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Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials

Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration*,[1]

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Abstract

Despite the enrolment of more than 3000 women in randomised trials, the benefits and risks of neoadjuvant chemotherapy in the treatment of locally advanced cervical cancer remain uncertain. We carried out a systematic review and meta-analysis of individual patient data to assess the effect of neoadjuvant chemotherapy in two comparisons. In the first comparison, of neoadjuvant chemotherapy followed by radical radiotherapy compared with the same radiotherapy alone, we obtained data from 18 trials and 2074 patients. When all trials were considered together, a high level of statistical heterogeneity suggested that the results could not be combined indiscriminately. A substantial amount of heterogeneity was explained by separate analyses of groups of trials. Trials using chemotherapy cycle lengths of 14 days and shorter (Hazard Ratio (HR)) = 0.83, 95% Confidence Interval (CI) = 0.69–1.00, $P = 0.046$) or cisplatin dose intensities greater than or equal to 25 mg/m^{2}per week (HR = 0.91, 95% CI = 0.78-1.05, $P = 0.20$) tended to show an advantage for neoadjuvant chemotherapy on survival. In contrast, trials using cycle lengths longer than 14 days (HR = 1.25, 95% CI = 1.07–1.46, $P = 0.005$) or cisplatin dose intensities lower than 25mg/m^2 per week (HR = 1.35, 95% CI = 1.11-1.14, $P = 0.002$) tended to show a detrimental effect of neoadjuvant chemotherapy on survival. In the second comparison, of neoadjuvant chemotherapy followed by surgery compared with radical radiotherapy alone, data from 5 trials and 872 patients were obtained. The combined results from all trials (HR = 0.65, 95% CI = 0.53–0.80, $P = 0.0004$) indicated a highly significant reduction in the risk of death with neoadjuvant chemotherapy, but there were some differences between the trials in their design and results. Despite some unexplained heterogeneity, the timing and dose intensity of cisplatin-based neoadjuvant chemotherapy appears to have an important impact on whether or not it benefits women with locally advanced cervical cancer and warrants further exploration.

Keywords: Systematic review; Meta-analysis; Individual patient data; Cervical neoplasms; Drug therapy; Chemotherapy; Adjuvant; Neoadjuvant

1. Introduction

The incidence of cervical cancer has declined in both North America and Europe. However, on a global scale, it is the second most common cancer in women, and is the most prevalent female malignancy in many developing countries [1]. Most patients (in the developed world) present with early disease, either confined to the cervix or with limited extension beyond it (International Federation of Gynecology and Obstetrics (FIGO) stages IB1–IIA). In the past, standard treatment was usually radical radiotherapy or radical hysterectomy, with node dissection, each giving 5-year survival rates of around 80–90% [2]. Radical radiotherapy, comprising external beam and intracavitary treatment, tended to be the treatment of choice for locally advanced disease (FIGO stages IIB, III and IVA) and offered an alternative to radical surgery for patients with tumours larger than 4 cm confined to the cervix (FIGO stage IB bulky) [3]. Pelvic radiotherapy offered a good chance of cure, but the maximum radiation dose that was given to patients was limited by normal tissue tolerance, particularly of the small bowel, rectum and bladder, and 5-year survival using radio-

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therapy ranged from approximately 60% for patients with stage IIB disease to only approximately 20% for patients with stage IV disease [2]. In 1999, a National Cancer Institute Alert, based on the results of five randomised trials recommended that concomitant chemoradiation should be considered instead of radiotherapy alone in women with cervical cancer. A subsequent systematic review and meta-analysis of data presented in publications suggested a large benefit of concomitant chemoradiotherapy on survival, progression-free survival and local and distant control rates [4]. Thus, for many, concomitant chemoradiotherapy has become the new 'standard of care' for locally advanced disease.

There are, however, still potential therapeutic advantages to giving chemotherapy alongside local treatments that were standard for locally advanced disease, prior to the widespread use of concomitant chemoradiotherapy. Neoadjuvant chemotherapy given before radiotherapy may reduce the tumour size and control micrometastatic disease. In addition, by giving chemotherapy prior to radiotherapy, rather than concomitantly, increased radiotherapy toxicity may be less likely. Chemotherapy given prior to surgery may render inoperable tumours (FIGO stages IIB–IIIB) operable and treat metastases. A number of randomised trials have explored the use of neoadjuvant chemotherapy as an adjunct to either radiotherapy or surgery in comparison with radiotherapy alone and cisplatin-based regimens have been favoured, because of the impressive response rates [3]. Most of these randomised trials have been relatively small and their results range from a significant increase in survival [5] to a significant reduction in survival with neoadjuvant chemotherapy [6]. Most trials, however, have shown inconclusive results. Nevertheless, the combination of the results of all relevant trials in a meta-analysis (within each treatment setting) might give sufficient statistical power to determine whether neoadjuvant chemotherapy is useful. A prior systematic review and meta-analysis based on published summary data extracted from trial reports was of limited value, because only a subset of the trials were published at the time of the analysis and, of those, some did not report sufficient survival data to allow an appropriate analysis to be performed [7]. As noted in the publication, the only analysis that could be carried out might be unrepresentative and potentially biased and no firm conclusions could be drawn.

We therefore initiated a systematic review and individual patient data (IPD) meta-analysis to collect, validate and re-analyse trial data on all randomised patients from all relevant trials. The advantages of collecting IPD over published summary data for a meta-analysis are many [8]. In particular, it allows us to summarise the effect of neoadjuvant chemotherapy from all, not just the published trials; it permits more sensitive time-to-event analysis and enables us to examine whether any effect of treatment differs between subgroups of patients. Furthermore, by seeking updated follow-up, it provides a unique opportunity to look at long-term survival and adverse effects in a relatively young group of women. This IPD meta-analysis was initiated and coordinated by the Medical Research Council (UK) Clinical Trials Unit and carried out by the Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration.

2. Patients and methods

This systematic review and meta-analysis followed a detailed, pre-specified protocol (March 1999), which set out the objectives, inclusion criteria for trials, data to be collected, and analyses to be done. These are summarised here, but a full protocol is available on request.

2.1. Treatment comparisons

Two related, but separate treatment comparisons were considered in the systematic review.

1. Neoadjuvant chemotherapy followed by local treatment versus the same local treatment.
2. Neoadjuvant chemotherapy followed by surgery (±radiotherapy) versus radical radiotherapy.

Comparison 1 investigates the effect of adding neoadjuvant chemotherapy to local treatment compared with the same local treatment. Comparison 2 investigates the effect of a combined neoadjuvant chemotherapy and surgical approach compared with what had been the more standard radiotherapy approach.

2.2. Trial inclusion criteria

To be included, trials had to be properly randomised and the treatment assignment done in such a way that the allocation could not be known beforehand. Trials had to include patients with locally advanced cervical cancer who had received neoadjuvant cytotoxic chemotherapy before radiotherapy or surgery or both treatments. Concurrent chemoradiotherapy trials were not included. The comparisons had to be unconfounded by use of additional agents or interventions. The protocol specified that patient enrolment should have started after 1 January 1975 and be completed by 30 June 1998. This would have meant excluding a lot of the randomised evidence and so the protocol was subsequently amended to include all closed trials at the time of the Collaborators' Conference (September 2000). Trials should have made one of the treatment comparisons described above. In comparison 2, trials that also used adjuvant radiotherapy in the neoadjuvant chemotherapy arm were included.

2.3. Trial identification

To avoid publication bias, both published and unpublished trials were included in the meta-analysis. Trials were identified by searching the bibliographic databases, Medline and Cancerlit, using a version of the optimal search strategy developed by the Cochrane Collaboration [9]. These were supplemented by hand searching reference lists of identified trial reports and of relevant books and review articles. The National Cancer Institute Physicians Data Query (PDQ) Clinical Protocols, United Kingdom Coordinating Committee for Cancer Research and Cochrane Controlled Trial registers were also searched to identify both completed and ongoing trials. All trial investigators who took part in the meta-analysis were asked to help add to this list of trials. Initial searches were completed for the period up to and including January 1998, and were updated regularly until December 2002, to identify any additional new material that had appeared. All abstracts were downloaded and full papers obtained for any abstracts judged potentially eligible for inclusion in the meta-analysis. Where there was uncertainty about the eligibility of a trial, this was discussed and resolved by consensus by the project secretariat and international advisory group.

2.4. Data collected

Up-to-date information on the date of randomisation, survival status, loco-regional recurrence status (pelvic), distant recurrence status (outside pelvis) and date of last follow-up was sought, as were details of treatment allocated, age, histological cell type, stage (FIGO); grade; performance status; lymph node involvement; site of lymph node involvement; treatment on recurrence; cause of death (including treatment-related toxicity) and whether cervical cancer was present at death. Late chronic effects of radiotherapy on the rectum, urinary tract and vagina, whilst uncommon, can be devastating for the women who are otherwise 'cured' of their cancer. Therefore, we also aimed to collect data on late bladder, gastrointestinal and vaginal radiation toxicity. To avoid potential bias, information was requested for all women randomised including those who had been excluded from the investigators' original analyses. All data were thoroughly checked for validity, consistency, plausibility and integrity of randomisation and follow-up [8]. Any queries were resolved and the final database entries verified by the responsible trial investigator, data manager or statistician.

2.5. Definition of endpoints

Overall survival, the primary endpoint, was defined as the time from randomisation until death (from any cause). Living patients were censored on the date of last follow-up. Loco-regional disease-free survival was defined as the time from randomisation until loco-regional progression or recurrence, or death (from any cause), whichever happened first. Those alive without loco-regional disease were censored on the date of last follow-up. Metastases-free survival was defined as the time from randomisation until metastases or death (from any cause), whichever happened first. Patients alive without metastases were censored on the date of last follow-up. However, if only the first sign of recurrent disease was recorded, patients having a local progression or recurrence were censored in the analysis of metastases-free survival and patients having metastases were censored in the analysis of loco-regional disease-free survival. Similarly, overall disease-free survival was taken as the time from randomisation until any local progression or recurrence, metastases or death (from any cause), whichever happened first. Patients alive without loco-regional disease or metastases were censored on the date of last follow-up.

2.6. Statistical analysis

All analyses, unless otherwise stated, were pre-specified in the protocol. Two separate sets of analyses were carried out according to the treatment comparisons (1 and 2) already described. All analyses were carried out on an intention-to-treat basis. Analyses of all endpoints were stratified by trial, and the log rank expected number of deaths and variance used to calculate individual trial hazard ratios (HRs) and overall pooled HRs using the fixed effect model [10]. Thus, the times to event (progression, recurrence or death) for individual patients were used within trials to calculate the HR, representing the overall risk of an event for those patients allocated to neoadjuvant chemotherapy compared with those allocated to no chemotherapy.

To explore the potential impact of trial design, we planned analyses that grouped trials by important aspects of their design that might influence the treatment effect. Therefore, these analyses focused mainly on variations in the neoadjuvant chemotherapy used, rather than differences in the non-randomised treatments. As specified in the protocol, trials were grouped according to frequency of chemotherapy cycles (>14-day cycles, $\leqslant 14$-day cycles), cisplatin dose intensity (<25 mg/m^2, $\geqslant 25$ mg/m^2), total dose of cisplatin ($\leqslant 150$ mg/m^2, >150 mg/m^2) local treatment used and whether adjuvant chemotherapy was also given. For each of these analyses, a hazard ratio was calculated for each group of trials and for all trials together. A test for quantitative interaction was used to investigate whether any substantial differences in the effect of neoadjuvant treatment existed between these trial groups. Because of the unanticipated level of heterogeneity across these trials, F-tests were also used to examine whether it was greater between groups compared with within groups.

These analyses were focused on the primary endpoint of survival, but were carried out on other endpoints to help support or refute any patterns found. Owing to an insufficient number of trials and further differences between the treatment approaches in comparison 2, these analyses were necessarily confined to comparison 1. To investigate the effects of neoadjuvant chemotherapy within subgroups of patients, stratified log-rank analyses were done on the primary endpoint of survival. These analyses examined whether the effect of neoadjuvant chemotherapy (and not prognosis) differs by patient subgroup. They were performed for each pre-specified subgroup, for example, separately comparing treatment versus control for patients with good performance status and treatment versus control for poor performance status within each trial. These results were then combined to give a pooled HR for good and for poor performance status patients across trials.

Results are also presented as absolute differences at 5 years, calculated using the overall HRs and the overall event rate in the control group [11], with confidence intervals calculated from the baseline event rate and the 95% Confidence Interval (CI) around the HR. Chi-square heterogeneity tests [12] were used to test for gross statistical heterogeneity across trials, and chi-square tests of interaction or trend were used to test for differences in outcome between subsets of trials or between subgroups of patients. Survival curves are presented as simple (non-stratified) Kaplan–Meier curves [13]. With the exception of the F-test, all P values quoted are two-sided.

3. Results

3.1. Treatment comparison 1

Searches identified 24 potentially eligible trials. Three were subsequently found to be ineligible, two because chemotherapy was given concurrently with radiotherapy [14,15] and one because it was ongoing at time of the original analysis (Gynecological Oncology Group Protocol 141). Twenty-one trials were therefore eligible for inclusion. Two unpublished trials could not be included, one because the patient data could not be located (44 patients, Protocol C1, Western General Hospital, Edinburgh, UK) and one because the data were incomplete and in a poor state, with few completed forms (<30 patients, Federation Nationale des Centres de Lutte Contre le Cancer Protocol COII, France). In addition, data were unavailable for one (72 patients) of two trials published [16] together because the investigator was unable to comply with the data collection deadline. Only the relevant treatment arms (comparing neoadjuvant chemotherapy plus radical radiotherapy to the same radiotherapy alone) were included for the two trials with multiple treatment arms [17,18]. We collected data on 83 of 92 patients who had been excluded from the investigators' analyses and they were reinstated in this meta-analysis. We were unable to obtain the excluded patients for two trials [19,20] or enough information to include another 19 patients from three trials [16,19,20] in the analyses. As the missing patients were few and distributed evenly across treatment arms, these trials were included. Therefore, the main results for comparison 1 are based on 2074 patients from 18 trials, representing 92% of patients from eligible randomised trials. Characteristics of the available eligible trials are shown in Table 1. Patient accrual varied from 27 to 260 in the available trials. Cisplatin was the main drug in all the chemotherapy regimens, with a planned total dose of between 100 and 320 mg/m^2 in 10–28-day cycles. Both the external beam radiotherapy dose and intracavitary radiotherapy dose varied (40–60.8 and 18–80 Gy, respectively), with a total dose in the range 55–80 Gy.

The patient characteristics, which reflect the eligibility criteria of individual trials, are given in Table 2. Investigators were sometimes unable to provide all of the data we requested (Table 2), but based on the available data, the women included in comparison 1 had a median age of 48 years (range 40–59 across trials) and a good performance status. Most had moderately or poorly differentiated, stage II-III tumours of squamous histology; the largest proportion had stage III (44%) tumours.

For survival, data were available for all 18 trials, comprising 2074 patients and 1084 deaths. The median follow-up across all trials is 5.7 years for surviving patients, ranging from 1.5 to 9.0 years in individual trials. The low median follow-up results from an older trial where the follow-up could not be updated [6]. Causes of death were provided for 17 trials. The results for the other endpoints are based on 16 trials and 1724 patients, because recurrence data was not supplied for two trials [16,21]. In the analysis of overall disease-free survival, there were 938 events and 780 (83%) of these first events were progressions or recurrences. For loco-regional disease-free survival, 911 events were recorded and of these 573 (63%) were local progressions or recurrences, and so this endpoint more evenly consists of progressions and recurrences or deaths. For metastases-free survival, there were 899 patients who had an event, 306 of whom (34%) developed metastases as their first event. Therefore, many patients died without metastases and these deaths contribute most to this endpoint.

For each of the outcomes measured, when all trials were combined, a highly significant level of statistical heterogeneity was evident, such that it is inappropriate to combine the trials in this way, and in fact suggests that these trials may not be addressing exactly the same question (Table 3). For survival, heterogeneity is best

Table 1
Characteristics of trials included in comparison 1

Trial [Ref.]	Accrual period	Comparison	Stage	Neoadjuvant CT	Duration of CT	Neoadjuvant CDDP total dose/intensity	Delay to primary treatment	External RT dose and duration	Intracavitary RT dose	Patients analysed (missing)
Chauvergne 1993 [19]	1982–1987	CT + RT vs RT	IIB–N1, III, M0	CDDP 80 mg/m^2 MTX 30 mg/m^2 CLB 20 mg/m^2 VCR 0.7 mg/m^2	Every 21 days for 2 cycles and a further 2 to responders	160–320 mg/m^2 27 mg/m^2/week	?	50 Gy	18 Gy	182 (13)
Souhami 1991 [20]	1984–1986	CT + RT vs RT	IIIB	CDDP 50 mg/m^2 BLM 120U VCR 1 mg/m^2 MMC 10 mg/m^2	Every 21 days for 3 cycles	150 mg/m^2 17 mg/m^2/week	21–28 days after CT	50 Gy in 25 F over 35 days	40 Gy	103 (4)
Tattersall 1992 [35]	1985–1990	CT + RT vs RT	IIB-IVA	CDDP 50 mg/m^2 VBL 4 mg/m^2 BLM 45 mg	Every 21 days for 3 cycles	150 mg/m^2 17 mg/m^2/week	21 days after CT	40–55 Gy in 20–25 F over 28–35 days	0	71 (0)
Herod 2000 [21]	1986–1995	CT + RT + CT vs RT	IIB-IVA, IIA (inoperable)	CDDP 50 mg/m^2 BLM 30 mg/m^2 IFOS 5 g/m^2	Every 28 days for 2–3 cycles	100–150 mg/m^2 12 mg/m^2/week	According to institutional policy	According to institutional policy	According to institutional policy	177 (0)
Sardi 1997 [5]	1987–1993	CT + RT (±S) vs RT (±S)	IB bulky	CDDP 50 mg/m^2 VCR 1 mg/m^2 BLM 25 mg/m^2	Every 10 days for 3 cycles	150 mg/m^2 35 mg/m^2/week	15–21 days after CT	50 Gy in 28–30 F over 45–50 days	25–35 Gy	210 (0)
Cardenas 1993 [36]	1987–1992	CT + RT vs RT	IIIB	CDDP 50 mg/m^2 EPI 75 mg/m^2 CTX 500 mg/m^2	Every 21 days for 4 cycles	200 mg/m^2 17 mg/m^2/week	21–42 days after CT	50 Gy over 42–45 days	33 Gy	30 (0)
Sardi 1998 [18]	1988–1993	CT + RT vs RT (vs S + RT vs CT + S)	IIB	CDDP 50 mg/m^2 VCR 1 mg/m^2 BLM 25 mg/m^2	Every 10 days for 3 cycles	150 mg/m^2 35 mg/m^2/week	7–15 days after CT	50–60 Gy 28–30 F over 45–50 days	25–35 Gy	147 (0)[a]
Cardenas 1991 [37]	1988–1992	CT + RT vs RT	IIB	CDDP 50 mg/m^2 EPI 75 mg/m^2 CTX 500 mg/m^2	Every 21 days for 4 cycles	200 mg/m^2 17 mg/m^2/week	21–42 days after CT	50 Gy over 42–45 days	33.2 Gy	31 (0)
Chiara 1994 [38]	1988–1992	CT + RT + CT vs RT	IIB-III	CDDP 60 mg/m^2	Every 15 days for 2 cycles before RT (and for 4 cycles after RT)	120 mg/m^2 28 mg/m^2/week	21–28 days after CT	60 Gy in 30 F over 62 days	40 Gy	64 (0)
Sardi 1996 [17]	1988–1993	CT + RT vs RT (vs CT + S + RT)	IIIB	CDDP 50 mg/m^2 VCR 1 mg/m^2 BLM 25 mg/m^2	Every 10 days for 3 cycles	150 mg/m^2 35 mg/m^2/week	7–15 days after CT	50–60 Gy in 25–28 F over 45–50 days	25–35 Gy	108 (0)[a]

(*continued on next page*)

Table 1 (*continued*)

Trial [Ref.]	Accrual period	Comparison	Stage	Neoadjuvant CT	Duration of CT	Neoadjuvant CDDP total dose/intensity	Delay to primary treatment	External RT dose and duration	Intracavitary RT dose	Patients analysed (missing)
PMB Group unpublished	1989–1991	CT + RT vs RT	IIB, III IVA, bulky IB, IIA	CDDP 60 mg/m^2 MTX 300 mg/m^2 BLM 30 mg	Every 14 days for 3 cycles	180 mg/m^2 30 mg/m^2/week	14 days after CT	42.5 in 20 F over 28 days	76–80 Gy	35 (0)
Sundfor 1996 [39]	1989–1992	CT + RT vs RT	IIIB-IVA	CDDP 100 mg/m^2 5-FU 5000 mg/m^2	Every 21 days for 3 cycles	300 mg/m^2 33 mg/m^2/week	21–28 days after CT	64.8 Gy in 36 F over 50 days	0	96 (0)
CCSG AOCOA [6]	1989–1993	CT + RT vs RT	IIB-IVA	CDDP 60 mg/m^2 EPI 110 mg/m^2	Every 21 days for 2–3 cycles	180 mg/m^2 20 mg/m^2/week	21 days after CT	40–50 Gy over 28–35 days	30–35 Gy	260 (0)
Kumar 1998 [16]	1990–1993	CT + RT vs RT	IIB-IVA	CDDP 50 mg/m^2 BLM 15 mg/m^2 IFOS 5 g/m^2 MESNA 3 g/m^2	Every 21 days for 2 cycles	100 mg/m^2 17 mg/m^2/week	14 days after 2nd CT cycle	40 Gy in 22 F + 10 Gy in 5 F over 35 days	30 Gy	173 (11)
Symonds 2000 [40]	1990–1995	CT + RT vs RT	IIB bulky, III, IVA	CDDP 50 mg/m^2 MTX 100 mg/m^2	Every 14 days for 3 cycles	150 mg/m^2 25 mg/m^2/week	14 days after CT	40–45 Gy in 20 F over 28 days	24–33.75 Gy	215 (0)
Leborgne 1997 [41]	1990–1993	CT + RT or S vs RT or S	IB-IVA (IB > 4cm)	CDDP 50 mg/m^2 VCR 3 mg/m^2 BLM 75 mg/m^2	Every 10 days for 3 cycles	150 mg/m^2 35 mg/m^2/week	14–42 days after CT	20–60 Gy in 10–30 F	30 Gy	97 (0)
MRC CeCa unpublished	1991–1995	CT + RT or S vs RT or S	IB-IVA	CDDP 50 mg/m^2 MTX 100 mg/m^2 Folinic acid 15 mg po/6 h 30 after start of CDDP and MTX	Every 14 days for 3 cycles	150 mg/m^2 25 mg/m^2	21 days after CT	46 Gy in 23 F over 32 days	20 Gy	48 (0)
LGOG unpublished	1991–1995	CT + RT vs RT	IIB, III IVA, bulky IB, IIA	CDDP 60 mg/m^2 MTX 300 mg/m^2 BLM 30 mg	Every 14 days for 3 cycles	180 mg/m^2 30 mg/m^2/week	14 days after CT	50 Gy over 39 days	28 Gy	27 (0)

PMB; after 'PMB' regimen; CCSG AOCOA, Cervical Cancer Study Group of the Asian Oceanian Clinical Oncology Association; MRC, Medical Research Council; LGOG, London Gynaecological Oncology Group; CT, chemotherapy; RT, radiotherapy; S, surgery; CDDP, cisplatin; MTX, methotrexate; CLB, chlorambucil; VCR, vincristine; BLM, bleomycin; MMC, mitomycin; VBL, vinblastine; IFOS, ifosfamide; EPI, epirubicin; CTX, cyclophosphamide; 5-FU, 5-fluorouracil; F, fractions; po, orally.

[a] Only relevant treatment arms included.

Table 2
Characteristics of patients included in comparison 1

	Neoadjuvant chemotherapy ($n=1026$) n (%)	No neoadjuvant chemotherapy ($n=1048$) n (%)	Total ($n=2074$)
Age (years)			
<35	134 (13)	139 (13)	273
35–50	491 (48)	454 (43)	945
51–65	329 (32)	372 (35)	701
>65	72 (7)	82 (8)	154
Unknown	0 (0)	1 (<1)	1
Stage[a]			
IB	126 (12)	130 (12)	256
II	291 (28)	320 (31)	611
III	418 (41)	418 (40)	836
IV	27 (3)	28 (3)	55
Unknown	164 (16)	152 (15)	316
Histology			
Squamous	958 (93)	976 (93)	1934
Adenocarcinoma	6 (1)	9 (1)	15
Other	54 (5)	58 (6)	112
Unknown	8 (1)	5 (<1)	13
Grade[b]			
Well differentiated	105 (10)	97 (9)	202
Moderately differentiated	299 (29)	334 (32)	633
Poorly differentiated	302 (29)	285 (27)	587
Unknown	320 (31)	332 (32)	652
Performance status[c]			
0	671 (65)	656 (63)	1327
1	230 (22)	240 (23)	470
2	55 (5)	57 (5)	112
3	14 (1)	11 (1)	25
Unknown	56 (5)	84 (8)	140
Lymph node status[d]			
Uninvolved	288 (28)	280 (27)	568
Involved	121 (12)	149 (14)	270
Unknown	617 (60)	619 (59)	1236

N.B. Percentages may not add up to 100% because of rounding off.
[a] Data missing completely for one trial [16].
[b] Data missing completely for three trials [6,20, MRC CeCa] and for a large proportion of patients in one trial [19].
[c] Data missing completely for one trial [41] and for a large proportion of patients in two trials [36,37].
[d] Data missing completely for eight trials [6,16,17,36,37,39,40, MRC CeCa] and for most patients in two trials [18,41].

accounted for by the pre-specified grouping of trials by chemotherapy cycle length or planned cisplatin dose intensity, as shown by the F-test (Table 4). Grouping trials by cycle length resulted in a significant variability in the direction of effect ($P=0.0009$, Fig. 1). Trials giving chemotherapy in cycles lasting longer than 14 days had a pooled HR of 1.25, representing a significant ($P=0.005$) 25% increase in the risk of death with neoadjuvant chemotherapy (Table 4). With shorter chemotherapy cycle lengths, the HR of 0.83 ($P=0.046$) suggests a significant 17% decrease in the risk of death (Table 4). These HRs translate into an absolute reduction in 5-year survival of 8% (from 45 to 37%) with long cycle lengths, and a 7% absolute improvement in 5-year survival (from 45 to 52%) with shorter cycles (Fig. 2). However, heterogeneity was still evident in this latter group ($P=0.002$). A sensitivity analysis excluding one very small trial (48 patients) with an extreme HR of 3.37 (MRC CeCa) reduces the heterogeneity substantially ($P=0.193$) and with the weight of evidence (HR = 0.76, 95% CI 0.62–0.92, $P=0.005$, Table 4) still favouring the short-cycle intensive administration of neoadjuvant chemotherapy.

Grouping trials by planned cisplatin dose intensity shows a similar difference in the direction of effect for survival ($P=0.002$, Fig. 3). The HR of 1.35 ($P=0.002$), for those trials using less than 25 mg/m^2 per week, indicates a significant 35% increase in the risk of death with neoadjuvant chemotherapy. In contrast, the HR for trials using a planned dose intensity of greater than or equal to 25 mg/m^2 per week is 0.91 ($P=0.200$), which suggests a potential 9% decrease in the risk of death with neoadjuvant chemotherapy. These HRs translate into an 11% absolute reduction in 5-year survival (from 45 to 34%) with lower dose intensities and a 3% absolute improvement in 5-year survival (from 45 to 48%) with the higher dose intensities. Considerable heterogeneity remains in the higher dose-intensity group ($P=0.001$). Unlike above, exclusion of any one trial is insufficient to explain this residual heterogeneity. For the other endpoints, grouping the trials by cycle length and cisplatin dose intensity produced patterns of results that are consistent with those for survival.

Grouping trials according to the total cisplatin dose, whether surgery was used as part of the local treatment or whether additional adjuvant chemotherapy was given, did not explain the heterogeneity in the survival results (F-test, Table 4). Furthermore, the groups did not appear to differ significantly in terms of the size and direction of effect (Table 4) and this was also the case for the other endpoints.

As there were already substantial differences in the direction of effect by trial group, it did not seem appropriate to carry out analyses to assess any differential effect of neoadjuvant chemotherapy by patient subgroup across all the trials. Instead, we carried out subgroup analyses within trial groups defined by the chemotherapy cycle length, where the heterogeneity was less. Together with missing baseline data, this limits the power of these analyses. Nevertheless, there was no evidence to suggest that chemotherapy was differentially effective in groups of patients defined by age (trend $P=0.384$, $P=0.762$), stage (trend $P=0.365$, $P=0.533$), histology (interaction $P=0.332$, $P=0.611$), grade (trend $P=0.757$, $P=0.779$) or performance status (interaction $P=0.647$, $P=0.660$) for trials with chemotherapy cycles lasting more than 14 days or 14 days or less, respectively. Data on nodal involvement were too sparse to warrant sub-group analyses.

Table 3
All endpoints in comparison 1

Endpoint	Number of events/patients	Hazard ratio (95% CI), *P* value	Heterogeneity *P* value
Survival	1084/2074	1.05 (0.94–1.19), 0.393	0.0003
Disease-free survival	938/1724	1.00 (0.88–1.14), 1.000	0.001
Loco-regional disease-free survival	911/1724	1.03 (0.90–1.17), 0.654	0.0002
Metastases-free survival	899/1724	1.00 (0.88–1.14), 1.000	0.002

CI, Confidence Interval.

Table 4
Overall survival by group of trials in comparison 1

Trial grouping	Number of trials	Number of events/patients	HR (95% CI), *P* value	Heterogeneity *P* value	F-test *P* value	Interaction *P* value
Chemotherapy cycle frequency)						
> 14 day cycles	11	639/1214	1.25 (1.07–1.46), 0.005	0.238		
⩽14 day cycles	7	445/860	0.83 (0.69–1.00), 0.046	0.002	0.036	0.0009
⩽14 day cycles[a] (−MRC CeCa)	6	417/812	0.76 (0.62–0.92), 0.005	0.193	0.00045	0.00008
Neoadjuvant cisplatin dose intensity						
< 25 mg/m^2	7	413/845	1.35 (1.11–1.64), 0.002	0.746		
⩾25 mg/m^2	11	671/1229	0.91 (0.78–1.05), 0.200	0.001	0.046	0.002
Neoadjuvant cisplatin total dose						
⩽150 mg/m^2	11	770/1413	1.03 (0.90–01.19), 0.646	0.0002		
> 150 mg/m^2	7	314/661	1.10 (0.88–1.38), 0.386	0.090	0.775	0.629
Local treatment						
Radiotherapy	17	1033/1864	1.09 (0.96–1.23), 0.169	0.001		
±Surgery + radiotherapy	1	51/210	0.53 (0.31–0.93), 0.025	NA	0.128	0.01
Chemotherapy scheduling						
Neoadjuvant chemotherapy	17	1046/2010	1.04 (0.92–1.17), 0.563	0.0003		
Neoadjuvant + adjuvant chemotherapy	1	38/64	1.65 (0.87–3.14), 0.125	NA	0.404	0.162

CI, Confidence interval; HR, Hazard ratio; NA, not available.
[a] Sensitivity analysis excluding one trial.

Although late radiation toxicity data were provided for more than half the trials, only a relatively small number of late effects on the bladder (91), intestine (117) and vagina (79) were recorded. Of these, there were 14 serious late events associated with the bladder, 21 associated with the gastrointestinal tract and three associated with the vagina. Although these data were not sufficient to warrant a formal analysis, there is little to suggest that serious late toxicity is a greater problem in the neoadjuvant chemotherapy arm compared with the control arm (5 versus 9, 10 versus 11 and 2 versus 1, respectively).

3.2. Treatment comparison 2

Preliminary searches identified seven trials that compared neoadjuvant chemotherapy plus surgery (±radiotherapy) versus radiotherapy alone, but one was subsequently found to be ineligible because neoadjuvant chemotherapy was given to all patients [22]. Therefore, six trials were eligible for inclusion. Data were not available for one trial, because we lost contact with the investigators [23]. Data from all randomised patients from the remaining five trials were made available and so the main results for this comparison are based on 872 patients, which represent 97% of the patients from known randomised trials.

Characteristics of the available trials are shown in Table 5. Patient accrual varied from 50 to 441. Cisplatin was the main drug in all of the chemotherapy regimens, with a planned total of dose between 100 and 300 mg/m^2 in 10–21-day cycles. One trial gave chemotherapy intra-arterially [24]. External beam radiotherapy and intracavitary radiotherapy doses in the control arm were very similar across trials (45–60 and 25–40 Gy, respectively). More than 90% of patients in two trials [17,18] received adjuvant radiotherapy as well as surgery in the neoadjuvant treatment arm and in two other trials [24,25] a smaller proportion of patients received additional radiotherapy (28 and 32%, respectively). Thus, in some cases a triple modality is being compared with radiotherapy.

Trial	Neoad CT (no. events/no. entered)	No Neoad CT	O-E	Variance
>14 day cycles				
Chauvergne, 1993	57/92	54/90	−0.47	27.66
Souhami, 1991	29/48	31/55	7.64	13.64
Tattersall, 1992	20/34	18/37	2.17	9.41
Herod, 2001	68/89	62/88	2.60	32.39
Cardenas, 1991	7/13	9/18	0.37	3.84
Cardenas, 1993	12/14	8/16	2.16	4.91
Chiara, 1994	22/32	16/32	4.68	9.33
Sundfor, 1996	31/48	35/48	−3.41	16.40
CCSG AOCOA	38/129	28/131	8.08	16.31
Kumar, 1998	49/88	34/85	7.43	20.73
LGOG	9/15	2/12	3.61	2.73
Sub-total	342/602	297/612	34.85	157.36
⩽14 day cycles				
Sardi, 1997	19/104	32/106	−7.97	12.69
Sardi, 1998	30/73	33/74	−4.61	15.56
Sardi, 1996	34/54	41/54	−10.61	17.89
PMB	9/16	15/19	−2.68	5.94
Symonds, 2000	68/105	76/110	−5.86	35.84
Leborgne, 1997	32/48	28/49	2.98	14.94
MRC CeCa	19/24	9/24	7.86	6.64
Sub-total	211/424	234/436	−20.89	109.48
Total	553/1026	531/1048	13.96	266.85

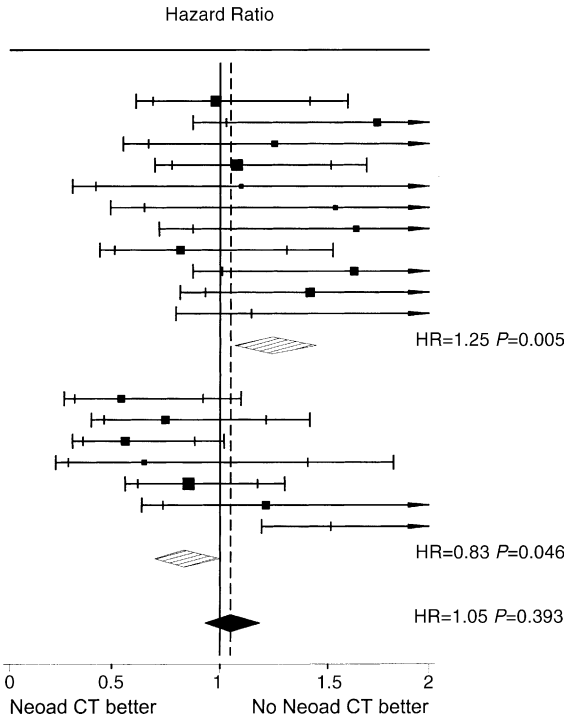

Fig. 1. Overall survival by planned neoadjuvant chemotherapy cycle length in comparison 1. The hazard ratio for each trial is represented by the square on each bar, the size of which is proportional to the amount of information available in the trial. The inner and outer limits of the bar indicate the 95 and 99% confidence intervals (CIs), respectively. The centre of the black diamond gives the overall hazard ratio when the results of all trials are combined. The extremes of this diamond give the 95% CI. The shaded diamonds represent the hazard ratios and 95% CIs for the groups of trials. Trial references are given in Table 1. Neoad CT, neoadjuvant chemotherapy. O–E, observed–expected.

We obtained most of the baseline data requested. Information on age, histology, stage, grade, performance status and lymph node status was provided for all trials, although, particularly for lymph node status, data were missing for some patients (Table 6). Overall, the patient characteristics are broadly similar to those in comparison 1, with women of a median age of 49 years (range 42–58 across trials), with good performance status and moderately or poorly differentiated, stage II-III tumours of squamous histology. However, there was a greater proportion of stage IB–II patients (74%) than in comparison 1.

Information on all endpoints and cause of death was provided for the 5 trials and 872 patients. The median follow-up across all trials is 5 years for surviving patients, ranging from 3.9 to 9.0 years in the individual trials. For the primary endpoint of survival, there were 368 deaths. For overall disease-free survival, there were 414 events and 368 (89%) of these first events were progressions or recurrences. There were 402 events in the analysis of loco-regional disease-free survival and, of these, 290 patients (72%) experienced a local progression or recurrence as the first event. Thus, both of these endpoints are dominated by progressions and recurrences. For metastases-free survival, there were 381 events, but metastases only accounted for 120 (31%) of them and so this endpoint mainly comprises deaths.

For survival, three trials had results that were significantly in favour of neoadjuvant chemotherapy [17,18,26], but the CIs for all of the individual trials are wide (Fig. 4). Combining the results of all trials gives an overall HR of 0.65 and a narrower overall CI, indicating a highly significant ($P=0.0004$) 35% reduction in the risk of death with neoadjuvant chemotherapy (Table 7, Fig. 4). The HR translates into a 14% absolute improvement in survival at 5 years, increasing it from 50 to 64% (Fig. 5). There is some indication of heterogeneity in the individual trial results ($P=0.06$), which seems to be due to one trial that has a result quite different from the others [25]. The results for overall disease-free survival and locoregional disease-free survival are very similar to those for survival, although there is a greater degree of heterogeneity (Table 7). The HR for both is 0.68 ($P=0.0001$), a statistically significant 32% reduction in the risk of progression, recurrence or death with neoadjuvant chemotherapy. This is equivalent to a 13% absolute improvement in both endpoints from 45 to 58%. For metastases-free survival, the HR is 0.63 ($P=0.00001$), equivalent to a significant 37% reduction in the risk of metastases or death (Table 7). In this case, there was no obvious

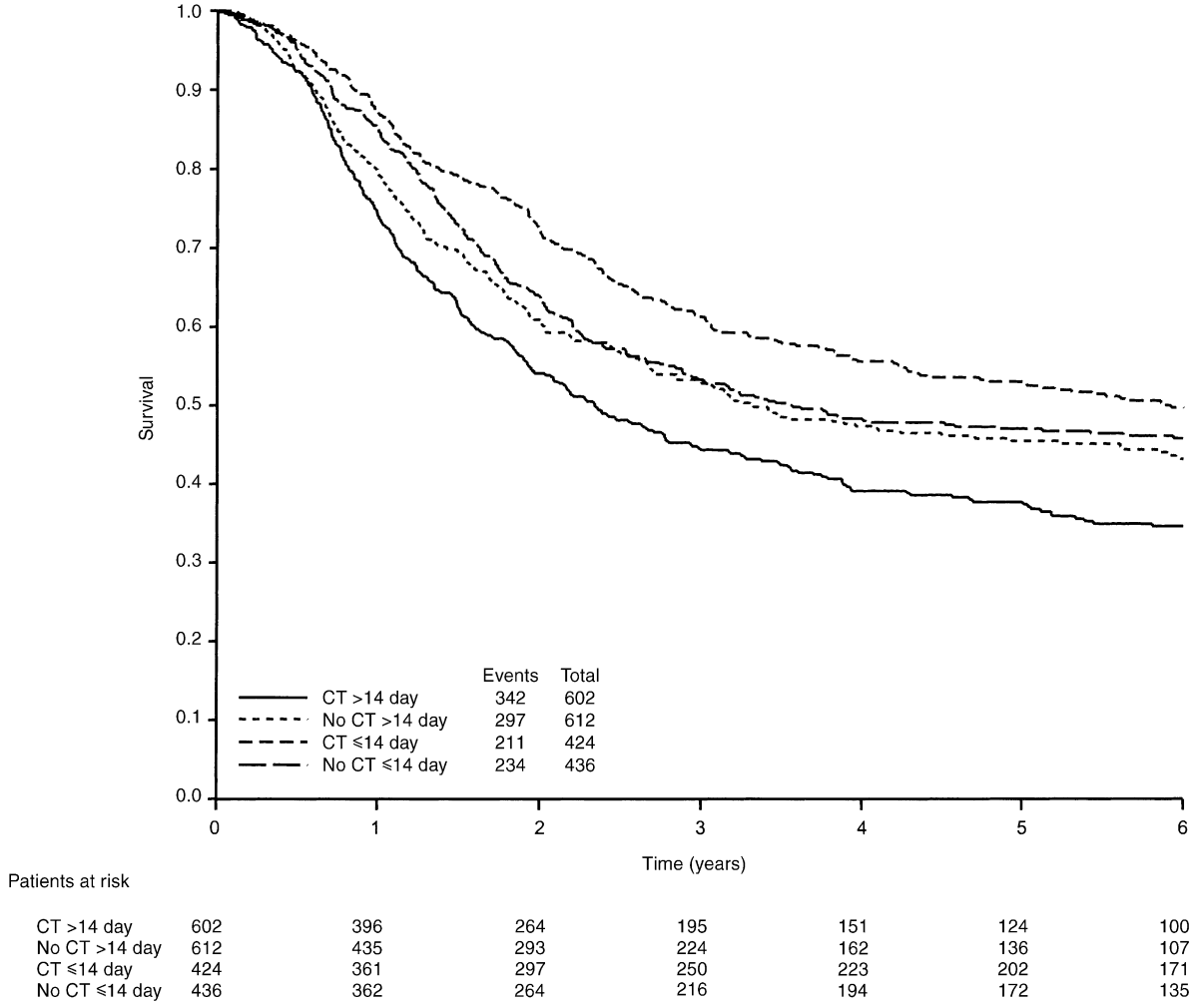

Fig. 2. Kaplan–Meier curves of overall survival by trial group (neoadjuvant chemotherapy cycle length >14 days or $\leqslant 14$ days) and treatment arm in comparison 1. Neoad CT, neoadjuvant chemotherapy.

statistical heterogeneity across trials ($P=0.217$) and the HR is equivalent to an absolute benefit of 15% at 5 years, increasing metastases-free survival from 45 to 60%.

There were fewer deaths (368) in this comparison and, in some cases, missing baseline data. Therefore, the power to determine whether there was evidence of a differential effect of neoadjuvant chemotherapy by predefined patient subgroups was very limited. Nevertheless, based on the available data, there was no evidence to suggest that the effect of neoadjuvant chemotherapy on survival varied across groups of patients defined by age (trend $P=0.363$), stage (trend $P=0.258$), histology (interaction $P=0.082$), grade (trend $P=0.781$) or performance status (interaction $P=0.713$). Determination of nodal status was largely confined to the neoadjuvant chemotherapy plus surgery arms of these trials (Table 6) and so any subgroup analysis by nodal status would lack power and be difficult to interpret.

4. Discussion

At the outset of this project, despite the enrolment of more than 3000 women in randomised trials, it was not clear whether neoadjuvant chemotherapy was effective in the treatment of locally advanced cervical cancer. In the interim, concomitant chemotherapy and radiotherapy has probably become a 'standard of care' for women with locally advanced disease. This was in response to a National Cancer Institute Alert based on the results of five randomised trials stating "strong consideration should be given to the incorporation of chemotherapy with radiotherapy in women who require radiotherapy for the treatment of cervical cancer". A subsequent systematic review and meta-analysis of the available published and unpublished summary data from 19 randomised trials of concomitant chemo-radiotherapy versus radiotherapy, showed a 29% reduction in the risk of death which translated into an

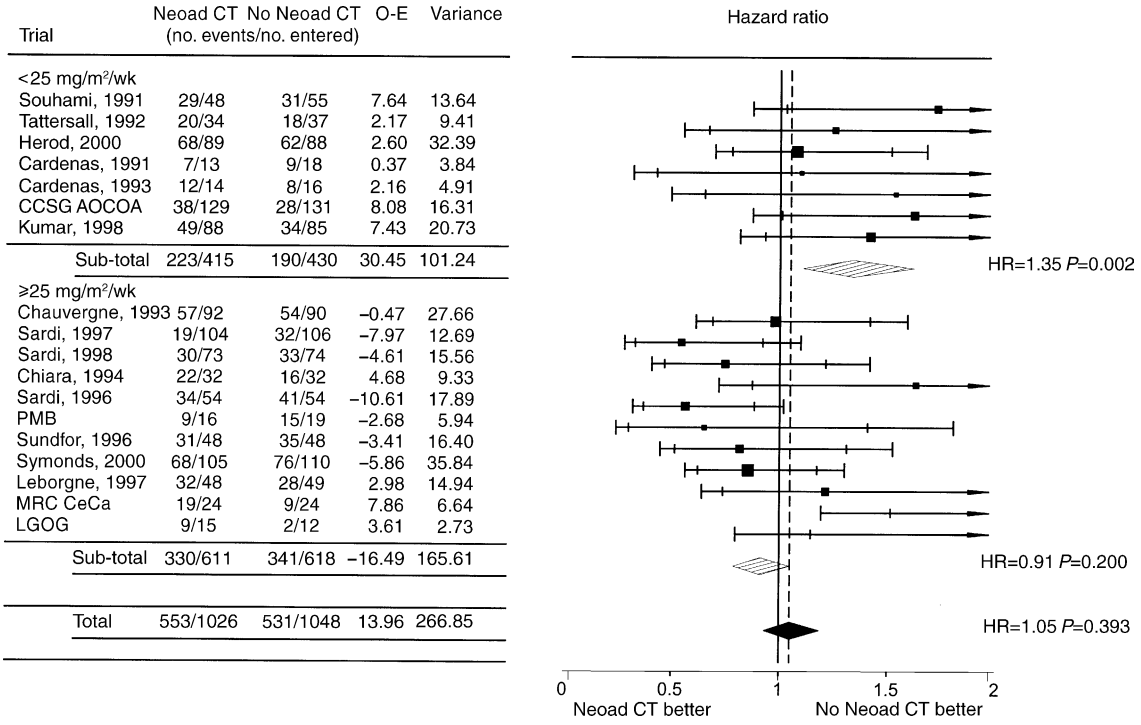

Fig. 3. Overall survival by planned cisplatin dose intensity in comparison 1. Symbols and conventions as in Fig. 1. Neoad CT, neoadjuvant chemotherapy.

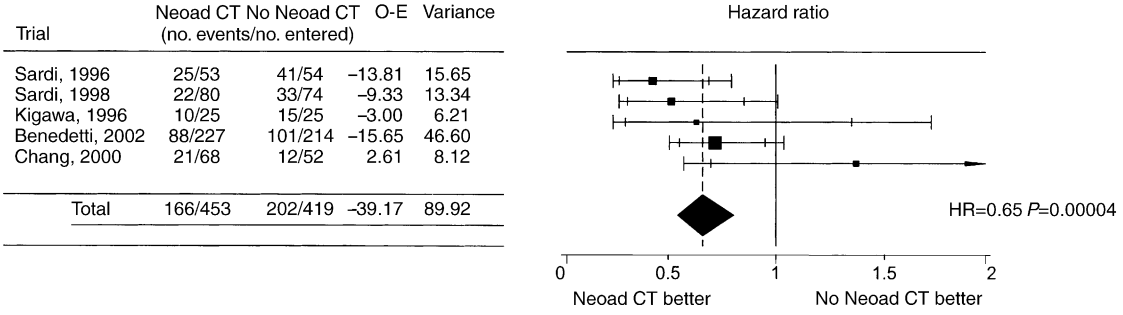

Fig. 4. Overall survival in comparison 2. Symbols and conventions as in Fig. 1. Neoad CT, neoadjuvant chemotherapy.

overall survival benefit of 12% at 5 years for this treatment [4] and it has become a standard against which new treatments are being tested. However, meta-analyses of published or other summary data may overestimate the treatment effect [27]. In addition, there are still a number of issues regarding the use of chemoradiotherapy, including which chemotherapy regimens and doses are optimal, precisely which patients benefit and whether postradiation adjuvant chemotherapy provides additional therapeutic gain [28]. Therefore, a similar systematic review and meta-analysis of individual patient data from the concomitant chemoradiotherapy trials is planned. As neoadjuvant chemotherapy may offer benefits similar to chemoradiotherapy when compared with local treatment, in a similar group of women, this current systematic review and meta-analysis aimed to provide a comprehensive, reliable and up-to-date estimate of the average effect of this treatment.

4.1. Treatment comparison 1

Ninety-three percent of the known randomised evidence comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy for locally advanced cervical cancer (comparison 1) was collected and reanalysed. Considering all trials together, there was no evidence of an effect of neoadjuvant chemotherapy on survival, or any of the other endpoints. However, there was a very high level of statistical heterogeneity, suggesting strongly that the results should not be combined in this way. A substantial proportion of heterogeneity is explained by prespecified analyses grouping trials according to the way they delivered the chemotherapy.

Table 5
Characteristics of trials included in comparison 2

Trial label [Ref.]	Accrual period	Comparison	Stage	Neoadjuvant CT	Duration of CT	CDDP total dose/intensity	Delay to primary treatment	External RT dose and duration (control arm)	Intracavitary RT dose (control arm)	Patients analysed (missing)
Sardi 1996 [17]	1988–1992	CT + S vs RT (CT + RT)	IIIB	CDDP 50 mg/m^2 VCR 1 mg/m^2 BLM 25 mg/m^2	Every 10 days for 3 cycles	150 mg/m^2 35 mg/m^2/week	15–21 days after CT	50–60 Gy in 25–33 F over 45–50 days	35–40 Gy	107 (0)[a]
Sardi 1998 [18]	1988–1993	CT + S vs RT (vs CT + RT vs S + RT)	IIB	CDDP 50 mg/m^2 VCR 1 mg/m^2 BLM 25 mg/m^2	Every 10 days for 3 cycles	150 mg/m^2 35 mg/m^2/week	15–21 days after CT	50 Gy in 25–27 F over 45–50 days	25–35 Gy	154 (0)[a]
Kigawa 1996 [24]	1989–1991	Intra-arterial CT ± S or ± RT vs RT	IIB-IIIB	CDDP 50 mg/m^2 BLM 30 mg/m^2	Every 21 days 2–3 cycles	100–150 mg/m^2 17 mg/m^2/week	21–28 days after CT	50 y in 25 F over 35 days	24–38 Gy	50 (0)
Benedetti-Panici 2002 [26]	1990–1996	CT + S or R vs RT	IB2-IIA $\geqslant$4 cm, IIB III	CDDP 80 mg/m^2 BLM 15 mg/m^2 or CDDP 50 mg/m^2 VCR 1 mg/m^2 BLM 30 mg/m^2 or CDDP 43 mg/m^2 IFOS 3.5 mg/m^2 or CDDP 40 mg/m^2	Every 21 days for 2 cycles Every 7 days for 6 cycles Every 7 days for 7 cycles (IFOS cycles 1, 4, 7 only) Every 7 days for 6 cycles	120 mg/m^2 20 mg/m^2/week 300 mg/m^2 50 mg/m^2/week 300 mg/m^2 43 mg/m^2/week 240 mg/m^2 40 mg/m^2/week	?	45–50 Gy over 35–42 days	20–30 Gy	441 (0)
Chang 2000 [25]	1992–1999	CT + S vs RT	Bulky IB, IIA	CDDP 50 mg/m^2 VCR 1 mg/m^2 BLM 25 mg/m^2	Every 10 days for 3 cycles	150 mg/m^2 35 mg/m^2/week	14–21 days after CT	50 Gy 25 F over 35 days	25.8 Gy	124 (0)

CT, chemotherapy; RT, radiotherapy; S, surgery; CDDP, cisplatin; VCR, vincristine; BLM, bleomycin; IFOS, ifosfamide; 5-FU, 5-fluorouracil; F, fractions.
[a] Only relevant treatment arms are included.

Table 6
Characteristics of patients included in comparison 2

	Neoadjuvant chemotherapy ($n=453$) *n* (%)	No neoadjuvant Chemotherapy ($n=419$) *n* (%)	Total ($n=872$)
Age (years)			
<35	37 (8)	44 (11)	81
35–50	234 (52)	176 (42)	410
51–65	145 (32)	158 (38)	303
>65	36 (8)	37 (9)	73
Unknown	1 (<1)	4 (1)	5
Stage			
IB/IIA	164 (36)	145 (35)	309
IIB	169 (37)	165 (39)	334
III	120 (26)	109 (26)	229
Unknown	0 (0)	0 (0)	0
Histology			
Squamous	427 (94)	396 (95)	823
Adenocarcinoma	9 (2)	8 (2)	17
Other	17 (4)	15 (4)	32
Unknown	0 (0)	0 (0)	0
Grade			
Well differentiated	35 (8)	44 (11)	79
Moderately differentiated	222 (49)	183 (44)	405
Poorly differentiated	186 (41)	164 (39)	350
Unknown	10 (2)	28 (7)	38
Performance status[a]			
0	324 (72)	300 (72)	624
1	57 (13)	64 (15)	121
2	4 (1)	3 (1)	7
Unknown	68 (15)	52 (12)	120
Lymph node status[b]			
Uninvolved	301 (66)	172 (41)	473
Involved	114 (25)	50 (12)	164
Unknown	38 (8)	197 (47)	235

N.B. Percentages may not add up to 100% because of rounding off.
[a] Data missing completely for one trial [25].
[b] Data missing completely on the radiotherapy arm for three trials [17,18,24] and for a large proportion of patients on the radiotherapy arm in one trial [25].

Such analyses yielded the intriguing observation that trials which gave more intensive chemotherapy in terms of a shorter cycle length and/or a higher dose intensity tended to show an advantage for neoadjuvant chemotherapy, whereas those that delivered chemotherapy in a less intensive and more prolonged manner, with a longer cycle length or a lower dose intensity, tended to show a detrimental effect of chemotherapy.

Among the planned analyses, grouping trials by the length of the chemotherapy cycle is the best explanation for the heterogeneity seen between trials. For trials giving cycles greater than 14 days, the pooled HR was 1.25, equivalent to an absolute detriment of 8% in 5-year survival. A detriment was also observed in overall and loco-regional disease-free survival and metastases-free survival. In contrast, trials using shorter cycle lengths gave a pooled HR of 0.83, equivalent to a 7% absolute improvement in 5-year survival. Results for overall and loco-regional disease-free survival and metastases-free survival similarly suggested a benefit for short-cycle chemotherapy. A comparable, but somewhat less persuasive, pattern was observed when trials were split according to the planned cisplatin dose intensity. The pooled HR of 1.35 from trials using less than 25 mg/m^2 per week suggests a significant 11% reduction in 5-year survival, with comparable reductions in overall and loco-regional disease-free survival and metastases-free survival. These results were homogeneous for each endpoint and significant for survival and locoregional disease-free survival. On the other hand, the HR of 0.91 for trials using dose intensities of cisplatin greater than 25 mg/m^2 per week suggests a potential 3% absolute improvement in 5-year survival, but this is not conventionally statistically significant. Similar absolute improvements in overall, loco-regional disease-free and metastases-free survival were demonstrated, but again these results were not conventionally significant.

If, as the results of this comparison suggest, short cycle, dose-intensive chemotherapy is beneficial and longer less intensive schedules are detrimental, then they may be informative about the biology of cervical cancer and the effects of drug treatment. Cervical tumours are rapidly proliferating with a median potential doubling time (Tpot) of only 4–4.5 days [29] and a relatively high growth fraction [30]. Following effective chemotherapy, tumours shrink, but tumour re-growth may be accelerated, particularly if the drug and dose schedule is not optimal. After a few cell divisions, the tumour volume may be restored, but the tumour cells may be less sensitive

Table 7
All endpoints in comparison 2

Endpoint	Number of events/patients	Hazard ratio (95% CI), *P* value	Heterogeneity *P* value
Survival	368/872	0.65 (0.53–0.80), 0.00004	0.06
Disease-free survival	414/872	0.68 (0.56–0.82), 0.0001	0.02
Loco-regional disease-free survival	402/872	0.68 (0.56–0.82), 0.0001	0.005
Metastases-free survival	381/872	0.63 (0.52–0.78), 0.00001	0.217

CI, Confidence interval.

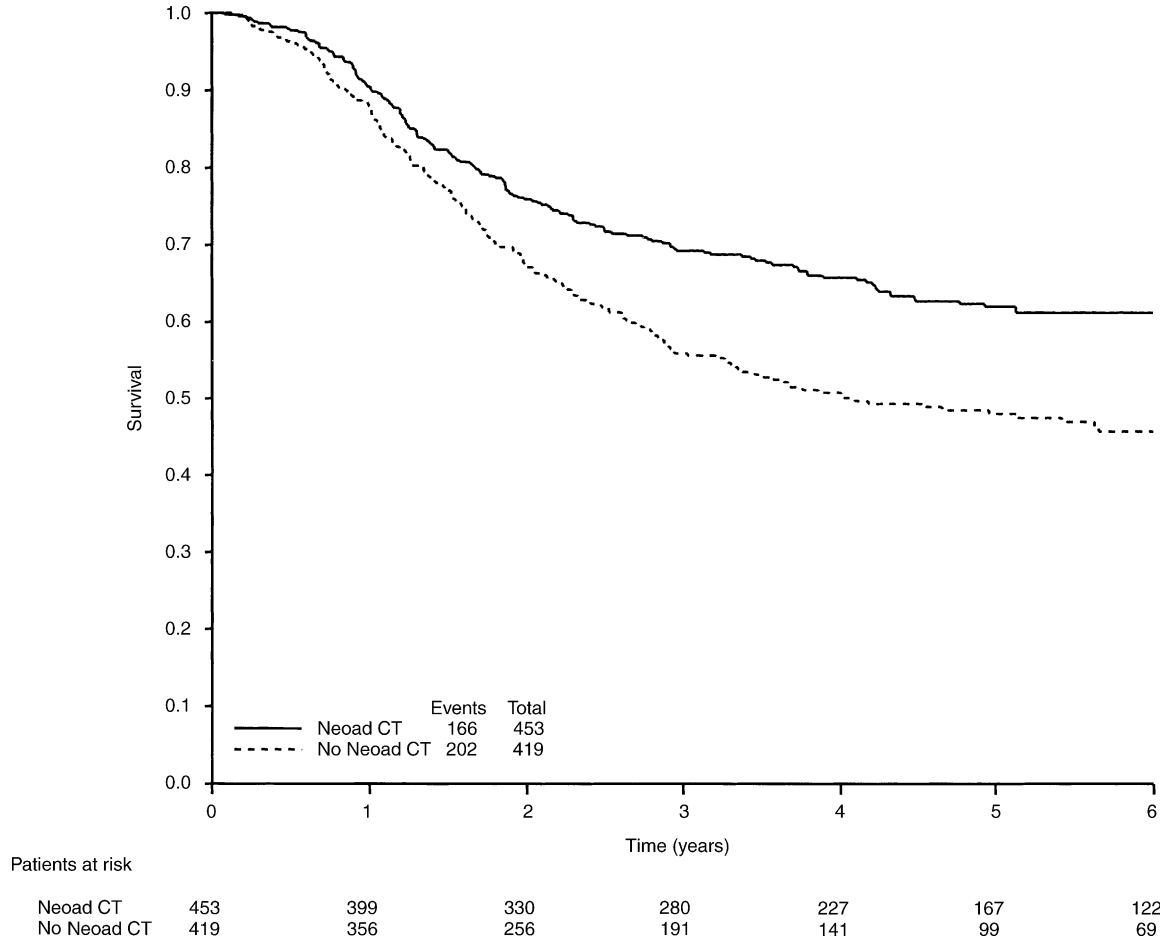

Fig. 5. Kaplan–Meier curves of overall survival in comparison 2. Neoad CT, neoadjuvant chemotherapy.

to chemotherapy and potentially less sensitive to conventionally fractionated radiotherapy, due to the changed growth kinetics. In this scenario, the scheduling of chemotherapy may be important, with short cycle, high dose-intensity chemotherapy being optimal to minimise the repopulation growth perturbations, which undermine radiation cytotoxicity. Conversely, long cycle and low dose-intensity chemotherapy would have less of an effect in reducing clonogenic cells, consequently enhancing their re-growth perturbations.

Whilst all the analyses by groups of trials were planned prospectively, chemotherapy cycle length and cisplatin dose intensity may not provide the correct or most important explanation for the differences in the effect of neoadjuvant chemotherapy across trials. Furthermore, these analyses are correlated, such that the some combination of cycle length and dose intensity may better discriminate between trials. Other factors relating to the scheduling of the treatment may have a role. By similar mechanisms to those described above, the hypothesis that prolongation of the duration of radiotherapy reduces local control by allowing extra time for repopulation with resistant cells, has been supported by a number of retrospective studies [31,32], but potential clinical and methodological biases have been highlighted in these analyses [33]. Nevertheless, variation in the duration of radiotherapy amongst the trials in this meta-analysis (Table 1) could contribute to the differences seen in local control and survival. Furthermore, if there is combined chemotherapy and radiotherapy cross-resistance, the duration of chemotherapy, the delay to radiotherapy and the duration of radiotherapy making up the overall treatment time, could each have an impact on prognosis. Interestingly, those trials giving more prolonged chemotherapy tended to be those with longer delays to radiotherapy and longer durations of radiotherapy and *vice versa* (Table 1).

As they were based only on the planned dose intensity of cisplatin, our analyses ignore the potential impact of other drugs in the regimens. Whilst an analysis by composite dose intensity may offer an alternative way of grouping these trials, many untestable assumptions would have to be made. In addition, the chemotherapy regimens appear more homogeneous within the subset of trials using higher dose intensities (Table 1). Alternatively, differences in the patient characteristics within trial groupings could lead to some differences in the effect of neoadjuvant chemotherapy. The eligibility criteria of

the individual trials do indeed lead to some differences in the types of patients included in the trials using short chemotherapy cycle lengths, compared with those using longer cycle lengths. However, within these two groups of trials, survival on control is very similar (Fig. 2) and there is no evidence that particular types of patients benefit more or less from chemotherapy.

Although, it is difficult to conduct comprehensive literature searches across cancer sites, we have found no other reports of qualitative differences in effect resulting from modest variations in the delivery of neoadjuvant chemotherapy. Of course this may mean that: the potential impact of chemotherapy dose and scheduling on the effects of neoadjuvant chemotherapy has not been formally explored; or it has been explored, but no such association has been noted or that no real variation in delivery exists between trials. For example, in head and neck cancer, another rapidly-proliferating, radio-responsive tumour, most randomised trials of neoadjuvant chemotherapy used similar 3-weekly cycles and a meta-analysis found a trend towards a survival benefit with no clear heterogeneity [34]. Alternatively, the heterogeneity in results we have identified may reflect known or unknown treatment-related, design, patient or indeed other factors that are peculiar to the particular trials and that we could not take account of in the meta-analyses. In addition, we cannot rule out the possibility that our results in cervical cancer are chance findings.

4.2. Treatment comparison 2

The meta-analysis was successful in collecting and re-analysing 97% of the known randomised evidence from trials comparing neoadjuvant chemotherapy plus surgery with radiotherapy for cervical cancer. However, the number of patients (872) and events (368) is not large and the results need to be interpreted with caution. In addition, some of the patients included in these trials would be considered as having localised disease (FIGO stage IB-IIA) and others would be considered to be locally advanced (FIGO stage IB bulky, IIB-IIIB) and as such, clinically, they would not often be considered together. This comparison is further complicated by the fact that intra-arterial chemotherapy was used in one trial [24] and by the use of pelvic radiotherapy in the neoadjuvant chemotherapy plus surgery arm. In two trials [17,18], almost all patients received pelvic radiotherapy and in another two trials [24,25] it was given to approximately 30% of patients. Therefore, there a number of possible confounding factors that we have been unable to tease out in the analysis. Nevertheless, the results are fairly consistent from trial to trial and suggest a highly significant effect of neoadjuvant chemotherapy. Although the HR of 0.65 indicates a 14% absolute overall improvement in 5-year survival, because baseline survival differs considerably by stage, this relative benefit translates into absolute improvements ranging from 8 to 14% at 2 years and 12 to 16% at 5 years. It is noteworthy that generally chemotherapy was intense and of short duration. Of course in this comparison, with surgery as the definitive local treatment, any potential radio-resistance with more prolonged or less dose-intensive regimens, is probably inconsequential.

4.3. Implications

Although, the overall results do not support the use of cisplatin-based neoadjuvant chemotherapy prior to radiotherapy for women with locally advanced cervical cancer, the more detailed preplanned analyses are emphasised. These imply that the timing and dose intensity of neoadjuvant chemotherapy has an important impact on whether it is beneficial. Prolonged or less dose-intensive chemotherapy seems to have a detrimental effect for women. Despite some remaining unexplained heterogeneity, they may also indicate that there are two alternative neoadjuvant strategies to improve long-term outcomes. One is a short cycle, dose-intensive course of cisplatin-based chemotherapy prior to radiotherapy. The second is similar chemotherapy given prior to surgery (with or without radiotherapy), which could provide a reasonable alternative to radical radiotherapy for earlier stage tumours and perhaps, more contentiously, for more advanced stages. However, given the problem of heterogeneity in comparison 1 and potential confounding factors and the small quantity of data available for comparison 2, further assessment of these approaches in randomised trials is probably required. For those planning to assess further the value of neoadjuvant chemotherapy, it may be valuable to compare the policies of neoadjuvant chemotherapy and concomitant chemoradiotherapy in terms of efficacy and toxicity or even to combine them in a single treatment approach. Our results suggest that in any such comparison, particularly where radiotherapy is the definitive treatment, it would be prudent to avoid potentially detrimental long cycles or low doses of chemotherapy. Rather, short-cycle, dose-intensive neoadjuvant chemotherapy, perhaps similar to that commonly given concurrently with radiation, would be preferable. Such a trial could be of considerable value, because there may be reasons why one or other approach would be preferable to individual women, clinicians or healthcare systems. For example, it might enable clinicians to take the pragmatic decision to use short-cycle, dose-intensive neoadjuvant chemotherapy when there is an unavoidable delay in being able to give radical radiotherapy or perhaps offer greater choice to women who have concerns about receiving chemotherapy and radiotherapy at the same time.

5. NACCCMA Collaboration

Collaboration participants: P. Benedetti-Panici (Libera Università "Campus Bio-Medico" di Roma, Rome, Italy), A. Bermudez (Buenos Aires University, Buenos Aires, Argentina), P. Blake (Royal Marsden Hospital, London, UK), J. Cárdenas (Centro Estatal de Cancerologia, Colima, Mexico), T.-C. Chang (Chang Gung Memorial Hospital, Linkou, Taiwan), S. Chiara (Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy), G. Di Paola (Buenos Aires University, Buenos Aires, Argentina), A. Floquet (Institut Bergonié, Bordeaux, France), D. Guthrie (Derbyshire Royal Infirmary, Derby, UK), J. Kigawa (Tottori University School of Medicine, Yonago, Japan), L. Kumar (All India Institute of Medical Sciences, New Delhi, India), F. Leborgne (Hospital Pereira Rossell, Montevideo, Uruguay), N. Lodge (Royal Marsden Hospital, London, UK), C. Poole (City Hospital Birmingham, Birmingham, UK), J. Sardi (Buenos Aires University, Buenos Aires, Argentina), L. Souhami (Hôpital Général de Montréal, Montréal, Canada), K. Sundfør (The Norwegian Radium Hospital, Oslo, Norway), P. Symonds (Leicester Royal Infirmary, Leicester, UK) and M. Tattersall (The University of Sydney, Sydney, Australia) collated and supplied the individual patient data from their trials, contributed to the discussion and interpretation of the results and commented on drafts of the report. The project was organised by the Advisory Group, S. Greggi, (Istituto Nazionale Tumori "Fondazione G. Pascale", Naples, Italy) D. Guthrie, V. Parker (COU-RAGE UK, Manchester, UK), M.K.B. Parmar (MRC Clinical Trials Unit, London, UK), J. Sardi, L.A. Stewart (MRC Clinical Trials Unit, London, UK), J.F. Tierney (MRC Clinical Trials Unit, London, UK), who were responsible for formulating the questions, developing the protocol and discussing the preliminary results. The secretariat, M.K.B. Parmar, L.A. Stewart and J.F. Tierney, were responsible for receiving, checking and analysing data. J.F. Tierney managed the project and J.F. Tierney drafted the report, with detailed input from L.A. Stewart and M.K.B. Parmar.

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