original article

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Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients

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On behalf of the Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MAC3-LC) Group

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Background: Despite several randomised trials comparing radiotherapy alone with concomitant radio-chemotherapy in patients with locally advanced non-small cell lung cancer (NSCLC), it is not clear whether the addition of chemotherapy improves survival.

Patients and methods: This meta-analysis was based on individual patient data from published and unpublished randomised trials which compared radiotherapy alone with the same radiotherapy combined with concomitant cisplatin- or carboplatin-based chemotherapy. Trials with accrual completed after 2000 were excluded. Trials were sought in electronic databases, clinical trial registries and by additional manual searches. The primary endpoint was overall survival analysed using the log-rank test stratified by trials.

Results: There were twelve eligible trials that included a total of 1921 patients. The data from 3 trials were not available. Therefore, the analysis was based on 9 trials including 1764 patients. Median follow-up was 7.2 years. The hazard ratio of death among patients treated with radio-chemotherapy compared to radiotherapy alone was 0.89 (95% confidence interval, 0.81–0.98; $P = 0.02$) corresponding to an absolute benefit of chemotherapy of 4% at 2 years. There was some evidence of heterogeneity among trials and sensitivity analyses did not lead to consistent results. The combination of platin with etoposide seemed more effective than platin alone.

Conclusions: Concomitant platin-based radio-chemotherapy may improve survival of patients with locally advanced NSCLC. However, the available data are insufficient to accurately define the size of such a potential treatment benefit and the optimal schedule of chemotherapy.

Key words: concomitant radio-chemotherapy, individual patient data, locally advanced non-small cell lung cancer, meta-analysis, randomised trial, systematic review

introduction

Lung cancer remains a major cause of death worldwide with over 1.1 million deaths per year [1]. Non-small cell lung cancer (NSCLC) accounts for at least 80% of all lung tumours. About 35% of these patients present with locally advanced non-metastatic disease [2] for whom radical thoracic radiotherapy is frequently part of treatment. The NSCLC Collaborative Group meta-analysis [3] showed that sequential cisplatin-based chemotherapy given in addition to radical radiotherapy prolonged survival in patients with locally advanced NSCLC. However, the prognosis for these patients remained poor with a 3-year survival rate of approximately 14%. Cytotoxic agents used as radiosensitisers given at the same time as radiotherapy have been evaluated against radiotherapy alone in several randomised trials [4–14]. A primary aim of this combined approach was to improve survival by increasing loco-regional control, while the sequential use of chemotherapy has been directed at reducing the rate of distant metastasis. However, the majority of the trials performed have reported inconclusive results and it is

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still controversial whether concomitant radio-chemotherapy does in fact improve survival of patients with locally advanced NSCLC. The size of most of these trials has not been large enough to detect a 5 to 10% increase in survival and there were also some heterogeneities in the trial designs.

The Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MAC3-LC) Group was therefore created to undertake a meta-analysis based on all available individual patient data from randomised trials. Combining the data of these trials could provide increased statistical power, time to event analyses conducted in intention-to-treat and subgroup analyses leading to greater ability to determine whether concomitant chemotherapy might lead to a moderate improvement in survival in patients with locally advanced NSCLC.

methods

selection criteria

Trials were eligible provided they randomised patients with locally advanced unresectable or inoperable NSCLC without distant metastasis to receive radiotherapy alone or radiotherapy combined with concomitant systemic chemotherapy based on cisplatin or carboplatin. Trials had to have been adequately randomised. Trials were considered if the radiotherapy regimen was the same in both arms. Patients should not have received prior radiotherapy or chemotherapy. Published and unpublished trials without language restriction were eligible. Trials with patient accrual completed after 2000 were ineligible.

search methods

Trials published between 1985 and 2002 were sought by searching electronic databases (Medline, Embase, Cancerlit) without language restriction, using the search terms: (*Carcinoma*, *Non-Small Cell Lung/drug therapy*, *lung neoplasms*) and (*Carcinoma*, *Non-Small Cell Lung/radiotherapy*, *lung neoplasms*) and (*clinical trial phase III*, *randomised controlled trials*). This was supplemented by manual searches (reference lists of trial publications, review articles, relevant books, meeting proceedings of American Society of Clinical Oncology and International Association for the Study of Lung Cancer). The Physician Data Query (PDQ) clinical trial registry and the Cochrane library were also searched and investigators and experts were asked to help identify trials.

individual patient data

Individual patient data were collected for all randomised patients. The following data were requested: gender, age, performance status at the time of randomisation, stage, histopathology, randomisation date, allocated treatment, and updated information on survival and on first recurrence. Data were checked for internal consistency and with published results. Amendments were made as necessary through discussion with the investigators.

statistical analysis

The main endpoint was overall survival which was evaluated from the time of randomisation until death due to any cause. Living patients were censored at the date of last follow-up. Secondary endpoints were event-free survival (time from randomisation until first event including death or relapse).

All analyses were conducted on an intention-to-treat basis, that is, all randomised patients were included in the analyses according to the allocated treatment. Follow-up was quantified by the reverse Kaplan-Meier method [15].

The statistical method for compiling the results and comparing the treatments of interest has been previously described [16]. Analyses were stratified by trials. The log-rank expected number of deaths and variance of the observed minus the expected number of deaths were used to calculate individual and overall pooled hazard ratios (HR) and their 95% confidence intervals (95%CI) by the fixed-effects model. Chi–square heterogeneity tests were used to test for statistical heterogeneity among trials. We used also the I^2 index [17] that express in percentage the proportion of variability of the results related to heterogeneity rather than to the sampling error. The absolute differences in the 2 and 5-year survival rates were calculated using the pooled hazard ratio and the survival rates at 2 and 5 years in the radiotherapy group with the assumption of proportional hazards [18]. Crude (non-stratified for trial) Kaplan-Meier survival curves were plotted. The same analyses were performed for event-free survival. Robustness of the results were explored by three sensitivity analyses excluding respectively small trials, oldest trials and trials with incomplete data. Indirect comparisons were performed to study whether the effect of concomitant radio-chemotherapy could differ according to the type of radio-chemotherapy combination. They compared effect of subsets of trials based on the type of chemotherapy that was utilized: daily versus weekly versus other schedules, carboplatin versus cisplatin, single drug versus two drugs. Similarly, indirect comparisons were performed regarding the type of radiotherapy regimen: split-course versus continuous, once daily versus twice daily radiation. An indirect comparison was also performed according to whether there was induction chemotherapy in both arms or not. Subgroup analyses were performed studying the interaction between the treatment effect and the following patients characteristics: gender, age, performance status, stage

Table 1. Characteristics of trials included in the meta-analysis

Trial	Accrual period	No. of analysed/ randomised patients	Patients alive	Median follow-up (years)
EORTC 08844 [5]	1984–89	330/331	9	15.8
HOGLUN 86.1 [6]	1986–92	237/241	19	6.7
Aviano [7]	1987–91	173/173	0	
Kragujevac 88 [8]	1988–89	169/169	23	4.0
PMCI 88.C091 [9]	1989–95	208/208	7	10.0
Kragujevac 90 [10]	1990–91	131/135	21	4.4
CALGB-ECOG [11]	1991–94	282/283	17	7.3
NCCTG 90.24.51 [12]	1992–93	74/75	8	7.2
NKB-CKVO 94.11 [13]	1994–98	160/160	3	7.4

EORTC, European Organisation for Research and Treatment of Cancer; HOGLUN, Hoosier Oncology Group Lung; PMCI, Peter MacCallum Cancer Institute; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; NCCTG, North Central Cancer Treatment Group; NKB-CKVO, Nederlandse Kanker Bestrijding – Commissie voor Klinisch Vergelijkend Onderzoek.

Table 2. Treatment characteristics in each trial

Trial	RT total dose	Number of fractions	RT duration (week)	CT modalities	Patients RT+CT	Number of RT alone
EORTC 08844 [5]	55 (30+25)	10 + 10 (split)	2 + 2 (+3 split)	a) CDDP 30 mg/m^2 on d_1 W_{1-2}, W_{6-7}	109	114
				b) CDDP 6 mg/m^2/d_{1-5} W_{1-2}, W_{6-7}	107	
HOGLUN 86.1 [6]	60–65	30–33	6–7	CDDP 70 mg/m^2 on d_1 W_1, W_3, W_6	117	120
Aviano [7]	45	15	3	CDDP 6 mg/m^2 d_{1-5} $W_{1, 2, 3}$	85	88
Kragujevac 88 [8]	64.8	54 (bid)	5.4	a) CBDCA 100 mg d_{1-2}, Etoposide 100 mg d_{1-3}, W_{1-5}	52	61
				b) CBDCA 200 mg d_{1-2}, Etoposide 100 mg d_{1-5}, $W_{1,}$ $W_{3,}$ W_5	56	
PMCI 88.C091 [9]						
Comparison #1	60	30	6	CBDCA 70 mg/m^2 d_{1-5} $W_{1,}$ W_5	56	53
Comparison #2	60	30 (bid)	3	CBDCA 70 mg/m^2 d_{1-5}, W_1	51	48
Kragujevac 90 [10]	69.6	58 (bid)	5.8	CBDCA 50 mg/d, Etoposide 50 mg/d×29	65	66
CALGB-ECOG [11]*	60	30	6	CBDCA 100 mg/m^2 on d_1 W_{1-6}	146	136
NCCTG 90.24.51 [12]	60 (30+30)	20 + 20 (bid and split)	2 + 2 (+2 split)	CDDP 30 mg/m^2, Etoposide 100 mg/m^2 d_{1-3} $W_{1,}$ W_4	38	36
NKB-CKVO 94.11 [13]	60	30	6	CBDCA 40 mg/m^2/48h ci d_{1-42}	77	83

*In the CALGBG-ECOG trial, patients received induction chemotherapy (vinblastine and cisplatin) in both arms.
Abbreviations: CT, chemotherapy; RT, radiotherapy; W, week; d, day; ci, continuous infusion; CDDP, cisplatin; CBDCA, carboplatin.

and histopathology. Indirect and subgroup analyses were determined a priori and written in the meta-analysis protocol. All *P* values were two-sided.

results

description of trials

Searches identified 12 eligible trials [4–14, unpublished RTOG 9701] that randomised 1921 patients with NSCLC between radiotherapy alone and concomitant platin-based radio-chemotherapy. Data of the 13 patients included in the unpublished RTOG 9701 trial were not available and we were unable to obtain individual data from two small trials [4, 14] including a total of 133 patients. In addition, the data from 11 patients who were randomised in the nine remaining trials were not available. Thus, the analysis of survival was based on 9 trials [5–13] including 1764 patients (1657 deaths) which corresponded to 92% of all patients randomised in the eligible trials.

Table 1 shows the characteristics of the included trials. The follow-up did not differ between the two groups: with a median of 7.2 years in the radiotherapy group and 7.4 years in the radio-chemotherapy group. Table 2 shows the treatment characteristics. The EORTC trial [5] and the Kragujevac 88 trial [8] randomised patients between three arms as they tested two different radio-chemotherapy schedules. The PMCI trial [9] used a 2 × 2 factorial design to compare radiotherapy given once daily and twice daily with and without concomitant carboplatin. Radiotherapy modalities varied between the different trials in terms of total dose, dose per fraction, number of daily doses as well as duration of overall treatment, two trials used split-course radiotherapy. Concurrent chemotherapy was based on cisplatin in four trials and on

Table 3. Patient characteristics

Characteristic	RT+CT N=959[‡]	RT alone N=805[‡]
Male	752 (78%)	630 (78%)
Median age (range) in years[£]	61 (36–83)	61 (31–82)
≤60 years	433 (45%)	371 (46%)
61–70 years	435 (46%)	357 (44%)
≥71 years	88 (9%)	76 (9%)
Performance status[†]		
0	427 (45%)	346 (43%)
1	476 (50%)	425 (53%)
2–3	54 (6%)	33 (4%)
Weight loss>5%*	229/740 (31%)	165/585 (28%)
Squamous carcinoma[$]	439/784 (56%)	392/675 (58%)
Stage[#]		
I	30 (3%)	28 (4%)
II	22 (2%)	18 (2%)
IIIa	548 (60%)	449 (58%)
IIIb	301 (33%)	273 (35%)
IV	8 (1%)	3 (0%)

[‡]Since two trials [5, 8] were 3-arm studies randomising patients between radiotherapy alone and two different concomitant radio-chemotherapy regimens, the overall number of patients included in the meta-analysis was lower in the radiotherapy arm than in the radio-chemotherapy arm.
[£]Data missing for four patients.
[†]Data missing for three patients.
*Data not available for 439 patients (in particular all patients from HOG LUN 861 and Aviano trials).
[$]Data not available for 305 patients (in particular all patients from the two Kragujevac trials).
[#]Data not available for 84 patients.

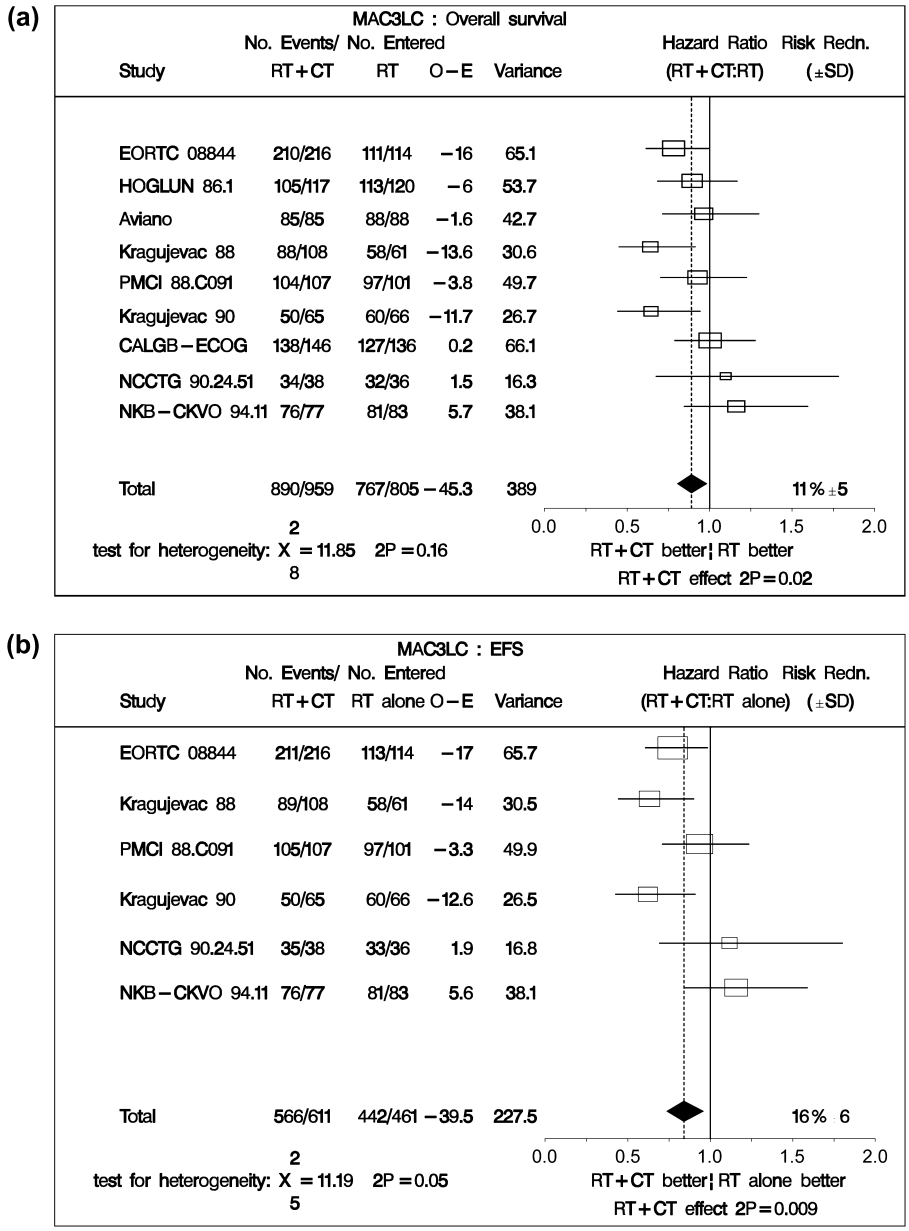

Figure 1. Hazard ratio plots for survival (**a**) and for event-free survival (EFS) (**b**). The centre of each empty square represents the hazard ratio for individual trial and each horizontal line its 95% confidence interval; the area of the square is proportional to the amount of information from the trial. The broken line and the centre of the solid diamond represent the pooled hazard ratio and the extremities of the diamond represent its 95% confidence interval. Event status was unknown for three trials (692 patients) which were excluded from the event-free analysis.

carboplatin in five trials. Etoposide was combined with cisplatin or carboplatin in three trials. Chemotherapy was given daily in four trials [5, 7, 10, 13], weekly in three trials [5, 8, 11], every 2, 3 or 4 weeks in four trials [6, 8, 9, 12]. In the CALGB-ECOG trial [11], patients received induction chemotherapy in both arms. There were no significant differences on main characteristics between treatment arms (Table 3).

overall survival and sensitivity analyses

The hazard ratio of death of radio-chemotherapy compared to radiotherapy alone was 0.89 (95% CI=0.81–0.98; $P = 0.02$) (Figure 1a). This corresponds to an absolute benefit of chemotherapy of 4% at 2 years and 2.2% at 5 years, increasing respectively the 2- and 5-year survival rates from 21.4% to 25.4%, and from 6.0% to 8.2% (Figure 2a).

The heterogeneity test was not significant ($P = 0.16$). However, the I^2 index indicated that 32% of the variability across trials was due to heterogeneity rather than chance. Sensitivity analyses were performed according to the size of the trials (exclusion of two small trials that randomised less than 150 patients [10, 12]), to the period of accrual (exclusion of two old trials that finished accrual before 1990 [5, 8]) and to the completeness of the data (exclusion of two trials in which the follow-up was not updated and the dates of randomisation and end-points were not available, but only the duration of

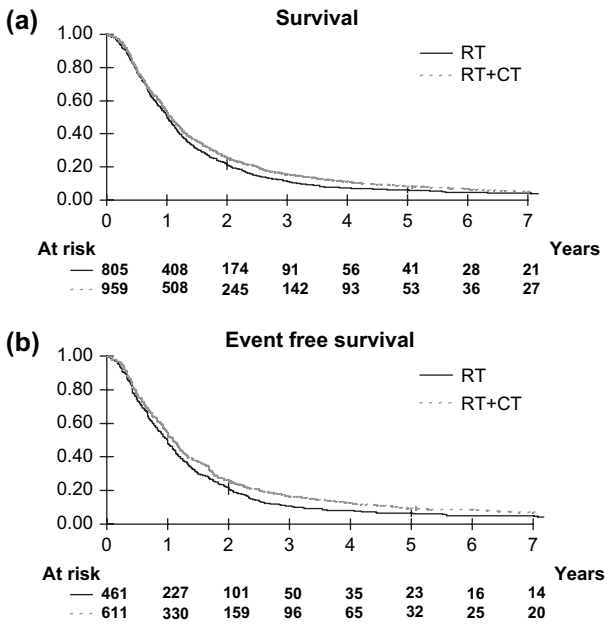

Figure 2. Kaplan-Meier curves for survival (**a**) and for event-free survival (**b**). Vertical bars denote 95% confidence interval of the actuarial rates. Event status was unknown for three trials (692 patients) which were excluded from the event-free survival analysis.

follow-up [8, 10]). As shown in Table 4, these analyses excluded 17–28% of the patients. The analyses which excluded old trials or trials with incomplete data decreased the heterogeneity between trials (I^2 = 5% and 0% respectively) and decreased also the size of the treatment effect (hazard ratios 0.95 and 0.94 respectively, not significantly different from 1).

event-free survival

Data on the patterns of first failure (metastases or loco-regional) were available for 1072 patients (61%). Concomitant chemotherapy significantly improved event-free survival (HR = 0.84, 95% CI = 0.74–0.96, P = 0.009) as shown in Figure 1b. The absolute benefit of chemotherapy was 6% at 2 years, increasing event-free survival from 21.3% to 27.3%, and 3.5% at 5 years from 6.4% to 9.9% (Figure 2b). There was, however, significant heterogeneity between trials (P = 0.05) and the I^2 index indicated that 55% of the variability across trials was due to heterogeneity rather than chance. Sensitivity analyses excluded between 20% and 47% of the patients (Table 4). In the analyses which excluded the old trials and the trials with incomplete data, the estimated size of the treatment effect decreased (HR 0.94 and 0.93 respectively, not significantly different from 1) but there was still some heterogeneity among trials.

indirect comparisons

The effect of concomitant chemotherapy on survival did not differ significantly according to the treatment schedule (daily versus weekly chemotherapy versus other schedules (P = 0.87), Table 5). There was no significant difference between cisplatin-and carboplatin-based chemotherapy (P = 0.88). The effect of single agent cisplatin or carboplatin (HR = 0.93) was lower (P = 0.05) than that of a two-drug (platin plus etoposide) combination (HR = 0.72) (Figure 3). The analysis of event-free survival showed similar result although the interaction was not significant. There was no significant heterogeneity between trials using platin alone (P = 0.47) but there was some evidence of heterogeneity between the three trials using platin plus etoposide (P = 0.16).

The effect of concomitant chemotherapy on survival did not differ significantly according to the type of radiotherapy: once-daily versus twice-daily radiotherapy (P = 0.22), continuous versus split-course radiotherapy (P = 0.53), and total radiation dose (P = 0.15).

The effect of concomitant chemotherapy in the trials without induction chemotherapy was significant and this effect was not significantly different from the effect in the trial which used induction chemotherapy (interaction test P = 0.29, Table 5). However, as only one trial [11], with 282 randomised patients, used induction chemotherapy, the analysis of the potential impact of induction chemotherapy on the effect of concomitant chemotherapy was rather uninformative.

subgroup analyses

Predefined subgroups of patients were analysed to determine whether the effect of concomitant chemotherapy varied across subgroups (Table 6). Data on gender, age, performance status were available for nearly all patients. Data on stage, pathological type and weight loss were available for 1680 (95%), 1459 (83%) and 1325 (75%) patients, respectively. There was no clear evidence that any subgroup of patients defined by gender, performance status, pathological type or weight loss benefited more or less from concomitant chemotherapy in terms of survival or event-free survival. However, the effect of concomitant chemotherapy appeared greater in patients with stage IIIa disease than in those with stage IIIb, both for survival (HR = 0.81 versus 1.01, P = 0.053), and for event-free survival (HR = 0.76 versus 1.02, P = 0.047).

Concomitant chemotherapy also appeared to have a differential effect on survival according to age category. The hazard ratios were 1.08 in the 804 patients younger that 61 years, 0.80 in the 792 patients with ages between 61 and 70 years and 0.67 in the 164 patients older than 70 years (test for trend P = 0.001). Only five trials [6, 9, 11–13] randomised patients older than 70 years. The difference was particularly marked between patients younger and older than 60. The results were quite similar for the event-free analysis, as shown in Table 6. Patients older than 60 had less advanced disease compared to the younger patients: 37% of stage IIIb among patients less than 61 years, and 32% among those 61 years or older (P = 0.03). However, this distribution does not explain the interaction between age and effect of chemotherapy because this interaction was observed only in patients with stage IIIb disease (data not shown).

discussion

This meta-analysis of individual patient data from nine randomised trials evaluating concomitant platin-based chemotherapy in 1764 patients with locally advanced NSCLC

Table 4. Results of the sensitivity analyses

	Overall survival					Event-free survival				
	Number of patients RT+CT/RT	Hazard ratio (95% CI)	*P*-value	Heterogeneity *P*-value	I^2	Number of patients RT+CT/RT	Hazard ratio (95% CI)	*P*-value	Heterogeneity *P*-value	I^2
All trials	959/805	0.89 (0.81–0.98)	0.02	0.16	32%	611/461	0.84 (0.74–0.96)	0.009	0.05	55%
Without 2 small trials	856/703	0.90 (0.81–1.004)	0.059	0.22	40%	508/359	0.86 (0.74–0.99)	0.03	0.06	61%
Without 2 old trials	635/630	0.95 (0.85–1.06)	0.36	0.39	5%	287/286	0.94 (0.79–1.11)	0.46	0.08	56%
Without 2 trials with incomplete data	786/678	0.94 (0.85–1.05)	0.27	0.58	0%	438/334	0.93 (0.80–1.08)	0.32	0.20	39%

CI, confidence interval.

Table 5. Indirect comparisons

	Overall survival			Event-free survival		
	Patients RT+CT/RT	HR of death (95% CI)	Interaction *P*-value	Patients RT+CT/RT	HR of death/event (95% CI)	Interaction *P*-value
Chemotherapy type*						
Daily	334/351	0.86 (0.73–1.00)		249/263	0.80 (0.67–0.96)	
Weekly	307/311	0.86 (0.73–1.01)		161/175	0.74 (0.59–0.93)	
Other	318/318	0.90 (0.77–1.06)	0.87	201/198	0.92 (0.75–1.12)	0.38
Cisplatin based	456/358	0.88 (0.76–1.02)		254/150	0.83 (0.67–1.03)	
Carboplatin based	503/447	0.90 (0.78–1.03)	0.88	357/311	0.85 (0.72–1.00)	0.86
Platin alone	748/642	0.93 (0.84–1.04)		400/298	0.91 (0.78–1.06)	
Platin+Etoposide	211/163	0.72 (0.58–0.91)	0.05	211/163	0.71 (0.57–0.90)	0.09
Radiotherapy type						
Once-daily RT	697/594	0.92 (0.82–1.03)		349/250	0.87 (0.73–1.04)	
Twice-daily RT	262/211	0.80 (0.66–0.98)	0.22	262/211	0.79 (0.65–0.97)	0.47
Continuous RT	705/655	0.90 (0.81–1.01)		357/311	0.85 (0.72–1.00)	
Split course	254/150	0.84 (0.67–1.04)	0.53	254/150	0.83 (0.67–1.03)	0.86
45–55 Gy	301/202	0.84 (0.70–1.02)		216/114	0.77 (0.60–0.98)	
60–65 Gy	593/537	0.94 (0.83–1.06)		330/281	0.93 (0.79–1.10)	
69.6 Gy	65/66	0.65 (0.44–0.94)	0.15	65/66	0.62 (0.42–0.91)	0.11
Induction CT: Yes	146/136	1.00 (0.79–1.28)		No available data		
No	813/669	0.87 (0.78–0.97)	0.29	611/461		

*Control radiotherapy arms were used twice in two trials. EORTC 8844 trial: RT arm was compared with weekly CT arm and with daily CT arm. Kragujevac 88 trial: RT arm was compared with weekly CT arm and with other schedule CT arm.

showed that concomitant chemotherapy could lead to a significant 11% relative reduction in mortality corresponding to a 4% absolute impact on overall survival at 2 years.

Nine meta-analyses exploring the role of chemotherapy in resectable or locally advanced NSCLC have been published since 1995 [19–27] (Tables 7 and 8). Only two of them were performed on individual patient data: the NSCLC Collaborative Group meta-analysis which was published in 1995 [3] and studied chemotherapy in early disease and locally advanced disease and the meta-analysis published by Hamada et al. [22] in 2005 which studied tegafur-uracil in resectable NSCLC, mainly p-stage I. The overlap of the trials included in the meta-analyses studying the same question is variable. Two recent literature-based meta-analyses explored the role of radio-chemotherapy versus radiotherapy alone [25–26]. The meta-analysis performed by Rakovitch et al. [25] was based on 10 trials: nine trials of platin-based chemotherapy and one trial using vindesine. Eight trials of our current analysis were included in this study. The meta-analysis performed by Rowell et al. [26] was based on 11 trials studying platin-based chemotherapy including the nine trials of our analysis. As these meta-analyses were based on published data, a time to event analysis could not be used. The analyses were based on mortality at specific time points calculated from the number of events given in papers or estimated from the published curves, which is a less reliable method than the use of individual patient data [27]. The relative risks of death (95% CI) at 2 years were respectively 0.92 (0.88–0.97) and 0.93 (0.87–0.99) in these two meta-analyses, consistent with our results. However, these results favouring concomitant radio-chemotherapy should be interpreted with caution because our meta-analysis showed that there was some heterogeneity across trials and the sensitivity analyses led to inconsistent results.

Two trials were eligible for our meta-analysis but were not included as fruitful communication with active investigators proved to be impossible [4, 14]. The first trial [4] randomised

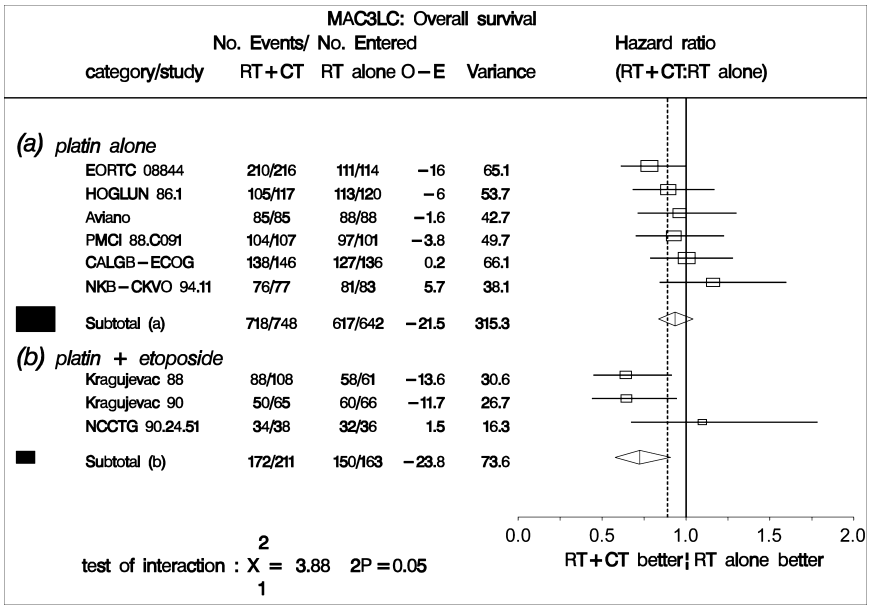

Figure 3. Hazard ratio plot for survival according to the number of agents (symbols as in Figure 1).

Table 6. Subgroup analyses

		Overall survival			Event-free survival		
		Patients RT+CT/RT	HR of death (95% CI)	Interaction *P*-value	Patients RT+CT/RT	HR of death/event (95% CI)	Interaction *P*-value
Gender	Male	752/630	0.87 (0.78–0.97)		494/360	0.80 (0.69–0.92)	
	Female	206/175	0.92 (0.74–1.15)	0.68	117/101	0.92 (0.68–1.25)	0.38
Age	≤60 years	433/371	1.08 (0.93–1.26)		289/224	1.01 (0.83–1.22)	
	61–70 years	435/357	0.80 (0.69–0.93)	0.004	277/198	0.74 (0.61–0.91)	0.07
	≥71 years	88/76	0.67 (0.48–0.94)	(0.001)[†]	45/39	0.70 (0.44–1.11)	(0.03)[†]
Performance status	0	427/346	0.91 (0.78–1.07)		245/170	0.79 (0.64–0.98)	
	1	476/425	0.91 (0.79–1.05)		326/270	0.93 (0.78–1.10)	
	2–3[#]	54/32	0.75 (0.45–1.26)	0.77	40/20	0.72 (0.39–1.33)	0.44
Stage*	I-II	52/44	0.96 (0.62–1.47)		43/33	0.83 (0.51–1.34)	
	IIIa	548/449	0.81 (0.71–0.93)	0.15	366/267	0.76 (0.64–0.91)	0.14
	IIIb	301/273	1.01 (0.85–1.20)	(0.053)[£]	182/154	1.012 (0.81–1.27)	(0.047)[£]
Histology	Squamous	439/392	0.96 (0.83–1.10)		273/201	0.89 (0.73–1.08)	
	Non squamous	345/283	0.92 (0.78–1.08)	0.72	165/132	0.99 (0.77–1.26)	0.50
Weight loss	<5%	511/420	0.84 (0.73–0.96)		383/302	0.79 (0.67–0.93)	
	>5%	229/165	0.95 (0.77–1.17)	0.35	215/150	0.91 (0.73–1.14)	0.31

[†]Test for trend, [#]only one PS2 patient was randomized in the NKB-CKVO trial and could not be included in the analysis stratified by trial, *Stage IV excluded. Only 2 stage II patients were included in the Aviano trial and randomized to the same arm and could not be included in the analysis stratified by trial, [£]Stage IIIa versus IIIb

95 patients between radiotherapy alone at 50 Gy and radiotherapy with weekly cisplatin (15 mg/m^2). The results suggested an advantage for concomitant chemotherapy but the difference was not significant (median survival: 16 versus 11 months, log-rank test $P = 0.18$). The second trial [14] randomised 38 patients following the completion of three cycles of induction chemotherapy, to receive either radiotherapy alone (60 Gy) or radiotherapy with daily cisplatin (4 mg/m^2). The median survival was 12 months in both arms. The inability to include these two trials should not have a major impact on the results. A third large trial [28] was not included because only completed accrual in 2003. This trial randomised 584 patients between radiotherapy alone at 66 Gy and radiotherapy plus daily carboplatin (15 mg/m^2). All patients received induction chemotherapy. The results on local control and overall survival did not show significant differences between the two arms, but more toxic deaths in the combined arm (21 versus 10 patients).

The magnitude of the absolute effect of concomitant platin-based chemotherapy on survival found in this meta-analysis is comparable to that of the meta-analysis [3] comparing sequential chemo-radiotherapy to radiotherapy

Table 7. Published meta-analyses studying post-operative chemotherapy in resectable non small cell lung cancer

Year of publication	First author [reference] Type of MA	Period of publication of the included trials	Results: Number of trials (number of patients) Hazard ratio of death (95% CI)		
			CDDP-based CT	UFT/tegafur-based CT	CT associated with RT
1995	NSCLCCG [3] MAP	1988–94 (accrual : 1979–91)	8 trials (1394 pt) 0.87 (0.74–1.02)	3 trials (918 pt) 0.89 (0.72–1.11)	6 trials (668 pt) 0.94 (0.79–1.11)
2004	Sedrakyan [19] MAL	1988–2004 (included all trials of the NSCLCCG MA and new trials)	12 trials (4912 pt) 0.89 (0.82–0.96)	6 trials (2288 pt) 0.83 (0.73–0.95)	/
2004	Hotta [20] MAL	2000–2004 (included only new trials since the NSCLCCG MA)	8 trials (3786 pt) 0.89 (0.82–0.98)	5 trials (1751 pt)* 0.80 (0.67–0.96)	/
2005	Berghmans [21] MAL	1986–2004	16 trials (including 5 of the NSCLCCG MA) 0.85 (0.77–0.93)	6 trials (including 1 of the NSCLCCG MA) 0.72 (0.61–0.85)	4 trials (including 2 of the NSCLCCG MA) 0.86 (0.77–0.97)
2005	Hamada [22] MAP	1996–2005 (accrual : 1985–97)	/	6 trials (2082 pt)* (including 1 of the NSCLCCG MA and all of the Hotta's MA) 0.76 (0.64–0.90)	/

MA, meta-analysis; MAP, meta-analysis of individual patient data; MAL, meta-analysis of the literature; CT, chemotherapy; RT, radiotherapy; UFT, tegafur-uracil; CDDP, cisplatin.
*UFT alone.

alone in NSCLC (4% at 2 years, 2% at 5 years). With sequential combinations, survival is believed to be improved by reducing distant metastases without impacting on local control which was poor in both arms [29–31]. In contrast, the rationale for concomitant radio-chemotherapy is based on improving local control by sensitising the tumour to radiation. Three recent trials have directly compared a sequential combination of chemotherapy followed by radiotherapy versus the same chemotherapy used concomitantly with radiotherapy [32–34]. They all suggested an improvement in both local control and survival with the concomitant combinations, but with greater toxicity. In these trials, chemotherapy was based on cisplatin plus one or two other drugs, vindesine plus mitomycin, vinorelbine or vinblastine. The delay to start radiotherapy in the sequential arm may be detrimental to patients as shown in the Czech study, where the proportion of patients who received radiotherapy was lower in the sequential arm mainly because of tumour progression before the radiotherapy start [33]. The preliminary results of the CALGB 39801 trial showed that the addition of induction chemotherapy prior to concomitant radio-chemotherapy increased the toxicity without leading to a significant survival increase in this early analysis [35]. A meta-analysis project of all the trials that compare directly sequential chemotherapy to concomitant chemotherapy has now been initiated [36].

In our study, indirect analyses showed no difference in the effect of concomitant chemotherapy according to the schedule of chemotherapy nor to the type of platin. There was a suggestion of a major effect with the combination of platin and etoposide as compared with platin alone, but as only three trials used this combination of drugs and two of them were those excluded in the sensitivity analyses (because of incomplete data), these results should be interpreted with caution. However, we know from randomised trials comparing cisplatin alone to cisplatin combinations that doublets provide better results in metastatic patients or patients with stage III disease not eligible for local treatment [37–39]. The advantage of two-drug combinations compared to single agents was also shown in a meta-analysis of chemotherapy in advanced NSCLC [40].

The subgroup analyses showed no clear larger or smaller effect according to gender, performance status, weight loss or histological type. The benefit of concomitant chemotherapy seemed to be greater in patients with stage IIIa disease than in patients with stage IIIb disease. Since concomitant radio-chemotherapy may improve survival through better local control, one can hypothesise that this approach may be more efficacious for patients with a lower risk of developing distant metastasis over time as it is the general case with stage IIIa. The analysis of the limited population of 728 stage III patients with information on distant metastasis in our meta-analysis, confirmed that stage IIIa patients developed significantly less distant metastasis than stage IIIb patients (data not shown).

The benefit of concomitant chemotherapy also seemed to be greater in older patients. However, this differential effect existed only among patients with stage IIIb disease. This may be a chance effect, but these results provide support for the inclusion of older patients in trials of concomitant radio-chemotherapy. Indeed, recent trials that have focused

Table 8. Published meta-analyses studying chemotherapy sequentially or concomitantly associated with radiotherapy in locally advanced non small cell lung cancer and current meta-analysis

Year of publication	First author [reference] Type of MA	Period of publication of the included trials	Results: Number of trials (number of patients) Hazard ratio of death (95% CI)					
		Type of CT	Sequential or concomitant CT		Sequential CT		Concomitant CT	
			All	Platin based	All	Platin based	All	Platin based
1995	NSCLCCG [3] MAP	1973–93 (accrual 1968–89) Only sequential	/	/	22 trials (3033 pt) 0.90 (0.83–0.97)	11 trials (1780 pt) 0.87 (0.79–0.96)	/	/
1995	Marino [23] MAL	1980–1994 Sequential and concomitant	14 trials (1887 pt) (4 trials of CC CT) Not available	10 trials (1410 pt) (3 trials of CC CT) 0.70 (0.5–0.9)*	/	/	/	/
1996	Pritchard [24] MAL	1987–1995 Sequential and concomitant	14 trials (2589 pt) 0.87 (0.81–0.94)**	11 trials (2158 pt) 0.85 (0.79–0.92)**	/	6 trials (1183 pt)) 0.83 (0.75–0.92)**	/	5 trials (975 pt) 0.88 (0.79–0.98)**
2004	Rakovitch [25] MAL	1988–1999 Only concomitant	/	/	/	/	10 trials (1802 pt) 0.92 (0.88–0.97)**	9 trials (1596 pt) Not available
2004	Rowell [26] MAL	1988–2004 (1 trial of hydroxyurea in 1974) Only concomitant	/	/	/	/	13 trials (2214 pt) 0.93 (0.88–0.98)**	11 trials (1945 pt) 0.93 (0.87–0.99)**
	Aupérin Current MA MAP	1992–2004 (accrual 1984–98) Only concomitant	/	/	/	/	/	9 trials (1764 pt) 0.89 (0.81–0.98)

MA, meta-analysis; MAL, meta-analysis of the literature; MAP, meta-analysis of individual patient data; CT, chemotherapy; CC CT, concomitant chemotherapy.
*Odds ratio of death at 2 years.
**Relative risk of death at 2 years.

on elderly populations of patients have supported the use of aggressive regimens for patients who meet the particular protocol eligibility requirements [41–43]. It might be also assumed that patients who are included in such trials are fit patients with minimal co-morbidities.

Concomitant chemotherapy leads to higher toxicity than radiotherapy alone. It was not possible to evaluate this question in this meta-analysis because we did not collect individual patient data on toxicity. The studies of Rakovitch et al. [25] and of Rowell et al. [26] estimated the relative risk of acute toxicity from the published data. Concomitant radio-chemotherapy significantly increased acute oesophagitis from 6–7% to 11% with a relative risk (RR) of respectively 1.8 ($P = 0.0008$) and 1.6 ($P = 0.001$) in these two studies. The risk of acute neutropenia was highly increased from 1–2% to 9–10% (RR = 9.2, $P < 0.00001$ [25] and RR = 3.1, $P = 0.003$ [26]). There was no significant increased risk of acute pneumonitis (RR = 1.4, $P = 0.16$ [25] and RR = 1.2, $P = 0.60$ [26]).

In conclusion, concomitant radio-chemotherapy has become a standard treatment of locally advanced NSCLC while the evidence of its benefit is weak. This study showed that concomitant platin-based radio-chemotherapy might moderately improve survival of these patients. However, the available data are insufficient and the treatment designs were too heterogeneous to reliably confirm this or to accurately define the size of such a potential treatment benefit and the optimum schedule of chemotherapy. A next step attempting to elucidate the remaining questions will be the update of the 1995 meta-analysis on locally advanced NSCLC. The aims of this project, which has now been initiated, are to update the estimation of the effect of the sequential chemotherapy by adding 13 new trials and of the concomitant chemotherapy by adding five new trials studying new agents like taxanes, and to

compare directly concomitant and sequential chemotherapy approaches.

appendix: MAC3-LC Group

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