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REVIEW ARTICLE

Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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A B S T R A C T

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.

Patients and Methods

We initiated a meta-analysis seeking updated individual patient data from all randomized trials to assess the effect of chemoradiotherapy on all outcomes. We prespecified analyses to investigate whether the effect of chemoradiotherapy differed by trial or patient characteristics.

Results

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, $P < .001$). A larger survival benefit was seen for the two 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, $P = .017$) and non–platinum-based (HR = 0.77, $P = .009$) 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. There was a suggestion of a difference in the size of the survival benefit with tumor stage, but not across other patient subgroups. Acute hematologic and GI toxicity was increased with chemoradiotherapy, but data were too sparse for an analysis of late toxicity.

Conclusion

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 randomized trials.

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INTRODUCTION

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.[1] A significant decline in incidence and mortality have been seen in North America, parts of Europe, Australia, and New Zealand, where screening programs have been implemented for some time.[1-5]

In 1999, after publication of five trials,[6-10] the National Cancer Institute (NCI) issued an alert recommending that "concomitant (cisplatin-based) chemoradiotherapy should be considered instead of radiotherapy alone in women with cervical cancer." This led to a change in the treatment for many women with cervical cancer.[11,12] Two systematic reviews[13-15] reported improved survival, progression-free survival, 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,[13] heterogeneity in trial results, and inconsistency in the definition of outcomes between trials.[15] 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.

We therefore initiated a systematic review and meta-analysis that aimed to collect, validate, and reanalyze IPD from all relevant randomized trials.[16] 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 the opportunity to look at these outcomes in the long-term. This IPD meta-analysis was initiated and coordinated by the Medical Research Council (United Kingdom) Clinical Trials Unit and carried out by the Chemoradiotherapy in Cervical Cancer Meta-Analysis Collaboration.

PATIENTS AND METHODS

The methods for this systematic review and meta-analysis followed a detailed, prespecified protocol (September 2004), a copy of which is available on request.

Trial Inclusion Criteria

Our inclusion criteria limited the main comparison to trials comparing concomitant chemoradiotherapy versus the same radiotherapy. However, given the importance to the NCI alert of two trials using hydroxyurea on the control arm[9,10] and one trial that gave extended-field radiotherapy on the control arm,[7,17] we analyzed these trials alongside the main comparison. For the main comparison, trials had to be properly randomized and should have aimed to randomly assign women with cervical cancer who had not received previous treatments likely to interfere with protocol treatments or comparisons. Trials should have been completed by the time of the final analyses (May 2007) and compared cytotoxic chemoradiotherapy (with or without surgery) with the same radiotherapy (with or without surgery). Chemotherapy should have been given on the experimental arm only. Trials were excluded if they used additional noncytotoxic treatments or only noncytotoxic radiosensitizers/radioprotectors on the experimental arm. Trials that used hydroxyurea as the sole chemotherapy agent have been considered in a prior systematic review[18,19] and are not included here.

Trial Identification

To avoid publication bias, published and unpublished trials were included in the meta-analysis. We searched MEDLINE and CancerLit using an optimal search strategy,[20] and also LILACS, the Physicians' Data Query, and other trials registers. These were supplemented from reference lists of identified trial reports and review articles and from meeting proceedings (International Gynecologic Cancer Society and the Society for Gynecologic Oncology, 1994 through 2007). Furthermore, all participating investigators were asked to supplement our provisional list of trials. Searches were regularly updated until November 2007.

Data Collection

We sought to collect up-to-date information for all patients randomly assigned, including those excluded from investigators' own analyses, on date of randomization, treatment allocation, tumor response, locoregional and distant progression/recurrence status, survival, cause of death, and acute and late toxicity. Baseline data on age, histology, International Federation of Gynecology and Obstetrics stage, tumor grade, performance status, and lymph node involvement were also sought. All data were checked for validity, consistency, and integrity of randomization and follow-up.[16] Inconsistencies were resolved, and final database entries were validated by the responsible trial investigator, data manager, or statistician.

Definition of Outcomes

The primary outcome, overall survival, was defined as the time from randomization 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 was defined as the time from randomization until locoregional recurrence/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 randomization 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 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 disease-free survival was defined as the time from randomization until locoregional recurrence, metastasis, or death by any cause. Time to locoregional recurrence was defined as the time from randomization 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 randomization until first metastasis; patients without metastases were censored on the date of last follow-up or death. For trials that only recorded the first event, the methods of censoring described above were used.

Investigators were asked to supply acute and late toxicity data according to criteria used in their own trials. All trials used a five-grade system where 0 signifies no toxicity and 5 signifies death, making it reasonable to combine the results.

Analysis

All analyses (unless otherwise stated) were prespecified in the meta-analysis protocol and were performed on an intention-to-treat basis. For 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.[21] For binary outcomes of response and toxicity, the number of events and numbers of patients were used to calculate Peto odds ratio estimates of treatment effect[21] for individual trials, which were pooled across trials using the stratified-by-trial, fixed-effect model.[21] Trial results were also combined using the random effects approach.[22]

Three four-arm trials in the meta-analysis[23-25] 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 analyzed as separate trials (denoted A and B; Table 1). Two three-arm trials[9,26] 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; however, for the meta-analysis plot, each chemoradiotherapy arm is compared with the radiotherapy control arm as though they were two trials (A and B).

To explore the impact of trial characteristics on the effect of chemoradiotherapy, we prespecified 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 (optimal radiotherapy of $\geq$ 45 Gy external beam plus brachytherapy [any dose], sub-optimal radiotherapy of $\geq$ 45 Gy external beam without brachytherapy or $<$ 45 Gy external beam with brachytherapy); planned radiotherapy duration ($\leq$ 8 weeks, $>$ 8 weeks). For the subset of trials that used cisplatin-based chemotherapy only, we also planned analyses of chemotherapy frequency ($\leq$ 1 weekly cycles of chemotherapy, $>$ 1 weekly cycles of chemotherapy) and chemotherapy dose-intensity ($\leq$ 25 mg/m^2/wk of cisplatin, $>$ 25 mg/m^2/wk of cisplatin). These analyses focused on the primary outcome of overall survival, with other outcomes carried out to support or refute any patterns found. For serious (grades 3 to 5) acute toxicity, trials were grouped according to their use of platinum-based chemoradiotherapy, non–platinum-based chemoradiotherapy, chemoradiotherapy plus additional chemotherapy, additional radiotherapy on the control arm, and additional hydroxyurea on the control arm, with HRs calculated for each group.

The effects of chemoradiotherapy within patient subgroups were investigated using similar stratified analyses. HRs were obtained for each predefined subgroup within each trial. These HRs were then combined to give overall HRs. χ^2 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.

Table 1. Characteristics of Included Studies

Trial	Accrual Period	Stage	Affected Para-Aortic Nodes Excluded?	Comparison	Concomitant CT (dose in mg/m^2)	CT Schedule: No. of Cycles	CT Schedule: Frequency (weeks)	RT (Gy)	BRT (Gy to point A)	RT Duration (days)	No. of Patients
Main analysis											
*Thomas (a)[24]	1987-1995	Ib (>5 cm) to IVa	No	RT *v* CTRT	IV FU 32 mg/m^2	2	3	50	40	< 56	116
*Thomas (b)[24]	1987-1995	Ib (>5 cm) to IVa	No	Hyperfractionated RT *v* hyperfractionated CTRT	IV FU 32 mg/m^2	2	3	50	40	< 56	118
*†Lorvidhaya (a)[25]	1987-1994	IIb, IIIb to IVa	No	RT *v* CTRT	MMC 10 mg/m^2 FU (oral) 4,200 mg	2	4	50	28	49-56	475
*†Lorvidhaya (b)[25]	1987-1994	IIb, IIIb to IVa	No	RT + Adj CT *v* CTRT + Adj CT	MMC 10 mg/m^2, FU (oral) 4,200 mg Adj FU 5,600 mg (oral)	2 3	4 4	50	28	49-56	451
Onishi[44]	1988-1998	IIb to IV	No	RT *v* CTRT	CDDP1: 100 mg/m^2 CDDP2: 50 mg/m^2 CBDCA: 100 mg/m^2	2 3 6	2-3 1 1	50	24	45-55	49
Roberts[49]	1991-2001	Ib2, II to IVa	No	RT *v* CTRT	MMC 30 mg/m^2	2	6	IB2-IIB: 40‡ III-IVA: 46‡	45-50 40-45	Not specified	248
Peters[8,46] SWOG8797	1991-1996	Ia2 to IIa	No	S + RT *v* S + CTRT + CT	CDDP 70 mg/m^2 FU 4,000 mg/m^2	4	3	49.3	None	42	268
Pearcey[43]	1991-1996	Ib-IIb (> 4 cm) III to IVa	No	RT *v* CTRT	CDDP 40 mg/m^2	5	1	45	24-35	46-56	259
Keys[6] GOG0123	1992-1997	Ib (bulky)	Yes	S + RT *v* S + CTRT	CDDP 40 mg/m^2	6	1	45	30	< 70	374
*Chen (a)[23]	1993-1994	IIb to III	No	RT *v* CTRT	CDDP 60 mg/m^2 FU 1,500 mg/m^2 VCR 2 mg/m^2	2	3	40	50	49	60
*Chen (b)[23]	1993-1994	IIb to III	No	RT + hyperthermia *v* CTRT + hyperthermia	CDDP 60 mg/m^2 FU 1,500 mg/m^2 VCR 2 mg/m^2	2	3	40	50	49	60
Pras	1995-1999	Ib to IIa >4 cm IIb to IVa	Yes	RT *v* CTRT	CDBCA 300 mg/m^2 FU 2,400 mg/m^2	3	4	45	35	> 56	54
Leborgne	1995-2004	Ib2 to IVb	No	RT *v* CTRT	CDDP 80 mg/m^2 FU 2,400 mg/m^2	2	4	40	42	40	340
Garipagaoglu[48]	1996-1997	IIb, IIIb	No	RT *v* CTRT	CDDP 120 mg/m^2	2	3	46-50	20	61-62	44
Kantardzic[45]	1996-1999	IIb to III	No	RT *v* CTRT + CT	CDDP 40 mg/m^2 BLM 15 mg/m^2	6 6	3 3	46	25-30	56-60	80
*Lanciano (a)[26] GOG0165	1997-1998	IIb, IIIb, IVa	Yes	RT *v* CTRT	CDDP 40 mg/m^2	6	1	45	30 (HDR) or 40 (LDR)	< 56	50
*Lanciano (b)[26] GOG0165	1997-1998	IIb, IIIb, IVa	Yes	RT *v* CTRT	FU 1,125 mg/m^2	6	1	45	30 (HDR) or 40 (LDR)	< 56	51
Lal[50]	2000-2006	II to IV	No	RT *v* CTRT	CDDP 35 mg/m^2	5	1	50	18	63	180
Cikaric[47]	2002-2003	IIb to IVa	No	RT *v* CTRT	CDDP 40 mg/m^2	5	1	46	35	45	200
Sensitivity analysis											
Whitney[10] GOG0085	1986-1990	IIb to IVa	Yes	RT + HU *v* CTRT	CDDP 50 mg/m^2 FU 4,000 mg/m^2	2	4	40.8 or 51 or 61.2	40 40 0	< 70	388
§Morris[7,17] RTOG9001	1990-1997	Ib to IIa (>4 cm or positive pelvic nodes) IIb to IVa	Yes	RT *v* CTRT	CDDP 75 mg/m^2 FU 4,000 mg/m^2	3	3	45	40	< 56	403
*Rose (a)[9] GOG0120	1992-1997	IIb to IVa	Yes	RT + HU *v* CTRT	CDDP 40 mg/m^2	6	1	40.8 or 51 or 61.2	40 40 0	70	384
*Rose (b)[9] GOG0120	1992-1997	IIb to IVa	Yes	RT + HU *v* CTRT + HU	CDDP 50 mg/m^2 FU 4,000 mg/m^2 HU (oral) 2 g/m^2	2 1	4 6	40.8 or 51 or 61.2	40 40 0	70	383

Abbreviations: CT, chemotherapy; RT, radiotherapy; BRT, brachytherapy; CTRT, chemoradiotherapy; IV, intravenous; FU, fluorouracil; MMC, mitomycin; Adj, adjuvant; CDDP, cisplatin; CDBCA, carboplatin; S, surgery; VCR, vincristine; BLM, bleomycin; HDR, high-dose rate; LDR, low-dose rate; HU, hydroxyurea; GOG, Gynecologic Oncology Group; RTOG, Radiation Therapy Oncology Group.

*Three-arm and four-arm trials were analyzed as two separate trials.

†After 673 patients were randomly assigned, FU was given 300 mg/day (oral) Monday through Friday for duration of external-beam radiotherapy.

‡With or without 8- to 10-Gy parametrial boost.

§Extended-field external-beam radiotherapy (to para-aortic nodes) given on the control arm.

Results are also presented as absolute differences, calculated from the overall HR and the control arm event rate.[27] χ^2 heterogeneity tests[28] and the I^2 statistic[29] were used to assess statistical heterogeneity across trials. Kaplan-Meier curves[30] are nonstratified. All *P* values are two-sided.

The main analyses described were limited to trials that compared concomitant chemotherapy and radical radiotherapy (with or without surgery) with the same radical radiotherapy (with or without surgery). However, to establish how sensitive the effect of chemoradiotherapy is to different trial designs and for completeness, the analyses were repeated including trials that used hydroxyurea or extended-field radiotherapy in the control arms.

Where IPD were not available, wherever possible, we calculated HRs and associated statistics from reported time-to-event analyses[31,32] and considered the impact on the analyses of IPD.

RESULTS

Main Analysis

We identified 25 randomized trials that were eligible for the main analysis. We were unable to include data from 10 trials (1,113 patients), either because data could not be located[33-38] (six trials, 814 patients) or because we were unable to make contact with the relevant investigators[39-42] (four trials, 299 patients). Data were therefore available for 3,452 women from 15 trials[23-26,43-50] (Leborgne, unpublished data; Pras, unpublished data). This includes 85% of women from trials that used cisplatin-based chemoradiotherapy and almost 80% of women from trials that used fluorouracil (FU)- and/or mitomycin-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 Table 1.

The 15 available trials accrued 44 to 926 patients between May 1987 and June 2006. Eleven trials used platinum-based chemoradiotherapy, either as a single agent (eight trials) or in combination regimens (three trials). Three trials used nonplatinum regimens comprising either FU, mitomycin, or a combination of the two. One three-arm trial randomly assigned patients to receive chemoradiotherapy either with cisplatin or FU.[26] Each of the trials aimed to prescribe external-beam radiation at a dose to the tumor of between 40 and 61.2 Gy, and all except one trial[8] (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 overall survival, disease-free survival, locoregional disease-free survival, and metastases-free survival were available for all trials, but tumor response was only available for two trials, preventing an analysis of this outcome.

Patient characteristics for the 15 trials are listed in Appendix Table A1 (online only). 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 nine 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 between 35 and 64 years of age, with good performance status. They had tumors that were largely of squamous cell histology (89%), stage IIb (36%), or stage III (36%), and moderately differentiated (35%). However, as there was generally no central pathology review, the precise definition of tumor grade may vary from trial to trial. Three trials excluded women with involved para-aortic nodes[6,26] (Pras, unpublished data), and para-aortic nodal status was either uninvolved (48%) or unknown (51%) for the vast majority of the women from the remaining trials.

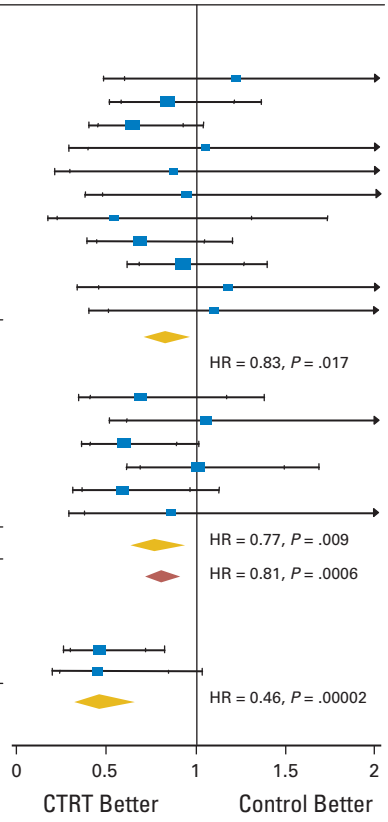
Overall survival data were supplied for 15 trials including 3,452 women, and 1,138 deaths have been recorded. Figure 1A shows the results for these trials, grouped according to whether chemoradiotherapy only was used or whether additional chemotherapy after chemoradiotherapy was administered. Although there was no evidence of statistical heterogeneity within each trial group (chemoradiotherapy only, $P = .646$, $I^2 = 0.00$; chemoradiotherapy plus adjuvant chemotherapy, $P = .945$, $I^2 = 0.00$), there was a large and significant difference between groups in the benefit of chemoradiotherapy (interaction $P = .004$). The HR for the two trials in which chemoradiotherapy plus adjuvant chemotherapy was administered is 0.46 (95% CI, 0.32 to 0.66; $P = .00002$), representing a 54% reduction in the risk of death and translating into an absolute benefit of 19% at 5 years (from 60% to 79%). 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. The HR of 0.81 (95% CI, 0.71 to 0.91) represents a highly significant ($P = .0006$), 19% relative reduction in the risk of death with chemoradiotherapy compared with radiotherapy and translates to an absolute survival benefit of 6% at 5 years (from 60% to 66%). The survival curves for these 13 trials and for the two trials in which adjuvant chemotherapy was used follow a similar pattern, although separation of the curves is greater with adjuvant chemotherapy, albeit that follow-up for one of the trials[45] in this group of trials is somewhat less mature (median follow-up 2.35 years) than that for the main group of 13 trials (overall median follow-up, 4.77 years; Fig 1B). The results are similar when the random effects model[22] was applied.

Subsequent prespecified analyses by trial group were therefore restricted to the 13 trials that had an unconfounded comparison of chemoradiotherapy versus radiation. 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), the planned radiotherapy dose, or the total planned duration of radiotherapy (Table 2). Similarly, for the eight trials that used cisplatin-based chemoradiotherapy, 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.

Data on overall disease-free survival, locoregional disease-free survival, and metastases-free survival were available from all of the 13 trials in the unconfounded comparison of chemoradiotherapy versus radiation. For disease-free survival, there were 1,376 events in total, of which 1,087 were recurrences or metastases and 289 were deaths (Appendix Fig A1, online only). The HR of 0.78 (95% CI, 0.70 to 0.87; $P = .000005$) translates to an absolute disease-free survival benefit of 8% at 5 years (from 50% to 58%). There were similar and significant absolute benefits of chemoradiotherapy on 5-year locoregional disease-free survival (9%; $P = .000003$), time to locoregional recurrence/progression (6%; $P = .00009$; Table 3), and metastases-free survival (7%; $P = .0004$). However, there was a smaller and less convincing improvement in time to metastases at 5 years (4%; $P = .037$; Table 3). Insufficient data were available to assess the impact of chemoradiotherapy on response.

A

Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of Chemoradiation *v* radiotherapy						
(a) Platinum-based CTRT						
Onishi[44] (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey[43] (CDDP)	53	130	60	129	-5.00	28.20
GOG0123[6] (CDDP)	49	185	69	189	-12.90	29.38
Chen[23] (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen[23] (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165[26] (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric[47] (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu[48] (CDDP)	9	22	8	22	0.70	4.23
Lal[50] (CDDP)	14	94	12	86	0.62	6.49
Sub-total	292	841	340	829	-29.89	157.23
(b) Non–platinum-based CTRT						
Thomas[24] (a) (FU)	24	57	32	58	-5.16	13.83
Thomas[24] (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts[49] (MMC)	25	124	39	124	-8.39	15.92
GOG0165[26] (b) (FU)	11	27	12	24	-0.82	5.55
Sub-total	180	729	216	729	-25.87	98.28
Total	472	1,570	544	1,534	-54.56	251.54
Trials of CTRT + adjuvant chemotherapy *v* radiotherapy						
SWOG8797[8,46] (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic[45] (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10



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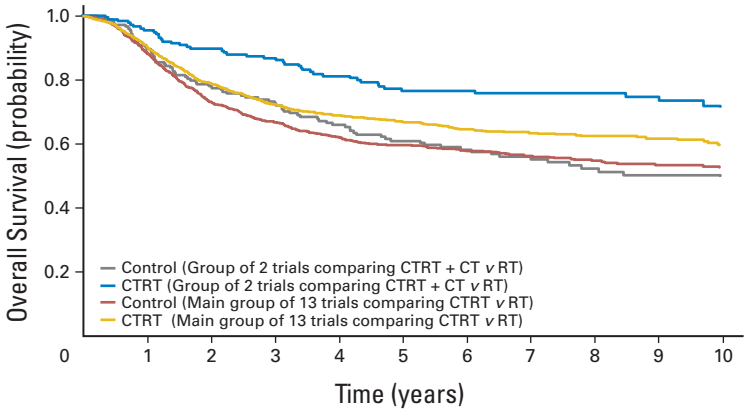

No. at risk

Main group of 13 trials (Additional numbers at risk on control arm due to double counting of control arm from one three-arm trial[26])

Control	1,558	1,244	921	760	610	499	350	274	192	131	81
CTRT	1,570	1,285	1,019	836	694	582	401	309	223	158	101

Group of two trials comparing CTRT + CT *v* RT

Control	173	155	133	121	106	95	82	67	51	35	21
CTRT	175	165	155	144	129	115	106	89	74	58	37

Fig 1. (A) Hazard ratio (HR) plot for survival. Each trial is represented by a square, the center of which gives the hazard ratio for that trial. Size of square is proportional to the information in that trial. Ends of horizontal bars denote 99% CI and inner bars mark 95% CI. Trials are ordered chronologically by date of start of trials (oldest first). The shaded diamonds give the overall hazard ratio for the combined results of all trials; the center denotes the hazard ratio, and the extremities, the 95% CI. Trials of chemoradiation versus radiotherapy: HR = 0.81 (95% CI, 0.71 to 0.91), $P = .0006$; heterogeneity $\chi^2 = 12.43$, $P = .646$; $I^2 = 0.00$. Trials of chemoradiotherapy + adjuvant chemotherapy versus radiotherapy: HR = 0.46 (95% CI, 0.32 to 0.66), $P = .00002$; heterogeneity $\chi^2 = 0.00$, $P = .945$; $I^2 = 0.00$. Interaction test: $\chi^2 = 8.39$, $df = 1$, $P = .004$. (B) Kaplan-Meier curves for survival. GOG, Gynecologic Oncology Group; SWOG, Southwest Oncology Group; FU, fluorouracil; MMC, mitomycin; CDDP, cisplatin; CDBCA, carboplatin; VCR, vincristine; BLM, bleomycin; CTRT, chemoradiotherapy; O-E, observed minus expected events.

Patient subgroup analyses were similarly restricted to the 13 trials in the unconfounded group that were able to supply data. A planned analysis based on iliac node involvement was not completed because there were insufficient data (Appendix Table A1). Also, as most patients for whom data was supplied had good performance status and either unknown or negative para-aortic nodal status, 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, tumor grade, or pelvic lymph node involvement, although the analyses by grade and pelvic node involvement were limited to eight and five trials, respectively (Appendix Table A2, online only). There was a suggestion of trend in

Table 2. Results of Trial Group Analyses for Survival

Variable	Main Analysis (13 trials) HR	95% CI	Interaction *P*
Planned chemotherapy type			
Platinum based	0.84	0.72 to 0.98	
Nonplatinum based	0.76	0.62 to 0.94	.48
Planned radiotherapy dose			
≥ 45 Gy + BRT	0.78	0.68 to 0.89	
< 45 Gy + BRT	0.93	0.70 to 1.24	.26
Planned radiotherapy duration, weeks			
≤ 8	0.83	0.72 to 0.96	
> 8	0.73	0.57 to 0.93	.35
Planned chemotherapy cycle length, weeks*			
≤ 1	0.74	0.60 to 0.92	
> 1	0.95	0.72 to 1.25	.16
Planned cisplatin dose-intensity, mg/m^2/wk*			
≤ 25	0.93	0.70 to 1.24	
> 25	0.76	0.62 to 0.96	.25
Cisplatin regimen*			
Single agent	0.76	0.62 to 0.93	
Combination	0.93	0.70 to 1.24	.25
Chemotherapy regimen			
Single agent	0.75	0.63 to 0.88	
Combination	0.86	0.71 to 1.04	.29

NOTE. Two trials in which additional adjuvant chemotherapy was administered on the treatment arm are excluded.
*Results are based only on trials in which cisplatin-based chemoradiation was administered.

the relative effect of chemoradiotherapy by tumor stage ($P = .017$), 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 Ib to IIa cervical cancer, 7% for women with stage IIb cervical cancer, and 3% for women with stage III to IVa cancer. This trend, however, was not supported in the analysis of disease-free survival (test for trend, $P = .073$; Fig 2).

For trials for which IPD were not available, it was only possible to estimate HRs for survival[31,32] for three[35,36,41] of the 10 trials, two of which contributed to the main group of 13 trials and one trial to the group of trials that used additional chemotherapy after chemoradiotherapy. However, incorporating them into the meta-analysis did not materially change the results for either group (data not shown).

Sensitivity Analyses

Three trials were included in the sensitivity analysis of trials of different designs.[9,10,17] Data were supplied for 1,366 women (100%), including 84 women who had been excluded from the investigator's original analyses. 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,[17] and in two trials, additional hydroxyurea was administered in the control arm.[9,10] The trials planned to give 40.8 to 61.2 Gy of external-beam radiation plus brachytherapy. The planned total duration for all radiotherapy (external-beam and brachytherapy) was fewer than 56 days[17] and fewer than 70 days.[9,10] The median follow-up for living patients across these trials was 8.4 years. Characteristics of these trials are shown in Table 1. Patient characteristics in the three trials 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 heterogeneity ($P = .12$; $I^2 = 28.28$). Moreover, Figure 3A illustrates that the treatment effect observed in trials using hydroxyurea on control (HR, 0.63; 95% CI, 0.52 to 0.76; $P = .0000008$) differed from that in the main analysis (test for interaction, $P = .029$), 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; $P = .000006$) also differed from that in the main analysis (test for interaction, $P = .004$), with an absolute survival benefit of 21% (from 50% to 71%) at 5 years. Although these benefits seem greater, the control group survival for both groups is lower than that for the main group of 13 trials (Fig 3B). 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.

Analyses of Toxicity

Data on overall acute hematologic toxicity and GI toxicity were supplied for 16 trials. Data were available on WBC and genitourinary toxicity for 14 trials, hemoglobin toxicity for 13 trials, platelet toxicity for 12 trials, and skin toxicity for 10 trials.

Serious hematologic toxicity increased by approximately two- to 10-fold in individual trials. However, for the group of trials that used hydroxyurea on the control arm, a high level of serious hematologic toxicity was evident on both arms but slightly greater

Table 3. Results of All Outcomes for the Main Analyses

Survival Measure	Main Analysis (13 trials) HR	95% CI	*P*	Absolute 5-Year Survival Benefit (%)
Overall disease-free survival	0.78	0.70 to 0.87	.000005	8
Locoregional disease-free survival	0.76	0.68 to 0.86	.000003	9
Metastases-free survival	0.81	0.72 to 0.91	.0004	7
Locoregional disease-free interval	0.74	0.64 to 0.86	.00009	6
Metastases-free interval	0.83	0.71 to 0.99	.037	4

NOTE. Two trials in which additional adjuvant chemotherapy was administered on the treatment arm are excluded.

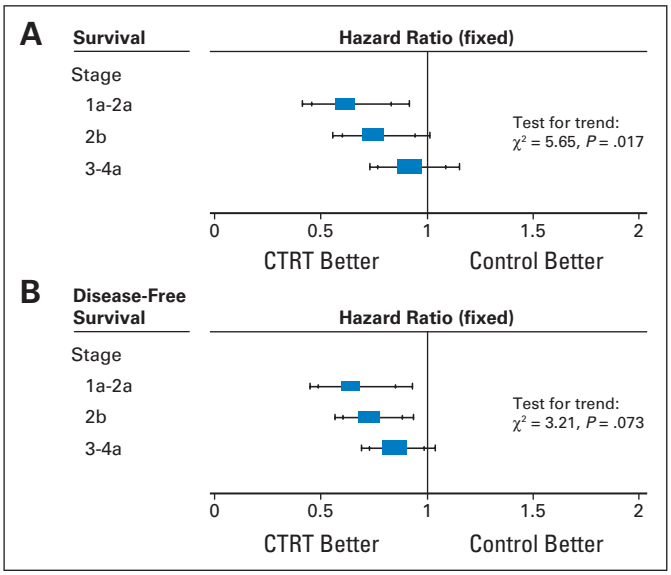

Fig 2. (A) Survival and (B) disease-free survival by tumor stage (main group of 13 trials only). CTRT, chemoradiotherapy.

on the control arm (odds ratio = 0.74; 95% CI, 0.53 to 1.03; $P = .075$). A similar pattern of results was observed for WBC toxicity, as most of the 517 events (92%) recorded for overall hematologic toxicity were WBC toxicities. There was a significant increase in serious GI toxicity for the groups of trials using platinum-based chemoradiotherapy ($P = .000002$), chemoradiotherapy plus additional chemotherapy ($P = .001$), and additional radiotherapy on the control arm ($P = .000002$). This increase was not observed for the group of trials using non–platinum-based chemoradiotherapy ($P = .465$), where the event rate was low (approximately 2%) on both arms, or for the trials in which hydroxyurea was administered on the control arm ($P = .591$), where the event rate was high (approximately 10%) on both arms. For acute hemoglobin toxicity, acute platelet toxicity, genitourinary toxicity, and skin toxicity, few serious events were recorded, making formal analyses 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 for only four trials. Furthermore, within these trials there were substantial missing data. Therefore, there were insufficient data available to assess whether serious late toxicity is affected by the type of treatment. The available data suggest 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 five studies that formed the basis of the 1999 NCI alert, and include 4,818 women. On the basis of the 15 trials in the main analysis, there was clear evidence that adding chemotherapy to radiotherapy improves both overall and disease-free survival. For the group of trials in which chemoradiotherapy alone was used, there was a 6% absolute survival benefit and an 8% disease-free survival benefit at 5 years, with no evidence of heterogeneity. These analyses endorse the recommendations made in the NCI alert, but with far greater reliability and precision regarding the gains of chemoradiotherapy.

The benefit of chemoradiotherapy on survival and disease-free survival was supported by similar benefits on the other outcomes analyzed, 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[15] and confirmed in this meta-analysis may indicate that it also has a modest systemic effect.

Larger benefits were seen for the trials in which additional chemotherapy was administered after 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[36] 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 administered after 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[13] and significant statistical heterogeneity.[14] Analyzing these trials separately facilitates interpretation and minimizes heterogeneity. There were larger absolute survival benefits for the group of trials in which hydroxyurea was administered on the control arm and for the single trial 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 three of 13 trials (529 patients) in the main analysis, thus including 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.[13-15] These benefits are, however, likely to be generalizable 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,[51] but this meta-analysis shows a significant benefit associated with nonplatinum regimens. However, as our results are not based on a direct comparison, we cannot be clear about the relative merits of platinum versus nonplatinum. The only randomized trial that has directly compared platinum (cisplatin) and non–platinum-based FU chemoradiotherapy closed early, because interim analyses suggested that FU-based chemoradiotherapy was unlikely to improve progression-free survival 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.[26] For women who are unable to tolerate cisplatin or when more easily tolerated chemotherapy is required, non–platinum-based chemoradiotherapy offers an additional option.

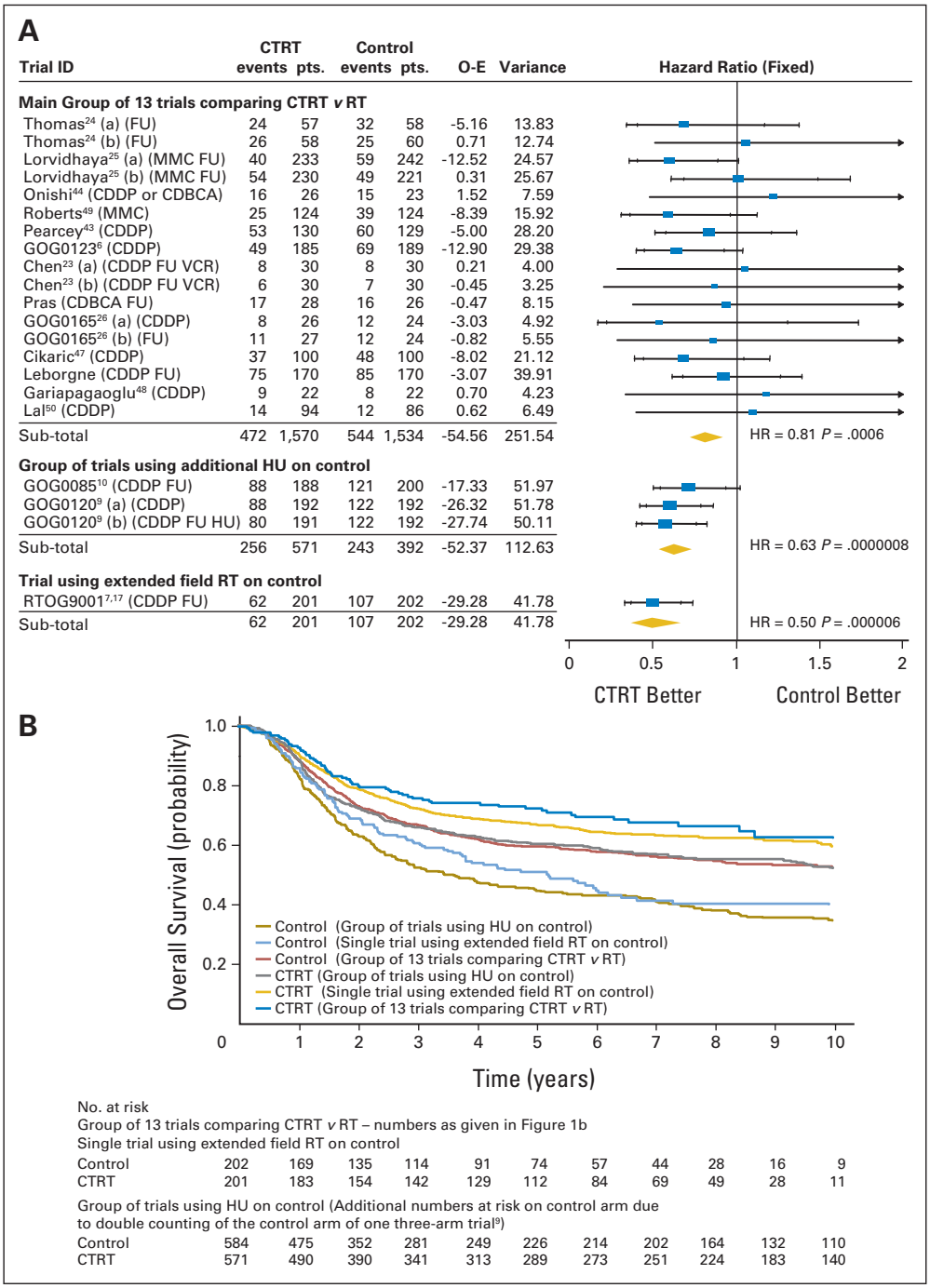

Fig 3. (A) Hazard ratio (HR) plot for survival (sensitivity analysis). Main group of trials: HR = 0.81 (95% CI, 0.71 to 0.91), $P = .0006$; heterogeneity $\chi^2 = 12.43$, $I^2 = 0.00$. Trials using HU on control arms: HR = 0.63 (95% CI, 0.54 to 0.74), $P = .00000002$; heterogeneity $\chi^2 = 1.39$, $I^2 = 0.00$. Trials using additional radiotherapy (RT) on control: HR = 0.50 (95% CI, 0.37 to 0.67), $P = .000006$. (B) Kaplan-Meier curves for survival (sensitivity analysis). GOG, Gynecologic Oncology Group; RTOG, Radiation Therapy Oncology Group; FU, fluorouracil; MMC, mitomycin; CDDP, cisplatin; CDBCA, carboplatin; VCR, vincristine; BLM, bleomycin; HU, hydroxyurea; CTRT, chemoradiotherapy; O-E, observed minus expected events.

Other planned analyses by trial characteristics were hampered because most trials gave radiotherapy over 8 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 seems 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 tumor stage, with estimated absolute survival benefits of 10% (stage Ia to IIa), 7% (stage IIb), and 3% (stage III to IVa) at 5 years. Even if this trend occurred by chance, applying the overall HR (0.81) to each of the stage subgroups gives an improvement in 5-year survival for all stages, thus confirming that 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 hematologic and GI toxicities, few of the trials in this meta-analysis measured late toxicity, and only one of the 28 trials eligible for inclusion in this meta-analysis reported quality-of-life

outcomes.[34] This highlights the need for prospective evaluations of treatment tolerability and quality of life 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 randomly assigned patients, would contribute to the main analysis. Although 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 effect to some degree. Since the final analyses were completed, we have become aware of one completed trial that compared weekly cisplatin-based chemoradiotherapy with radiotherapy alone in 160 patients[52] and one large ongoing trial of chemoradiotherapy versus radiotherapy (NC00193791), both from India. Once completed, we will seek inclusion of these trials in an updated analysis.

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 nonplatinum regimens and to investigate whether additional chemotherapy offers additional benefits. 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 organizational difficulties, particularly in the developing world, mean that in countries unable to implement such programs, 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. Nevertheless, 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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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