoradiotherapy versus the same radiotherapy, there was a 6% improvement in 5-year survival with chemoradiotherapy (hazard ratio (HR) = 0.81, $P < 0.001$). A larger survival benefit was seen for the two further trials in which chemotherapy was administered after chemoradiotherapy. There was a significant survival benefit for both the group of trials that used platinum-based (HR = 0.83, $P = 0.017$) and non-platinum based (HR = 0.77, $P = 0.009$) chemoradiotherapy, but no evidence of a difference in the size of the benefit by radiotherapy or chemotherapy dose or scheduling was seen. Chemoradiotherapy also reduced local and distant recurrence and progression and improved disease-free survival (DFS). There was a suggestion of a difference in the size of the survival benefit with tumour stage, but not across other patient subgroups. Acute haematological and gastro-intestinal toxicity were increased with chemoradiotherapy, but data were too sparse for an analysis of late toxicity.

Authors' conclusions

These results endorse the recommendations of the NCI alert, but also demonstrate their applicability to all women and a benefit of non-platinum based chemoradiotherapy. Furthermore, although these results suggest an additional benefit from adjuvant chemotherapy this requires testing in RCTs.

PLAIN LANGUAGE SUMMARY

Chemoradiotherapy for cervical cancer: results of a meta-analysis

Women with cervical cancer that is too big to be removed by surgery, or has spread to the tissues around the cervix (often called locally advanced cervical cancer) may be treated with radiotherapy (treatment with x-rays). They might also get chemotherapy (drug treatment) alongside radiotherapy. This is called chemoradiotherapy (or chemoradiation). This review brought together 18 randomised controlled trials (RCTs) that were carried out in many countries. The results of the review showed that women who had chemoradiotherapy for cervical cancer were likely to live for longer than women who had just radiotherapy. Five years after being treated, 66 out of every 100 women who received chemoradiotherapy were still alive compared with 60 out of every 100 who just had radiotherapy. Women who received chemoradiotherapy were also less likely to have the cancer come back or spread to other parts of the body. Chemoradiotherapy helped all women, even those with bigger tumours, or tumours that had spread more. Also, the different drugs that had been used in the trials (cisplatin, 5-fluorouracil or mitomycin-C) all helped women to live longer or stop the cancer from coming back or spreading. Some of the short term side effects were worse for women who received chemoradiotherapy. Doctors can usually help women to cope with the short term side effects of their treatment. Unfortunately, there was not enough information to be certain whether the long-term side effects are worse with chemoradiotherapy or not.

The review also seemed to show that women who have extra chemotherapy (after they have had chemoradiotherapy) live longer than those who just have chemoradiotherapy. However, the researchers are less certain about these results and suggest that new RCTs are needed to find out whether giving extra chemotherapy is better for women with cervical cancer, or not.

BACKGROUND

Cervical cancer is the second most common cancer among women worldwide and the main cancer affecting women in sub-Saharan Africa, Central America and south-central Asia (Parkin 2002). A significant decline in incidence and mortality have been seen in North America, parts of Europe, Australia and New Zealand, where screening programmes have been implemented for some time (Arbyn 2007; Australian Institute of Health and Welfare 2007; Canadian Cancer Society 2007; Ries 2006).

In 1999, after publication of five trials (Keys 1999; Morris 1999;

Peters 2000; Rose 1999a; Rose 1999b; Whitney 1999) the NCI issued an alert (National Cancer Institute 1999) recommending that 'concomitant chemoradiotherapy should be considered instead of radiotherapy alone in women with cervical cancer'. This has led to a change in the treatment for many women with cervical cancer (Pearcey 2007; Trimble 2007). Two subsequent reviews (Green 2001; Green 2005; Lukka 2002) reported improvements in survival, progression-free survival (PFS) and recurrence rates with chemoradiotherapy. However, interpretation of the benefits were complicated by the use of different treatments on the control

arms of the included studies (Lukka 2002) heterogeneity in trial results and inconsistency in the definition of outcomes between trials (Green 2005). The authors concluded that an individual patient data (IPD) meta-analysis would be required to obtain time-to-event analyses of local and distant recurrence, more reliable estimates of effect in patient subgroups, and a better attribution of relative toxicities.

OBJECTIVES

We therefore initiated a systematic review and meta-analysis that aimed to collect, validate and re-analyse IPD from all relevant RCTs (Stewart 1995). This permits time-to-event analyses and investigation of differences in the effect of chemoradiotherapy by trial or patient characteristics and, by seeking updated follow-up, provides a unique opportunity to look at these outcomes in the long-term. This IPD meta-analysis was initiated and coordinated by the Medical Research Council (UK) Clinical Trials Unit and carried out by the Concomitant chemoradiotherapy in Cervical Cancer Meta-analysis Collaboration (CCCMAC).

METHODS

Criteria for considering studies for this review

Types of studies

The methods for this systematic review and meta-analysis followed a detailed, pre-specified protocol (September 2004, a copy of which is available on request). Trials had to be properly randomised and should have completed patient accrual by the time of the final analyses (May 2007).

Types of participants

Women with locally advanced cancer of the uterine cervix who had not received any previous treatments likely to interfere with protocol treatments or comparisons.

Types of interventions

Our inclusion criteria limited the main analysis to trials that compared concomitant chemotherapy and radical radiotherapy (with or without surgery) with the same radical radiotherapy (with or without surgery). However, given the importance of two trials using hydroxyurea on the control arm (Rose 1999a; Rose 1999b; Whitney 1999) and one trial giving extended field radiotherapy on the control arm (Morris 1999) to the NCI alert (National Cancer Institute 1999) and for completeness, we analysed these

trials alongside the main comparison to establish how sensitive the effect of chemoradiotherapy is to different trial designs. Chemotherapy should have been given on the experimental arm only. Trials were excluded if they used additional non-cytotoxic treatments or only non-cytotoxic radiosensitisers/radioprotectors on the experimental arm. Trials that used hydroxyurea as the sole chemotherapy agent have been considered in a prior systematic review (Symonds 2004a; Symonds 2004b) and have not been included here.

Types of outcome measures

The primary outcome, overall survival (OS), was defined as the time from randomisation until death by any cause. Living patients were censored on the date of last follow-up. Locoregional progression/recurrence and metastases were supplied as classified in the individual trials. Locoregional disease free survival (DFS) was defined as the time from randomisation until locoregional recurrence or progression or death by any cause. Patients alive with no locoregional disease were censored on the date of last follow-up. Metastases-free survival was defined as the time from randomisation until first metastasis or death by any cause. Patients alive without metastases were censored on the date of last follow-up. In trials where only the first recurrence (either locoregional or distant) was recorded, patients with metastatic disease were censored in the analysis of locoregional recurrence and those with locoregional disease were censored in the analysis of metastases. Overall DFS was defined as the time from randomisation until locoregional recurrence, metastasis or death by any cause. For the exploratory analyses of time to locoregional recurrence and time to metastases, time to locoregional recurrence was defined as the time from randomisation until the first local recurrence or progression. Patients without local recurrence or progression were censored on the date of last follow up or death. Time to metastases was defined as the time from randomisation until first metastases. Patients without metastases were censored on the date of last follow up or death. For trials that only recorded the first recurrence event, the methods of censoring described above were used.

Investigators were asked to supply acute and late toxicity data according to the criteria used in their own trials. Although different scales were used to measure both, each was based on a 5-grade system where 0 signifies no toxicity and 5 signifies death, making it reasonable to combine the results.

Search methods for identification of studies

To avoid publication bias, published and unpublished trials were included in the meta-analysis. We searched Medline and CancerLit using an optimal search strategy (Dickersin 1995)(Appendix 1) and also LILACS (Appendix 2), the Physician Data Query (Open and Closed Protocols), and other trial registers. These were supplemented from reference lists of identified trial reports and review

articles and meeting proceedings of the International Gynecologic Cancer Society and the Society for Gynecologic Oncology (1994 to 2009). Furthermore, all participating investigators were asked to supplement our provisional list of trials. Searches were regularly updated until October 2009.

The search strategies used have been developed and executed by the author team.

Data collection and analysis

We sought to collect up-to-date information for all patients randomised, including those excluded from the investigators' own analyses, on date of randomisation, treatment allocation, tumour response, locoregional and distant progression/recurrence status, survival, cause of death, and acute and late toxicity. Baseline data on age, histology, FIGO stage, tumour grade, performance status and lymph node involvement were also sought. All data were thoroughly checked for validity, consistency and integrity of randomisation and follow-up (Stewart 1995). Inconsistencies were resolved and final database entries validated by the responsible trial investigator, data manager or statistician.

All analyses (unless otherwise stated) were pre-specified in the meta-analysis protocol (available on request) and were performed on an intention-to-treat (ITT) basis. For all survival and recurrence outcomes, individual times to event were used to obtain hazard ratio (HR) estimates of treatment effect for individual trials, which were pooled across trials, using a stratified-by-trial, fixed-effect model (Yusuf 1985). For binary outcomes such as response and toxicity, the number of events and numbers of patients were used to calculate Peto odds ratio (OR) estimates of treatment effect (Yusuf 1985) for individual trials which were pooled across trials, using the stratified-by-trial fixed-effect model (Yusuf 1985). Trial results were also combined using the random effects approach (DerSimonian 1986).

Three 4-arm trials in the meta-analysis (Chen 1997a; Chen 1997b; Lorvidhaya 2003a; Lorvidhaya 2003b; Thomas 1998a; Thomas 1998b) used a factorial design to assess the impact of two treatments at once, one of which was chemoradiotherapy. Each was split into two unconfounded comparisons of chemoradiotherapy versus radiotherapy and analysed as though they were separate trials (a) and (b) (Characteristics of included studies). Two three-arm trials (Lanciano 2005a; Lanciano 2005b; Rose 1999a, Rose 1999b) in the meta-analysis compared two different forms of chemoradiotherapy with a single control arm. The treatment arms were combined and compared with the control group for analysis for both trials.

To explore the impact of trial characteristics on the effect of chemoradiotherapy, we pre-specified analyses that grouped trials according to chemotherapy scheduling (chemotherapy entirely during radiotherapy, chemotherapy during and after radiotherapy), chemotherapy type (platinum-based chemotherapy, non-platinum based chemotherapy), planned radiotherapy dose ('op-

timal' radiotherapy of greater than or equal to 45Gy external beam plus brachytherapy (any dose), 'sub-optimal' radiotherapy of greater than 45Gy external beam without brachytherapy or less than 45Gy external beam with or without brachytherapy), planned radiotherapy duration (less than or equal to 8 weeks, greater than 8 weeks). For the subset of trials that used cisplatin-based chemotherapy only, we also planned analyses of chemotherapy cycle length (less than or equal to one week, greater than one week) and chemotherapy dose intensity (less than or equal to 25mg/m²/week cisplatin, greater than 25mg/m²/week cisplatin). Hazard ratios (HRs) were calculated for each trial group and for all trials together. These analyses focused on the primary outcome of OS and were also carried out on the other outcomes to support or refute any patterns found. For 'serious' acute toxicity, defined as grades 3 to 5, trials were grouped according to their use of platinum-based chemoradiotherapy, non platinum-based chemoradiotherapy, chemoradiotherapy plus additional chemotherapy, extended field radiotherapy on the control arm and additional hydroxyurea on the control arm, with HRs calculated for each group.

The effects of chemoradiotherapy within subgroups of patients were investigated using similar stratified analyses. HRs were obtained for each pre-defined subgroup within each trial, for example, a HR for patients with good performance status and a HR for patients with poor performance status. These HRs were then combined to give overall HRs, e.g. for good and poor performance patients. Chi-square tests for interaction or trend were used to investigate whether there were any substantial differences in the effect of concomitant chemoradiotherapy between different groups of trials or subgroups of patients.

Results are also presented as absolute differences, calculated from the overall HR and the control arm event rate (Parmar 1995). Chi square heterogeneity tests (ABOC 1995) and the I² statistic (Higgins 2003) were used to assess statistical heterogeneity across trials. Kaplan-Meier curves are non-stratified (Kaplan 1958). All P-values are two-sided.

Where IPD were not available, wherever possible we calculated HRs and associated statistics from reported time to event analyses (Parmar 1998; Tierney 2007) and considered the impact on the analyses of IPD.

Selection of studies

All titles and abstracts, identified by both electronic searching and by hand searching of conference proceedings, were checked and full publications were obtained for those thought to be potentially relevant. These were assessed independently by two review authors (CV, JT) to reach consensus on their eligibility for inclusion in the review. Individual patient data was sought from trial authors including updated follow-up, where available.

Assessment of risk of bias in included studies

The methodological quality of included studies was assessed using the risk of bias tool (Table 1) and checked with a second review author. Trials were individually assessed for risk of bias on the basis of adequate sequence generation, allocation concealment, blinding, whether incomplete outcome data was presented or if there was evidence of selective outcome reporting (Characteristics of included studies). Trials considered to be free of substantial biases that might affect the results were included in the meta-analysis, with any potential sources of bias are clearly highlighted (Risk of bias in included studies).

Table 1. Patient characteristics

Subgroup	chemoradiotherapy(1745 Patients)	Control (1707 patients)	Total (3452 Patients)
Age	233 (13%)	249 (15%)	482
<35	873 (50%)	775 (45%)	1648
35-50	538 (31%)	555 (33%)	1093
>50-65	98 (6%)	125 (7%)	223
>65	3(<1%)	3 (<1%)	6
Unknown	47.00	47.00	47.00
Median age	20-87	20-91	20-91
Range			
Histology	1541(88%)	1531 (89%)	3072
Squamous cell	87 (5%)	90 (5%)	177
Adenocarcinoma	51 (3%)	32 (2%)	83
Adenosquamous	32 (2%)	17 (1%)	49
Other	34 (2%)	37 (2%)	71
Unknown			
Stage	413(24%)		830
1a-2a	625 (36%)	417 (24%)	1226
2b	667 (38%)	601 (35%)	1325
3-4a	40 (2%)	658 (39%)	71
Unknown		31 (2%)	
Grade	157 (9%)	155 (9%)	
Well differentiated	600 (34%)	594 (35%)	312
Moderately well differentiated	223 (13%)	195 (11%)	1194
Poorly / undifferentiated	765 (44%)	763 (45%)	418
Unknown			1528
Performance status	692 (40%)	655 (38%)	1347
0	498 (29%)	508 (30%)	1006
1	29 (2%)	23 (1%)	52
2	1(0%)	0 (0%)	1
3-4	525 (30%)	521 (31%)	1046
Unknown			

Table 1. Patient characteristics (Continued)

Pelvic node involvement	191(11%)	173 (10%)	364
Involved	535 (31%)	549 (32%)	1084
Not involved	1019 (58%)	985 (58%)	2004
Unknown			
Para-aortic node involvement	32 (2%)	21 (1%)	53
Involved	823 (47%)	801 (47%)	1624
Not involved	890 (51%)	885 (52%)	1775
Unknown			
Iliac node involvement	50(3%)	55 (3%)	105
Involved	591 (34%)	591 (35%)	1182
Not involved	1104 (63%)	1061 (62%)	2165
Unknown			

RESULTS

Description of studies

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

Main analysis

Trials comparing radiotherapy with concomitant chemotherapy plus the same radiotherapy

We identified 25 randomised trials that were eligible for the main analysis. We were unable to include data from 10 trials (1113 patients), either because data could not be located (6 trials, 814 patients) ([Fernandez 1995](#); [Lira-Puerto 1989](#); [Singh 1985](#); [Tseng 1997](#); [Wong 1989](#); [Wong 1999](#)) or because we were unable to make contact with the relevant investigators (4 trials, 299 patients) ([Bulnes 1986](#); [Dawel 1997](#); [Hernandez 1991](#); [Singh 2003](#)). Data were therefore available for 3452 women from 15 trials ([Chen 1997a](#); [Chen 1997b](#); [Cikaric 2005](#); [GaripaÄŸaoÄŸlu 2004](#); [Kantardzic 2004](#); [Keys 1999](#); [Lal 2004](#); [Lanciano 2005a](#); [Lanciano 2005b](#); [Leborgne 1995](#); [Lorvidhaya 2003a](#); [Lorvidhaya 2003b](#); [Onishi 2000](#); [Pearcey 2002](#); [Peters 2000](#); [Pras 1995](#); [Roberts 2000](#); [Thomas 1998a](#); [Thomas 1998b](#)). This includes 85% of women from trials that used cisplatin-based chemoradiotherapy and almost 80% of women from trials that used 5FU and / or mitomycin-C based (66% of all women who took part in trials of non-

platinum based) chemoradiotherapy. Data were obtained for 118 women (100%) who were excluded from the investigators' original analyses and reinstated in the meta-analysis. Characteristics of the included trials are shown in [Characteristics of included studies](#).

The 15 available trials accrued 44 to 926 patients between May 1987 and June 2006. Eleven trials used platinum-based chemoradiotherapy in the experimental arm, either as a single agent (6 trials [Cikaric 2005](#); [GaripaÄŸaoÄŸlu 2004](#); [Keys 1999](#); [Lal 2004](#); [Onishi 2000](#), [Pearcey 2002](#)) or in combination regimens (5 trials [Chen 1997a](#); [Chen 1997b](#); [Kantardzic 2004](#); [Leborgne 1995](#); [Peters 2000](#); [Pras 1995](#)). Three trials ([Lorvidhaya 2003a](#); [Lorvidhaya 2003b](#); [Roberts 2000](#); [Thomas 1998a](#); [Thomas 1998b](#)) used non-platinum regimens comprising either 5FU, mitomycin-C or a combination of the two. One three-arm trial randomised patients to receive chemoradiotherapy either with cisplatin or 5FU ([Lanciano 2005a](#); [Lanciano 2005b](#)). Each of the trials aimed to prescribe external beam radiation at a dose to the tumour of between 40 - 61.2Gy and all except one trial ([Peters 2000](#)) (which used primary hysterectomy) also used brachytherapy. The planned total duration of all radiotherapy (external beam plus brachytherapy) was from 40 to 70 days across all trials. The median follow up for living patients across all 15 trials was 5.2 years. Data on OS, DFS, locoregional DFS and metastases-free survival were available for all trials, but tumour response was only available in full for two trials ([Kantardzic 2004](#); [Pras 1995](#), preventing an analysis of this outcome).

Patient characteristics for the 15 trials are given in [Table 1](#). Data on age were provided for all trials, data on histology and stage were provided for 14 trials, data on performance status were provided for 12 trials, and data on grade were available for 9 trials. Data on

pelvic node involvement and iliac node involvement were available for six trials, with para-aortic node involvement available for nine trials. On the basis of the available data, women were mostly aged between 35 and 64 years of age, with good performance status. They had tumours that were largely of squamous cell histology (89%), stage 2b (36%) or stage 3 (36%), and moderately differentiated (35%). However, as there was generally no central pathology review, the precise definition of tumour grade may vary from trial to trial. Three trials excluded women with involved para-aortic nodes (Keys 1999; Lanciano 2005a; Lanciano 2005b; Pras 1995) and para-aortic nodal status was either uninvolved (48%) or unknown (51%) for the vast majority of the women from the remaining trials.

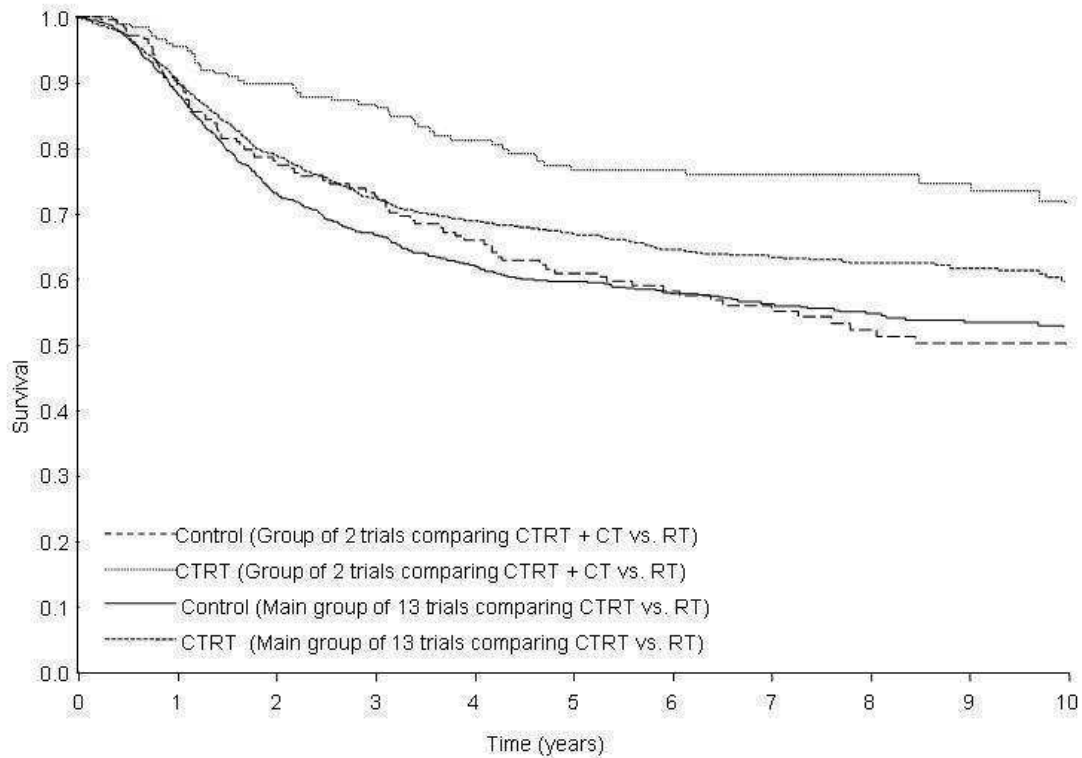
Risk of bias in included studies

IPD for all included trials was checked for integrity of randomisation. There were no unusual patterns of randomisation noted and patient characteristics were well balanced across the treatment arms for all included trials. All trials reported adequate concealment of allocation, except for one trial (Pras 1995) for which no details were available. The nature of the treatment interventions is such that blinding was not appropriate for any of the trials. IPD were supplied for all outcomes except for acute and late toxicity, largely because these data were not collected or recorded for the individual trials. However, some of the trials that were able to supply late toxicity outcomes had substantial missing data (Chen 1997a; Chen 1997b; Lorvidhaya 2003a; Lorvidhaya 2003b; Onishi 2000; Thomas 1998a; Thomas 1998b) which may lead to bias in any analyses of these outcomes.

Effects of interventions

OS data were supplied for 15 trials including 3452 women and 1138 deaths have been recorded (Chen 1997a; Chen 1997b; Cikaric 2005; Garipa Yao Lu 2004; Kantardzic 2004; Keys 1999; Lal 2004; Lanciano 2005a; Lanciano 2005b; Leborgne 1995; Lorvidhaya 2003a; Lorvidhaya 2003b; Onishi 2000; Pearcey 2002; Peters 2000; Pras 1995; Roberts 2000; Thomas 1998a; Thomas 1998b). The results for these trials are grouped according to whether chemoradiotherapy only was used or whether additional chemotherapy after chemoradiotherapy was administered (Analysis 1.1). Although there was no evidence of statistical heterogeneity within each trial group (chemoradiotherapy only $P = 0.65$, $I^2 = 0.00$; chemoradiotherapy plus adjuvant chemotherapy $P = 0.95$, $I^2 = 0.00$), there was a large and significant difference between groups in the benefit of chemoradiotherapy (interaction $P = 0.004$). The HR for the two trials that gave chemoradiotherapy plus adjuvant chemotherapy of 0.46 (95% CI 0.32 to 0.66, $P < 0.001$), represents a 54% reduction in the risk of death with this treatment and translates into an absolute survival benefit of 19% at 5 years (from 60% to 79%) (Kantardzic 2004; Peters 2000). However, the most reliable and unconfounded estimate of the effect of chemoradiotherapy alone is obtained from the 13 trials whose design did not include the use of additional chemotherapy (Analysis 2.1). The HR for this group of 0.81 (95% CI 0.71 to 0.91) represents a highly significant ($P < 0.001$), 19% relative reduction in the risk of death with chemoradiotherapy compared with radiotherapy and translates to an absolute survival benefit of 6% at five years (from 60% to 66%). The survival curves for these 13 trials and for the two trials that used adjuvant chemotherapy follow a similar pattern, although separation of the curves is greater with adjuvant chemotherapy (Figure 1), albeit that follow-up for one of the trials (Kantardzic 2004) in this group is somewhat less mature (median follow-up 2.35 years) than for the main group of 13 trials (overall median follow-up 4.77 years). The results are similar when a random effects model was applied (DerSimonian 1986).

Figure 1. Simple (unstratified) Kaplan Meier Curves for Overall Survival: chemoradiotherapy versus radiotherapy and chemoradiotherapy plus chemotherapy versus radiotherapy
CTRT - chemoradiotherapyCT - chemotherapyRT - radiotherapy



Subsequent pre-specified analyses by trial group were therefore restricted to the 13 trials that had an unconfounded comparison of chemoradiotherapy versus radiation (Chen 1997a; Chen 1997b; Cikaric 2005; GaripaÄŸaoÄŸlu 2004; Keys 1999; Lal 2004; Lanciano 2005a; Lanciano 2005b; Leborgne 1995; Lorvidhaya 2003a; Lorvidhaya 2003b; Onishi 2000; Pearcey 2002; Pras 1995; Roberts 2000; Thomas 1998a; Thomas 1998b). We found no evidence of a difference in the size of the effect of chemoradiotherapy when trials were grouped according to the type of chemotherapy they had used (platinum-based or non-platinum-based) (Analysis 2.1) the planned radiotherapy dose or the total planned duration of radiation (Table 2). Similarly, for the ten trials that used cisplatin-based chemoradiotherapy (Chen 1997a; Chen 1997b; Cikaric 2005; GaripaÄŸaoÄŸlu 2004; Keys 1999; Lal 2004; Lanciano 2005a; Leborgne 1995; Onishi 2000; Pearcey 2002; Pras 1995), we found no evidence that the effect of chemoradiotherapy differed according to the cycle length or the dose intensity of cisplatin used (Table 2). However, the power of these analyses, particularly those involving just the cisplatin-based chemoradiotherapy trials, is limited.

Table 2. Results of trial group analyses for overall survival (Main group of 13 trials only)

	HR(95%CI)	Interaction p-value
Planned Chemotherapy type	0.84 (0.72-0.98)	
Platinum based	0.76 (0.62-0.94)	0.48
Non-platinum based		
Planned Radiotherapy dose		
> 45 Gy + BRT	0.78 (0.68-0.89)	0.26
< 45 Gy + BRT	0.93 (0.70-1.24)	
Planned Radiotherapy duration	0.83 (0.72-0.96)	
< 8 weeks	0.73 (0.57-0.93)	0.35
> 8 weeks		
Planned chemotherapy cycle length		
< 1 week	0.74 (0.60-0.92)	0.16
> 1 week	0.95 (0.72-1.25)	
Planned Cisplatin dose intensity	0.93 (0.70-1.24)	
< 25mg/m ² /week	0.76 (0.62-0.96)	0.25
> 25mg/m ² /week		
Cisplatin regimen	0.76 (0.62-0.93)	
Single-agent	0.93 (0.70-1.24)	0.25
Combination		
Chemotherapy regimen	0.75 (0.63-0.88)	
Single agent	0.86 (0.71-1.04)	0.29
Combination		

Data on overall DFS, locoregional DFS and metastases free survival were available from all of the 13 trials in the unconfounded comparison of chemoradiotherapy versus radiation. For DFS, there were 1376 events in total, of which 1087 were recurrences or metastases and 289 were deaths (Figure 2). The HR of 0.78 (95% CI 0.70 to 0.87, $P < 0.001$) translates to an absolute DFS benefit of 8% at 5 years (from 50% to 58%). There were similar and significant absolute benefits of chemoradiotherapy on 5-year locoregional DFS (9%, $P < 0.001$), time to locoregional recurrence/progression (6%, $P = 0.00009$) and metastases-free survival (7%, $P < 0.001$). However, there was a smaller and less convincing improvement in time to metastases at 5 years (4%, $P = 0.04$). Insufficient data were available to assess the impact of chemoradiotherapy on response (Table 3).

Figure 2. Flow diagram showing deaths and recurrences (Chemoradiotherapy versus radiotherapy trials only)

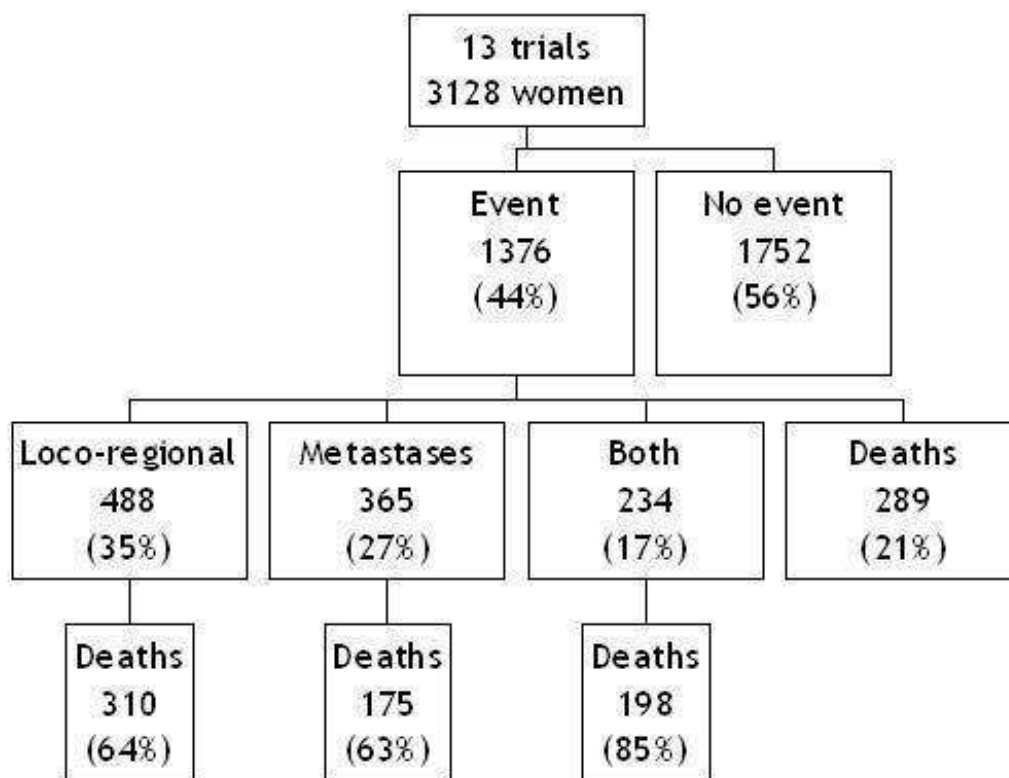


Table 3. Results of all outcomes (Main group of 13 trials only)

	HR(95%CI)	P-value	Absolute benefit (5 years)
Overall disease-free survival	0.78 (0.70-0.87)	0.000005	8%
Locoregional disease-free survival	0.76 (0.68-0.86)	0.000003	9%
Metastases-free survival	0.81 (0.72-0.91)	0.0004	7%
Locoregional disease-free interval	0.74 (0.64-0.86)	0.00009	6%
Metastases-free interval	0.83 (0.71-0.99)	0.037	4%

Patient subgroup analyses were similarly restricted to those 13 trials in the unconfounded group that were able to supply data. A planned analysis based on iliac node involvement was not completed as there were insufficient data (Table 1). Also, most patients for whom data were supplied had good performance status and either unknown or negative para-aortic nodal status, so there was little to gain from analyses of these subgroups. We found no evidence to suggest that the effect of chemoradiotherapy differed in groups of women defined by age, histology, tumour grade or whether they had pelvic lymph node involvement, although the analyses by grade and pelvic node involvement were limited to eight and five trials respectively (Table 4). There was a suggestion of trend in the relative effect of chemoradiotherapy by tumour stage ($P = 0.017$), with the benefit of chemoradiotherapy decreasing with increasing stage. The HRs obtained for each stage translate to 5-year survival benefits of 10% for women with stages 1b to 2a cervical cancer, 7% for women with stage 2b cervical cancer, and 3% for women with stage 3 to 4a cancer. However, there was no significant trend for the analysis of DFS by stage (test for trend, $P = 0.073$) (Figure 3).

Figure 3. Subgroup analysis for FIGO stage for chemoradiotherapy versus radiotherapy trials only (Overall survival and Disease-free survival)

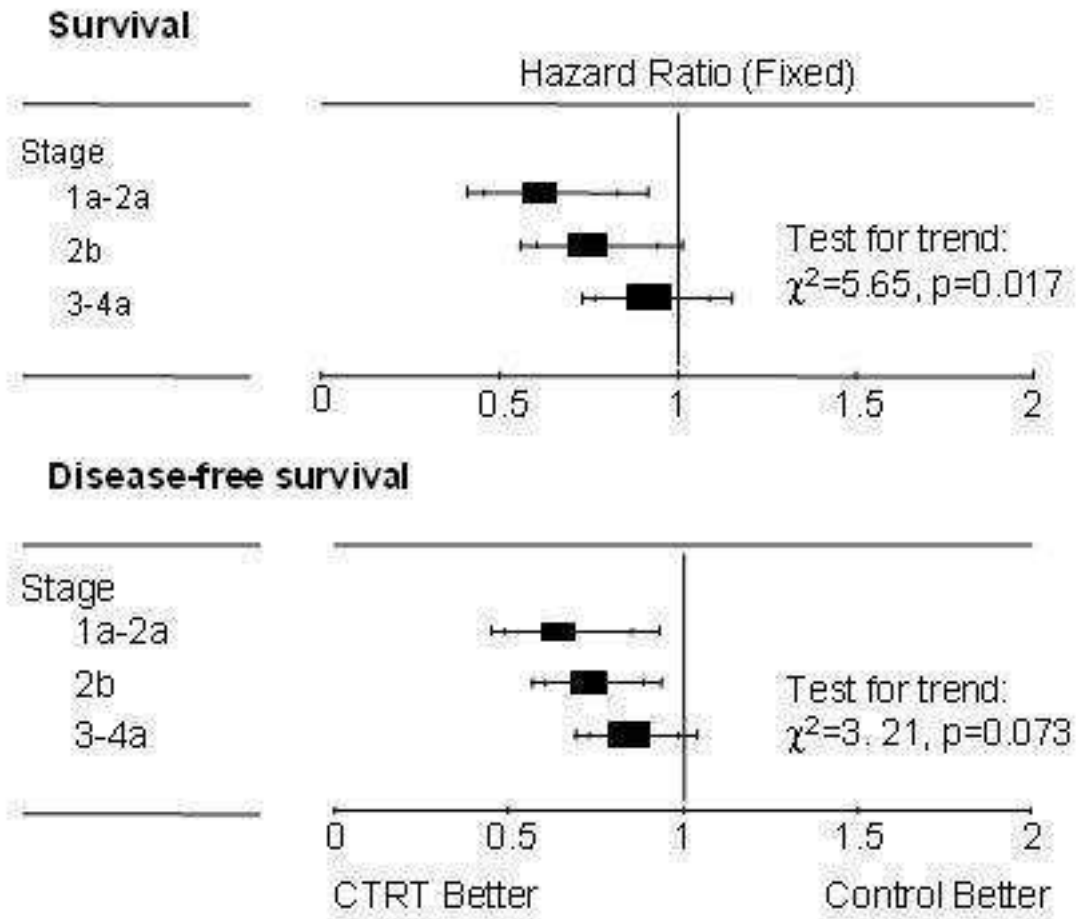


Table 4. Patient subgroup analyses

Patient Subgroup	χ^2	P-value
Age (<35, 35 to 49, 50 to 64, ≥65)	0.61*	0.436
Stage (1a to 2a, 2b, 3 to 4a)	5.65*	0.017
Histology (Squamous, Adenosquamous or adenocarcinoma)	0.00	0.992
Grade (Well / moderately well differentiated, poorly differentiated)	0.00	0.961

Table 4. Patient subgroup analyses (Continued)

Pelvic node involvement (Not involved, Involved)	0.49	0.483
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*Test for trend (otherwise Test for Interaction)

For trials for which IPD were not available, it was only possible to estimate HRs for survival (Parmar 1998; Tierney 2007) for three of the 10 trials, two of which contribute to the main group of 13 trials (Hernandez 1991; Tseng 1997) and one to the group of trials that used additional chemotherapy after chemoradiotherapy (Wong 1999). However, incorporating them into the meta-analysis did not materially change the results for either group (data not shown).

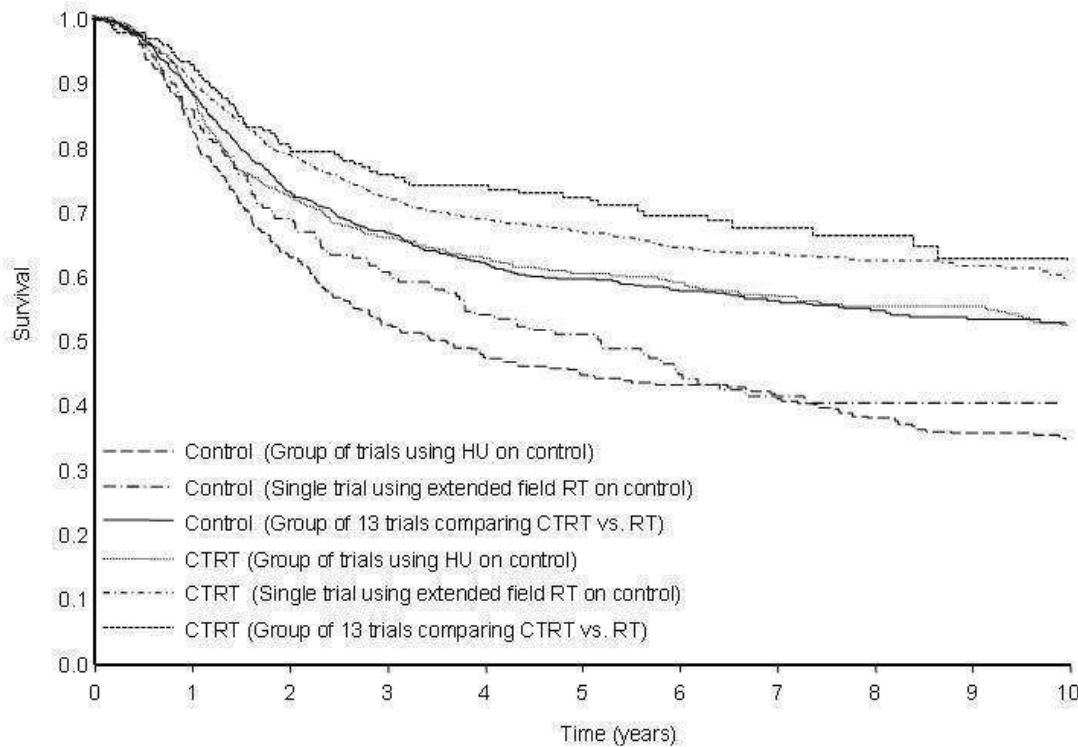
Sensitivity analyses

Trials of different design

Three trials were included in the sensitivity analysis of trials of different designs (Morris 1999; Rose 1999a; Rose 1999b; Whitney 1999). Data were supplied for 1366 women (100%), including 84 women who had been excluded from the investigator's original analyses and were reinstated in the meta-analysis. The three trials recruited 388 to 575 women between August 1986 and October 1997. All used platinum-based chemoradiotherapy; however in one trial, extended field radiotherapy was administered in the control arm (Morris 1999) and in two trials, additional hydroxyurea (HU) was administered in the control arm (Rose 1999a; Rose 1999b; Whitney 1999). The three trials planned to give between 40.8 to 61.2Gy external beam radiation plus brachytherapy. The planned total duration for all radiotherapy (external beam

and brachytherapy) was less than 56 days (Morris 1999) and fewer than 70 days (Rose 1999a; Rose 1999b; Whitney 1999). The median follow-up for living patients across these trials was 8.4 years (see Characteristics of included studies). Patient characteristics in the three trials included in the sensitivity analyses were broadly similar to those in the main analyses, however women with para-aortic nodal involvement were actively excluded from each trial. Inclusion of the three trials alongside the 13 trials of the main analysis substantially increased overall heterogeneity ($P = 0.12$, $I^2 = 28.28$). Moreover, Analysis 3.1 illustrates that the treatment effect observed in trials using HU on control (HR 0.63 95% CI 0.52 to 0.76, $P < 0.001$) differed to that in the main analysis (test for interaction, $P = 0.03$), with an absolute survival benefit of 15% (from 45% to 60%) at 5 years. The effect of the trial using extended field radiotherapy on the control arm (HR 0.50 95% CI 0.37 to 0.67, $P < 0.001$) also differed from that in the main analysis (test for interaction, $P = 0.004$), with an absolute survival benefit of 21% (from 50% to 71%) at 5 years. Whilst these benefits seem greater, the control group survival for both groups is lower than that for the main group of 13 trials (Figure 4). Because these trials differ from the trials in the main analysis in terms of both trial design and the size of the treatment effect, the best estimate of the effect of chemoradiotherapy over radiotherapy remains that from the unconfounded analysis of 6% at 5 years.

Figure 4. Simple (unstratified) Kaplan Meier Curves for Overall Survival: Chemoradiotherapy versus radiotherapy plus sensitivity analysis of other trial designs CTRT - chemoradiotherapy; RT - radiotherapy; HU - hydroxyurea



Analyses of toxicity

Data on overall acute haematological toxicity and GI toxicity were supplied for 16 trials. Data were available on white blood cell and genitourinary toxicity for 14 trials, haemoglobin toxicity from 13 trials, platelet toxicity from 12 trials and skin toxicity from 10 trials.

Serious haematological toxicity increased by approximately two-fold to ten-fold in individual trials. However, for the group of trials that used HU on the control arm, a high level of serious haematological toxicity was evident on both arms (slightly greater on the control arm, OR 0.74, 95% CI 0.53 to 1.03, $P = 0.08$). A similar pattern of results was observed for white blood cell toxicity, which accounted for most (92%, 517 events) of the overall haematological toxicity. There was a significant increase in serious GI toxicity for the groups of trials using platinum-based chemoradiotherapy ($P = 0.000002$), chemoradiotherapy plus additional chemotherapy ($P = 0.001$) and additional radiotherapy on the control arm ($P = 0.000002$). This increase was not observed for the group of trials

using non-platinum based chemoradiotherapy ($P = 0.465$), where the event rate was low (approximately 2%) on both arms, or for the trials that gave HU on the control arm ($P = 0.591$), where the event rate was high (approximately 10%) on both arms. For acute haemoglobin toxicity, acute platelet toxicity, genitourinary toxicity and skin toxicity, very few serious events were recorded and so formal analyses were inappropriate.

Data on late toxicity were not recorded for the majority of trials in the meta-analysis. Data on late rectal toxicity were available for seven trials, late bladder toxicity for five trials and late intestinal and late vaginal toxicity available for only four trials. Furthermore, within these trials there was substantial missing data for the trials that were able to supply data. Therefore, there was insufficient data available to assess whether serious late toxicity is affected by the type of treatment. The available data suggests that only a small number of women across all trials (1 to 3%) experienced serious late toxicities, including nine deaths, but these data may not represent the true levels of late toxicity across all trials.

DISCUSSION

Our findings are based on the results of 18 trials from 11 countries worldwide, including the 5 studies that formed the basis of the NCI alert in 1999 (National Cancer Institute 1999). Based on the main analysis, there was clear evidence that adding chemotherapy to radiotherapy improves both OS and DFS. For the group of 13 trials in which chemoradiotherapy alone was used, there was a 6% absolute survival benefit and an 8% DFS benefit at 5 years, with no evidence of heterogeneity. These analyses endorse the recommendations made in the 1999 NCI alert (National Cancer Institute 1999) but with far greater reliability and precision regarding the gains of chemoradiotherapy.

The benefit of chemoradiotherapy on OS and DFS was supported by similar benefits on the other outcomes analysed, although the evidence for time to metastases was less compelling. Chemoradiotherapy is thought to exert its major beneficial effects by improving local disease control. However, the benefit of chemoradiotherapy on metastases, suggested previously (Green 2005) and confirmed in this meta-analysis may indicate that it has a modest systemic effect.

Larger benefits were seen for the trials in which additional chemotherapy was administered following chemoradiotherapy, with an absolute improvement of 19% at 5 years. However this result is based on two relatively small trials of differing design and with less mature follow up and is therefore not conclusive. Inclusion of published summary data from one unavailable trial does not materially alter the estimate of effect for this group. Furthermore, we cannot be certain that the larger benefit is not due to factors other than the additional chemotherapy following chemoradiotherapy. Nevertheless, the results are promising and may warrant a direct comparison with chemoradiotherapy alone.

Inclusion of trials that used additional treatments on the control arm in previous meta-analyses led to difficulties in interpretation (Lukka 2002) and significant statistical heterogeneity (Green 2001). Analysing these trials separately facilitates interpretation and minimises heterogeneity. There were larger absolute survival benefits for the group of trials in which HU was administered on the control arm and for the single in which extended field radiotherapy was administered on the control arm. However, these trials all excluded women with surgically identified positive para-aortic nodes (compared with only two out of 13 trials in the main analysis) and so included women who may have been more likely to benefit from chemoradiotherapy. Furthermore, this highly selected group of women is unlikely to be representative of the general population of women with cervical cancer. Patient selection may also explain why the benefits observed in this meta-analysis are smaller than had been previously reported (Green 2001; Green 2005; Lukka 2002). These benefits are, however, more likely to be generalisable to more women with cervical cancer.

Importantly, this meta-analysis shows that the benefit associated

with chemoradiotherapy may not depend on the use of platinum. Previous recommendations have been limited to platinum-based chemoradiotherapy (National Cancer Institute 1999) but this meta-analysis shows a significant benefit also associated with non-platinum regimens, specifically those containing 5-FU and/or mitomycin-C. However, as our results are not based on a direct comparison, we cannot be clear about the relative merits of platinum versus non-platinum. The only randomised trial that has directly compared platinum (cisplatin) and non-platinum-based (5FU) chemoradiotherapy closed early because interim analyses suggested that 5FU-based chemoradiotherapy was unlikely to significantly improve PFS compared with cisplatin, even if full accrual had been completed. Furthermore, because it closed early, it was underpowered to detect a difference between the two chemoradiotherapy regimens (Lanciano 2005a; Lanciano 2005b). For women who are unable to tolerate cisplatin, or more easily tolerated chemotherapy is required, non-cisplatin based chemoradiotherapy perhaps offers an additional option.

Other planned analyses by trial characteristics were hampered, because most trials had planned to give radiotherapy over eight weeks or less in addition to weekly, high dose-intensity cisplatin-based chemotherapy, and so should be interpreted cautiously. Nevertheless, we found no evidence to suggest that the effect of chemoradiotherapy differs by any of the trial characteristics investigated. Currently therefore, there is insufficient evidence to suggest that any one treatment type, dose or schedule is better than any other.

The effect of chemoradiotherapy appears consistent across patient subgroups defined by age, histology, grade or pelvic node involvement. There was however the suggestion of a decreasing relative effect of chemoradiotherapy on survival with increasing tumour stage, with estimated absolute survival benefit of 10% (stage 1a to 2a), 7% (stage 2b) and 3% (stage 3 to 4a) at 5 years. Even if this trend had occurred by chance, applying the overall HR (0.81) to each of the stage subgroups gives an improvement in OS at 5 years for all stages, thus confirming chemoradiotherapy benefits women with all stages of cervical cancer, although the size of the benefit may vary.

Although chemoradiotherapy increases some serious acute toxicity, particularly haematological and GI toxicities, few of the trials in this meta-analysis measured late toxicity and only one of the 25 trials eligible for inclusion in this main analysis reported quality of life (QoL) outcomes (Lira-Puerto 1989). This highlights the need for prospective evaluations of treatment tolerability and QoL in future trials that investigate the use of new or targeted therapies.

Although this meta-analysis provides the most comprehensive and up to date summary of the effects of chemoradiotherapy and is based on a large number of women from the large majority of the international trials, IPD from 10 trials were unavailable and might impact on these results. Nine of these trials including 891 randomised patients would contribute to the main analysis. Al-

though HR estimates based on the publications of three unavailable trials suggest that their inclusion would not change the results, and all of the unavailable data would only contribute 20% more data to the main analysis, it is possible that inclusion of IPD from these trials could modify our estimate of treatment effect to some degree. Since the final analyses were completed, we have also become aware of one completed trial that compared weekly cisplatin based chemoradiotherapy with radiotherapy alone in 160 patients (Mitra 2006) and one large ongoing trial of chemoradiotherapy versus radiotherapy (NCT00193791), both from India. Once completed, we will seek inclusion of these recent trials in an updated analysis.

AUTHORS' CONCLUSIONS

Implications for practice

This meta-analysis provides an unconfounded estimate of the effect of chemoradiotherapy compared with radiotherapy. Adding chemotherapy to radiotherapy offers a modest, but significant, additional benefit on all outcomes and for all stages of disease. There is also the potential to use both platinum and non-platinum regimens. With wider implementation of national screening and vaccination programs it is likely that the incidence of cervical cancer will continue to decrease. However, financial and organisational difficulties, particularly in the developing world, mean that in countries unable to implement such programmes, substantial numbers of women will continue to be affected by cervical cancer. Even access to radiotherapy continues to be a barrier to effective treatment in large parts of the world.

Implications for research

Effective and affordable treatments, such as those used in this meta-analysis, provide a standard against which promising new

drug regimens or novel treatment approaches should be compared. There is also the potential to investigate whether additional chemotherapy offers additional benefits. Prospective evaluations of the late effects of chemoradiotherapy must be included in future trials that aim to improve treatment tolerability and quality of life with existing regimens, or that investigate the use of new or targeted therapies.

ACKNOWLEDGEMENTS

We are grateful to the UK Medical Research Council for funding this work and to the UK National Coordinating Centre for Research Capacity Development for funding Claire Vale through a post-doctoral award. We would like to thank all those patients who took part in these trials and contributed to this research. The meta-analysis would not have been possible without the collaborating institutions that kindly supplied their trial data or without the help of those responsible for maintaining, updating and preparing trial data (David S Alberts, Mark Brady, Slobodan Cikaric, Hongwei Chen, Ketayun Dinshaw, Patricia J Eifel, Melahat Garipagaoglu, Anders Jakobsen, Nermina Kantardzic, Henry Keys, Punita Lal, Rachele Lanciano, Felix Leborgne, Vicharn Lorvidhaya, Hiroshi Onishi, Mahesh KB Parmar, Robert G Pearcey, Elizabeth Pras, Kenneth Roberts, Peter G Rose, Lesley A Stewart, Jayne F Tierney, Gillian Thomas, Ted Trimble, Claire Vale, Charles W. Whitney). We would also like to thank the Patient Research Partners (Alison Nightingale, Andrea Whelan, Nicolette Spera and Sue Davidson) for their comments and contributions throughout the project. We are also grateful to the Director of Licensing, American Society of Clinical Oncology for granting permission to re-publish this review, originally published in the *Journal of Clinical Oncology* (CCCMAC 2008).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chen 1997a

Methods	RCT 1993 to 1994	
Participants	60 patients Stage IIB to IIIB	
Interventions	Radiotherapy versus concomitant chemoradiotherapy (Cisplatin)	
Outcomes	Survival, disease free survival, local and distant recurrence, acute toxicity, late toxicity	
Notes	4-arm trial (with Chen B below)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Sealed envelope
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes. NB. Substantial proportion of data missing for late toxicity outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Chen 1997b

Methods	RCT 1993 to 1994	
Participants	60 patients Stage IIB to IIIB	
Interventions	Radiotherapy plus hypothermia versus concomitant chemoradiotherapy (Cisplatin) plus hypothermia	

Chen 1997b (Continued)

Outcomes	Survival, disease free survival, local and distant recurrence, acute toxicity, late toxicity	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Sealed envelope
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes. NB. Substantial proportion of data missing for late toxicity outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Cikaric 2005

Methods	RCT 2002-2003	
Participants	200 patients Stage IIB to IVA	
Interventions	Radiotherapy versus concomitant chemoradiotherapy (Cisplatin)	
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Sealed envelope

Cikaric 2005 (Continued)

Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Garipis et al 2004

Methods	RCT 1996 to 1997	
Participants	44 patients Stage IIB, IIIB	
Interventions	Radiotherapy versus concomitant chemoradiotherapy (Cisplatin)	
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity	
Notes		

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Sealed envelope
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Kantardzic 2004

Methods	RCT 1996 to 1999	
Participants	80 patients Stage IIB to III	
Interventions	Radiotherapy versus concomitant chemoradiotherapy plus additional chemotherapy (cisplatin + bleomycin)	
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Central telephone
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Keys 1999

Methods	RCT 1993-1997	
Participants	374 patients Stage IB (bulky)	
Interventions	Radiotherapy plus hysterectomy versus concomitant chemoradiotherapy (Cisplatin) plus hysterectomy	
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity	
Notes		
<i>Risk of bias</i>		

Keys 1999 (Continued)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Central telephone
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Lal 2004

Methods	RCT 2000-2006
Participants	180 patients Stage II to IV
Interventions	Radiotherapy versus concomitant chemoradiotherapy (Cisplatin)
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	'List - blinded from the trial coordinator'
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)

Lal 2004 (Continued)

Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias
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Lanciano 2005a

Methods	RCT 1997 to 1998
Participants	50 patients Stage IIB, IIIB, IVA
Interventions	Radiotherapy versus concomitant chemoradiotherapy (Cisplatin)
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity
Notes	3-arm trial with Lanciano (b) NB Control arm is the same for both trials

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Central telephone
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Lanciano 2005b

Methods	RCT 1997 to 1998
Participants	51 Patients Stage IIB, IIIB, IVA
Interventions	Radiotherapy versus concomitant chemoradiotherapy (5-FU)

Lanciano 2005b (Continued)

Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity	
Notes	3-arm trial with Lanciano (b) NB Control arm is the same for both trials	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Central telephone
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Leborgne 1995

Methods	RCT 1995-2004	
Participants	340 patients Stage IB2 to IVB	
Interventions	Radiotherapy versus concomitant chemoradiotherapy (Cisplatin, 5-FU)	
Outcomes	Survival, disease-free survival, local and distant recurrence	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Sealed envelope

Leborgne 1995 (Continued)

Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except acute toxicity and late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except acute toxicity and late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Lorvidhaya 2003a

Methods	RCT 1987 to 1994	
Participants	475 patients Stage IIB, IIIB, IVA	
Interventions	Radiotherapy versus concomitant chemoradiotherapy (5-FU, Mitomycin C)	
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity	
Notes	4-arm trial with Lorvidhaya (b)	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Sealed envelope
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes. NB. Substantial proportion of data missing for late toxicity outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Lorvidhaya 2003b

Methods	RCT 1987 to 1994
Participants	451 patients Stage IIB, IIIB, IVA
Interventions	Radiotherapy plus adjuvant chemotherapy versus concomitant chemoradiotherapy (5-FU, Mitomycin C) plus adjuvant chemotherapy
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity
Notes	4-arm trial with Lorvidhaya (b)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Sealed envelope
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes. NB. Substantial proportion of data missing for late toxicity outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Morris 1999

Methods	RCT 1990 to 1997
Participants	403 patients Stage IB or IIA (>4cm or positive nodes only); IIB to IVA
Interventions	Extended field radiotherapy versus concomitant chemoradiotherapy (Cisplatin, 5-FU)
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity
Notes	Included in sensitivity analysis only as control arm RT differs to that on treatment arm

Risk of bias

Morris 1999 (Continued)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Central telephone
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Onishi 2000

Methods	RCT 1988 to 1998
Participants	49 patients Stage IIb to IV
Interventions	Radiotherapy versus concomitant chemoradiotherapy (cisplatin or carboplatin)
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Sealed envelope
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes. NB. Substantial proportion of data missing for late toxicity outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)

Onishi 2000 (Continued)

Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias
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Pearcey 2002

Methods	RCT 1991 to 1996
Participants	259 patients Stage IB to IIB (> 4cm); III to IVA
Interventions	Radiotherapy versus concomitant chemoradiotherapy (cisplatin)
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Central telephone
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Peters 2000

Methods	RCT 1991 to 1996
Participants	268 patients Stage IA2 to IIA
Interventions	Surgery plus radiotherapy versus surgery plus concomitant chemoradiotherapy plus additional chemotherapy

Peters 2000 (Continued)

Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	'Assignment given by telephone upon study registration'
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Pras 1995

Methods	RCT 1995 to 1999	
Participants	54 patients Stage IB to IIA (> 4cm); IIB to IVA	
Interventions	Radiotherapy versus concomitant chemoradiotherapy (carboplatin)	
Outcomes	Survival, disease-free survival, local and distant recurrence	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Blinding? All outcomes	Yes	Trial was not blinded due to nature of treatment interventions

Pras 1995 (Continued)

Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except acute toxicity and late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except acute toxicity, late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Roberts 2000

Methods	RCT 1991 to 2001
Participants	248 patients Stage IB2, II to IVa
Interventions	Radiotherapy versus concomitant chemoradiotherapy (Mitomycin C)
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Central telephone
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Rose 1999a

Methods	RCT 1992 to 1997
Participants	384 patients Stage IIB to IVA
Interventions	Radiotherapy plus hydroxyurea versus concomitant chemoradiotherapy (cisplatin)
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity
Notes	3-arm trial - shares the same control arm as Rose (b) Only included in the sensitivity analysis due to use of additional hydroxyurea on the control arm only

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Central telephone
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Rose 1999b

Methods	RCT 1992 to 1997
Participants	383 patients Stage IIB to IVA
Interventions	Radiotherapy plus hydroxyurea versus concomitant chemoradiotherapy (cisplatin, 5-FU) plus hydroxyurea
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity

Rose 1999b (Continued)

Notes	3-arm trial - shares the same control arm as Rose (b) Only included in the sensitivity analysis due to use of additional hydroxyurea on the control arm only	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment?	Yes	Central telephone
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Thomas 1998a

Methods	RCT 1987 to 1995	
Participants	116 women Stage IB (>5cm) to IVA	
Interventions	Radiotherapy versus concomitant chemoradiotherapy (5-FU)	
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity	
Notes	4-arm trial with Thomas (b)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions

Thomas 1998a (Continued)

Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes. NB. Substantial proportion of data missing for late toxicity outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Thomas 1998b

Methods	RCT 1987 to 1995
Participants	118 women Stage IB (>5cm) to IVA
Interventions	Hyperfractionated radiotherapy versus concomitant chemotherapy (5-FU)and hyperfractionated radiotherapy
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity, late toxicity
Notes	4-arm trial with Thomas (a)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes. NB. Substantial proportion of data missing for late toxicity outcomes
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Whitney 1999

Methods	RCT 1986 to 1990
Participants	388 patients Stage IIB to IVA
Interventions	Radiotherapy plus hydroxyurea versus concomitant chemoradiotherapy (cisplatin, 5FU)
Outcomes	Survival, disease-free survival, local and distant recurrence, acute toxicity
Notes	Only included in the sensitivity analysis due to use of additional hydroxyurea on the control arm only

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Data checks on IPD provided suggest adequate sequence generation
Blinding? All outcomes	No	Trial was not blinded due to nature of treatment interventions
Incomplete outcome data addressed? All outcomes	Yes	IPD provided for all outcomes except late toxicity
Free of selective reporting?	Yes	N/A (IPD supplied for all outcomes except late toxicity)
Free of other bias?	Yes	Data checks on IPD provided suggest study is free of follow-up bias

Characteristics of excluded studies [ordered by study ID]

Bulnes 1986	Unable to make contact with the relevant investigators.
Dawel 1997	Unable to make contact with the relevant investigators.
Fernandez 1995	Data could not be located.
Hernandez 1991	Unable to make contact with the relevant investigators.
Lira-Puerto 1989	Data could not be located.
Singh 1985	Data could not be located.

(Continued)

Singh 2003	Unable to make contact with the relevant investigators.
Tseng 1997	Data could not be located.
Wong 1989	Data could not be located.
Wong 1999	Data could not be located.

DATA AND ANALYSES

Comparison 1. Chemoradiotherapy ± chemotherapy versus radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	18		Hazard Ratio (95% CI)	Subtotals only
1.1 Trials of chemoradiotherapy versus radiotherapy	16	3104	Hazard Ratio (95% CI)	0.81 [0.71, 0.91]
1.2 Trials of chemoradiotherapy plus chemotherapy versus radiotherapy	2	348	Hazard Ratio (95% CI)	0.46 [0.32, 0.66]

Comparison 2. Chemoradiotherapy versus Radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	17		Hazard Ratio (95% CI)	Subtotals only
1.1 Platinum based chemoradiotherapy	11	1670	Hazard Ratio (95% CI)	0.83 [0.71, 0.97]
1.2 Non-platinum based chemoradiotherapy	6	1458	Hazard Ratio (95% CI)	0.77 [0.63, 0.94]

Comparison 3. Chemoradiotherapy versus radiotherapy (plus sensitivity analysis of other trial designs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall Survival	20		Hazard Ratio (95% CI)	Subtotals only
1.1 Main group of 13 trials comparing chemoradiotherapy versus radiotherapy	16	3104	Hazard Ratio (95% CI)	0.81 [0.71, 0.91]
1.2 Group of trials using hydroxyurea on the control arm	3	1155	Hazard Ratio (95% CI)	0.63 [0.54, 0.74]
1.3 Trial using extended field radiotherapy on the control arm	1	403	Hazard Ratio (95% CI)	0.50 [0.37, 0.67]

HISTORY

Review first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

Concept and design: Claire Vale, Jayne F. Tierney, Lesley A. Stewart. **Administrative support:** Claire Vale. **Provision of study materials or patients:** David S. Alberts, Hongwei Chen, Slobodan Cikaric, Patricia J. Eifel, Melahat Garipagaoglu, Henry Keys, Nermina Kantardzic, Punita Lal, Rachele Lanciano, Felix Leborgne, Vicharn Lorvidhaya, Hiroshi Onishi, Robert G. Pearcey, Elizabeth Pras, Kenneth Roberts, Peter G. Rose, Gillian Thomas, Charles W. Whitney. **Collection and assembly of data:** Claire Vale. **Data analysis and interpretation:** Claire Vale, Jayne F. Tierney, Lesley A. Stewart, Mark Brady, Ketayun Dinshaw, Anders Jakobsen, Mahesh KB Parmar, Gillian Thomas, Ted Trimble, David S. Alberts, Hongwei Chen, Slobodan Cikaric, Patricia J Eifel, Melahat Garipagaoglu, Henry Keys, Nermina Kantardzic, Punita Lal, Rachele Lanciano, Felix Leborgne, Vicharn Lorvidhaya, Hiroshi Onishi, Robert G. Pearcey, Elizabeth Pras, Kenneth Roberts, Peter G. Rose, Charles W. Whitney. **Manuscript writing:** Claire Vale, Jayne F. Tierney, Lesley A. Stewart, Mark Brady, Ketayun Dinshaw, Anders Jakobsen, Mahesh K.B. Parmar, Gillian Thomas, Ted Trimble. **Final approval of manuscript:** Claire Vale, Jayne F. Tierney, Lesley A. Stewart, Mark Brady, Ketayun Dinshaw, Anders Jakobsen, Mahesh K.B. Parmar, Gillian Thomas, Ted Trimble, David S. Alberts, Hongwei Chen, Slobodan Cikaric, Patricia J. Eifel, Melahat Garipagaoglu, Henry Keys, Nermina Kantardzic, Punita Lal, Rachele Lanciano, Felix Leborgne, Vicharn Lorvidhaya, Hiroshi Onishi, Robert G. Pearcey, Elizabeth Pras, Kenneth Roberts, Peter G. Rose, Charles W. Whitney.

DECLARATIONS OF INTEREST

There were no conflicts of interest declared.

SOURCES OF SUPPORT

Internal sources

- UK Medical Research Council, UK.

External sources

- No sources of support supplied