A Systematic Review and Meta-analysis of the Literature: Chemotherapy and Surgery versus Surgery Alone in Non-small Cell Lung Cancer

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Background: The effectiveness of preoperative chemotherapy in the treatment of non-small cell lung cancer has remained unclear despite the conduct of several randomized controlled trials (RCTs).
Methods: A systematic review and meta-analysis was carried out to assess the effectiveness of preoperative chemotherapy in non-small cell lung cancer. This involved identifying eligible RCTs and extracting aggregate data from the abstracts or reports of these RCTs. Hazard ratios were calculated from these published summary statistics and then combined to give pooled estimates of treatment efficacy.
Results: Twelve eligible RCTs were identified, from which data from seven RCTs, including 988 patients (75% of eligible patients), could be combined in a systematic review and meta-analysis. Preoperative chemotherapy improved survival with a hazard ratio of 0.82 (95% confidence interval, 0.69–0.97; $p = 0.02$). This is equivalent to an absolute benefit of 6%, increasing overall survival across all stages of disease from 14% to 20% at 5 years. There was no evidence of statistical heterogeneity.
Conclusions: This analysis shows a significant benefit of preoperative chemotherapy and is currently the best estimate of the effectiveness of this therapy, but this is based on a small number of trials and patients. This current analysis was unable to address important questions such as whether particular types of patients may benefit more or less from preoperative chemotherapy or whether the early stopping of a number of included RCTs impacted on the results. To assess this, an individual patient data meta-analysis is required.

Key Words: Non-small cell lung cancer, Chemotherapy, Surgery, Systematic review.

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Worldwide, more than 1 million new cases of lung cancer are diagnosed each year,[1] approximately 80% of which are of non-small cell type,[2] comprising adenocarcinomas, squamous cell carcinomas, and large cell carcinomas. Many patients are diagnosed when they already have an advanced form of the disease and, as a consequence, 5-year survival across all stages of disease is approximately 14%.[3] Surgery is generally regarded as the best treatment option, but only approximately 25% of non-small cell lung cancer (NSCLC) tumors are suitable for potentially curative resection.[4] A further 20% of patients with locally advanced disease undergo radical thoracic radiotherapy. The remaining patients, with late-stage or metastatic disease, are usually treated palliatively.

The role of chemotherapy in treating NSCLC has been extensively tested in clinical trials since the 1960s, and chemotherapy has been reported as being both beneficial and detrimental. An individual patient data (IPD) meta-analysis[5] published in 1995, which is currently being updated,[6] found some evidence that chemotherapy given after surgery may improve survival. However, this project did not explore the use of chemotherapy given before surgery, as few trials had been completed at that time.

The proposed benefits of preoperative chemotherapy are a reduction in tumor size such that tumors become easier to remove surgically, and inoperable tumors becoming potentially operable. Preoperative chemotherapy may also assist the early eradication of metastases that are clinically undetectable, which could lead to better control of distant recurrence. Chemotherapy given before surgery may also be better tolerated than postoperative chemotherapy, as the patient is more able to cope with side effects when not recovering from major surgery.

There are, however, proposed disadvantages to this treatment. While the patient is receiving chemotherapy, a potentially curative operation is being delayed. If the chemotherapy being given is ineffective or only minimally effective, this delay could prove detrimental and could lead to the disease spreading.[7–9]

Preoperative chemotherapy has shown a benefit in other disease areas. An IPD meta-analysis of preoperative chemotherapy in invasive bladder cancer[10] has shown a 14% relative improvement in overall survival ($p = 0.003$) for patients receiving the treatment, and a systematic review of published aggregate data regarding esophageal cancer[11] showed a significant benefit of the treatment at 5 years ($p = 0.02$).

PATIENTS AND METHODS

At the outset, a search of MEDLINE (1966–2005) and the Cochrane Library[12] established that no systematic review

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of preoperative chemotherapy in patients with NSCLC had already been carried out and a protocol for this systematic review was written (available on request). This specified eligibility criteria such that included trials had to be properly randomized (i.e., in a way that precluded prior knowledge of treatment assigned), be unconfounded by differences between treatment arms, have included patients with NSCLC, and have compared first-line chemotherapy followed by surgery with surgery alone. Trials of patients who had received chemotherapy as second-line treatment or who had a previous malignancy were excluded, and there were no language restrictions.

Published randomized controlled trials (RCTs) were found by searching MEDLINE (1966–2005) and the Cochrane Library using established search strategies.[13] Unpublished and ongoing trials were found by searching a selection of Trial Registers (cancer.gov, the *meta*Register, clinicaltrials.gov, and the UK Coordinating Committee on Cancer Research National Register of Cancer Trials). The proceedings of the largest international meetings in oncology were searched for trials published only as abstracts. Reference lists of relevant publications and book chapters were also searched. Searches were carried out in November of 2004 and August of 2005. Results of the searches are displayed in Figure 1.[14]

Eligible RCTs were assessed for quality using a component approach. This involved assessing the methodologic aspects of each trial using the CONSORT[15] statement as a guide to which variables to assess. Data were extracted independently by two researchers, and any anomalies were resolved by discussion.

The primary endpoint was overall survival, with planned additional endpoints of local recurrence-free survival, distant recurrence-free survival, and overall recurrence-free survival. Where possible, analyses included all reported randomized patients.

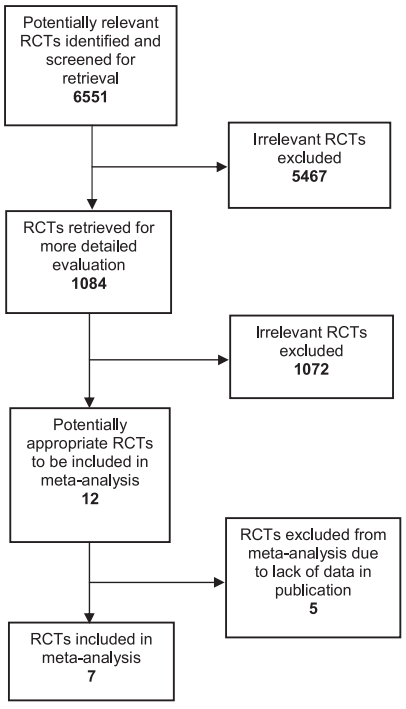


FIGURE 1. Results of searches for RCTs.

For meta-analyses of the time-to-event outcomes, the most appropriate statistic is the hazard ratio (HR). If provided in a trial report, the HR and associated variances were used directly in the meta-analysis. Alternatively, using the methods described by Parmar et al.,[16] they were estimated indirectly from other summary statistics (95% confidence intervals [CI], p values, total number of events) or from data extracted from published Kaplan-Meier curves.[16] In the latter method, the numbers at risk are adjusted (reduced), where appropriate, to allow for immature follow-up. Where feasible, a number of methods were used to indirectly estimate the trial HR to check its reliability. The estimated log HR and variance were then combined across all trials using the fixed effect model to give a pooled HR.[17] This represents the overall risk of an event on preoperative chemotherapy and surgery versus surgery alone.

Overall survival was estimated primarily using the fixed effect model, with the random effects model used as a sensitivity analysis. Absolute differences at relevant time points were calculated by multiplying the log of the baseline event rate for patients not allocated preoperative chemotherapy by the hazard ratio. This value was then subtracted from the baseline event rate to give a percentage improvement or detriment in the outcome. Confidence intervals for absolute differences were similarly calculated from the baseline event rate and the hazard ratio at the 95% confidence interval boundary values.

The χ^2 heterogeneity test was used to test for gross statistical heterogeneity. The I^2 statistic[18] was used as a measure of consistency between trials. Where appropriate, a test for interaction was carried out to see whether there was any difference between subgroups of trials being compared. Tests for publication bias were carried out.

RESULTS

Searches identified 12 eligible rcts[19–30] (1310 patients) that were assessed for methodologic quality. No RCTs gave full details of randomization. Four[20,21,23,27] reported randomizing patients centrally through a data center and the remaining eight simply reported being "randomized." No trials reported concealment of allocation, but two[21,22] used a central telephone, and would imply a level of allocation concealment. Two trials reported details of their stratification factors.[21,29] Three RCTs[20,23,29] described their sample size calculations, and the remainder did not report any of these factors.

Eight RCTs did not reach their planned accrual for a variety of reasons. Three[23,25,27] closed early because of poor accrual, three[19–21] because of a significant difference between the treatments being tested in the trial, and two[29,30] because of the results of other trials. It was unclear whether one trial[27] reached its target accrual, as the only publication of this RCT is the report of interim analyses. The remaining three trials[22,24,26] appear to have reached their target accrual.

TABLE 1. Characteristics of Eligible Trials*

Trial	Recruitment	No. of Patients	Chemotherapy	Additional Treatment	Extent of Resection	Disease Stage†	Informed Consent Sought	Data Extraction Possible
Dautzenberg et al., 1990[19]	1985–1987	26	Cisplatin, cyclophosphamide, vindesine	Postoperative chemotherapy on preoperative chemotherapy arm only	Complete and incomplete	I, II, III	No	Yes
Roth et al., 1994[20]	1987–1993	60	Cisplatin, cyclophosphamide, etoposide	If patients responded to preoperative chemotherapy, 3 cycles given postoperatively	Complete and incomplete	IIIa	Yes	Yes
Rosell et al., 1994[21]	1989–1991	60	Cisplatin, mitomycin, ifosfamide	Postoperative RT on both arms	Complete and incomplete	IIIa	Yes	Yes
Depierre et al., 2002[22]	1991–1997	373	Cisplatin, mitomycin, ifosfamide	If surgery incomplete, patients received postoperative RT (all patients) or chemotherapy (preoperative chemotherapy patients only)	Complete and incomplete	I, II, IIIa	Yes	Yes
JCOG 9209, 2003[23]	1993–1998	62	Cisplatin, vindesine	If surgery incomplete patients received postoperative RT on both arms	Complete and incomplete	IIIa	Yes	Yes
De Boer et al., 1999[24]	1995–1997	22	Cisplatin, mitomycin, vinblastine	NR	Complete and incomplete	Ib, II, IIIa	Yes	No
MRC BLT,2004[25]	1995–2001	13	Cisplatin, mitomycin, ifosfamide or Cisplatin, mitomycin, vinblastine or Cisplatin, vindesine or Cisplatin, vinorelbine	RT given to 14% patients but no split between preoperative/ postoperative chemotherapy patients	Complete and incomplete	I, II, III	Yes	No
Yi et al., 2003[26]	1998–2001	84	Cisplatin, mitomycin, vindesine	Postoperative chemotherapy on preoperative chemotherapy arm only	Unknown	I, II, III	NR	No
Sorensen et al., 2005[27]	1998–2004	90	Carboplatin, paclitaxel	If surgery incomplete, patients received postoperative RT on both arms	Complete and incomplete	Ia, IIa, IIb, IIIa/T3	NR	Yes
Wu et al., 2002[28]	1999–?	48	Carboplatin, docetaxel	If surgery incomplete, patients received postoperative RT on both arms	Complete and incomplete	IIIa	NR	No
SWOG S9900, 2005[29]	1999–2004	354	Carboplatin, paclitaxel	NR	At least lobectomy and mediastinal nodal sampling	Ib, II, IIIa	Yes	Yes
ChE.S.T, 2005[30]	2000–2004	236	Cisplatin, gemcitabine	NR		Ib, IIa, IIb, IIIa	NR	No

*Trials are ordered by dates of patient recruitment. †Disease stage as reported in the publications; no allowances have been made for changes to staging system. NR, not recorded; RT, radiotherapy.

TABLE 2. Assessment of Methodologic Quality of RCTs*

Trial	Randomization Method	Method of Allocation Concealment	Stratification Factors	Sample Size Calculation	Outcomes Assessed	Quality of Life Assessed	Analyses Methods	Survival Curves Displayed	Patient Exclusions	Planned Accrual Achieved
Dautzenberg et al., 1990[19]	Reported as randomized	NR	NR	NR	Overall survival, disease-free interval	NR	Log-rank test	Yes	NR	No; stopped early because of progression on chemotherapy arm
Roth et al., 1994[20]	Lists, blocks	Central data center	NR	12% increase in 3-yr survival; 80% power	Overall survival	NR	Kaplan-Meier log-rank test, Cox model	Yes	NR	No; stopped because of significant difference between treatments
Rosell et al., 1994[21]	Reported as randomized	Central telephone	Stage, location of tumor, histology, N2 lymph nodes	NR	Overall survival, disease-free survival	NR	Kaplan-Meier Log-rank test, Brookmeyer-Crowley (CIs)	Yes	NR	No; stopped because of significant difference in survival between arms
Depierre et al., 2002[22]	Reported as randomized	Central telephone	Center	Designed to detect a 45% increase on no-chemotherapy arm and 60% increase on chemotherapy arm for 2-yr survival; 90% power	Overall survival, disease-free survival, response rate, toxicity	NR	Kaplan-Meier log-rank test, Cox model	Yes	8 on chemotherapy arm, 10 on no-chemotherapy arm; all ineligible and not analyzed	Yes
JCOG 9209, 2003[23]	Reported as randomized	NR	NR	15% increase in survival at 3 yr in chemotherapy arm; 80% power	Overall survival, disease-free survival	NR	Kaplan-Meier log-rank test, χ^2	Yes	NR	No; stopped because of poor recruitment
De Boer et al., 1999[24]	Reported as randomized	NR	NR	NR	NR	Yes	No	No	NR	Yes
MRC BLT, 2004[25]	Reported as randomized	Central telephone	Center chemotherapy, chemotherapy timing, gender, histology, performance status	5% difference in survival; 20% power	Overall survival, progression-free survival, disease-free survival	No	Intention to treat	Yes; but for all patients; no split by chemotherapy timing	NR	No; stopped because of poor recruitment *Trials are ordered by dates of patient recruitment. NR, not recorded.

TABLE 2. Continued

Trial	Randomization Method	Method of Allocation Concealment	Stratification Factors	Sample Size Calculation	Outcomes Assessed	Quality of Life Assessed	Analyses Methods	Survival Curves Displayed	Patient Exclusions	Planned Accrual Achieved
Yi et al., 2003[26]	Reported as randomized	NR	NR	NR	Overall survival	NR	Kappa value	Yes	Reported as no exclusions	Yes
Sorensen et al., 2005[27]	Reported as randomized	NR	NR	NR	Overall survival, disease-free survival	NR	NR	Yes	NR	No; stopped because of poor accrual
Wu et al., 2002[28]	Reported as randomized	NR	NR	NR	NR	NR	Overall relative risk	No	NR	NR; only publication is of an interim analysis
SWOG 9900, 2005[29]	Reported as randomized	NR	Stage	Designed to detect a 33% increase in median survival and 10% increase in 5-yr survival; 81% power	Progression-free survival, overall survival	NR	Log-rank test	Yes	19 patients excluded; no split by arm; all exclusions ineligible and not analyzed	No; stopped because of results of adjuvant trials
Ch.E.S.T., 2005[30]	Reported as randomized	NR	NR	NR	Progression-free survival,overall survivalresponse to chemotherapy,toxicity	NR	Log-rank test	No	NR	No; stopped because of significant results of other studies

*Trials are ordered by dates of patient recruitment. NR, not recorded.

Only two RCTs[22,29] reported patient exclusions. They are the two largest RCTs identified for inclusion in the systematic review, and both excluded approximately 5% of patients before analysis. In both trials, all exclusions were because of patients being found to be ineligible after randomization.

Two RCTs[24,28] did not report which endpoints had been analyzed. Ten RCTs[19–23,25–27,29,30] analyzed the endpoint of overall survival. One RCT[19] analyzed the endpoint of disease-free interval, five RCTs[21–23,25,27] analyzed disease-free survival, and three[25,29,30] analyzed progression-free survival. Definitions of how the endpoints were calculated were given for four RCTs.[21–23,25] The methods of analyses were well reported for most trials. Quality of life was only assessed in one RCT.[24]

Two RCTs[24–27] did not report any methods of analyses, seven RCTs[19–23,29,30] reported using the log-rank test, and four[20–23] reported using Kaplan-Meier survival curves. In addition, one trial[25] reported using intention-to-treat analysis and two[20,22] reported using Cox models. For all but three RCTs,[24,28,30] survival curves were presented in the published articles.

Of the 12 RCTs initially eligible for inclusion in the systematic review, data on survival could be extracted from seven trials,[19–23,27,29] which included 988 patients and represented 75% of the randomized evidence. Two trials[20,21] reported long-term follow-up in addition to the initial results; for data extraction, the articles that reported long-term follow-up were used.[31,32] The publications of four trials did not contain enough data for extraction.[24,26,28,30] The remaining trial[25] treated patients with either preoperative or postoperative chemotherapy. However, there were only a few patients who received preoperative chemotherapy, and these patients were not reported independently from the patients who received postoperative chemotherapy. Further details of all 12 eligible RCTs are shown in Tables 1 and 2.

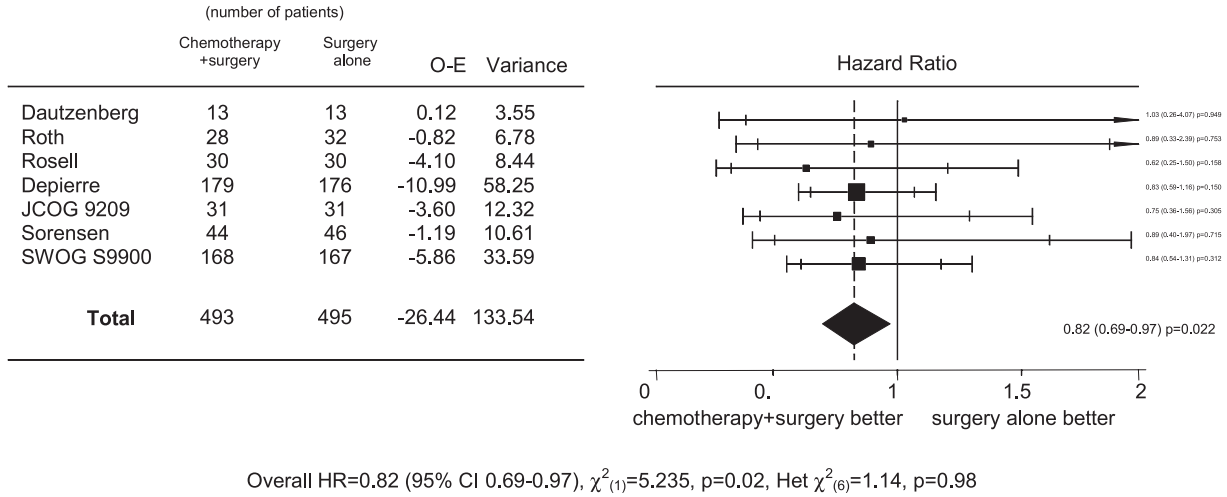
Although subgroup analyses of patient-level characteristics had been planned, data were limited and not reported in a consistent way in the publications; thus, analysis was not possible or advisable. In general, the RCTs consisted of patients aged between 32 and 83 years, of which nearly 80% were men with a good performance status. Half were of squamous cell histologic type, and a quarter had adenocarcinoma.

Overall Survival

Survival data were available for all seven RCTs (988 patients). For five RCTs,[19,23,27,31,32] the only data available were those extracted from the published curves. For one trial,[22] the p value and number of events and the published curve were available; and for one trial,[29] the hazard ratio and confidence intervals were available. There was no clear evidence of statistical heterogeneity ($\chi^2_{[6]} = 1.14$; $p = 0.98$; $I^2 = 0$) and therefore no obvious difference between trial results, meaning that the trials were similar enough to be combined.

Although the confidence intervals for individual trial results were wide and the results of all trials are inconclusive, all but one hazard ratio estimate were in favor of preoperative chemotherapy (Figure 2).

The combined results showed a significant increase in survival associated with the use of preoperative chemotherapy ($p = 0.02$). The hazard ratio of 0.82 (95% CI, 0.69–0.97) represents an overall 18% relative reduction in the risk of death on preoperative chemotherapy. This is equivalent to an absolute improvement of 6% at 5 years, increasing overall survival from 14% to 20%. However, survival varies by stage of disease, and using the baseline survival from the various



Overall HR=0.82 (95% CI 0.69-0.97), $\chi^2_{(1)}$=5.235, p=0.02, Het $\chi^2_{(6)}$=1.14, p=0.98

FIGURE 2. Hazard ratio plot for overall survival. Each individual trial is represented by a *square*, the center of which denotes the hazard ratio for that trial. The extremities of the *horizontal bars* denote the 99% CIs and the *inner bars* mark the 95% CIs. The size of the *square* is directly proportional to the amount of information in the trial. The *filled diamond* at the bottom of the plot gives an overall hazard ratio for the combined results of all trials. The center of the *diamond* denotes the hazard ratio for all trials and the extremities the 95% CIs. Trials are ordered chronologically by the age of the trial, with the oldest listed first.

TABLE 3. Five-Year Survival by Stage*

Stage	5-Year Survival (%)	Absolute Benefit (%)	New 5-Year Survival (%)
Ia	75	4	79
Ib	55	6	61
IIa	50	7	57
IIb	40	7	47
IIIa	15–35	6–7	21–42
IIIb	5–10	3–5	8–15

*Figures for 5-year survival by stage as reported by van Zandwijk. [4]

stages gives a range in benefit of 3 to 7% for individual stages of disease (Table 3).

As specified in the protocol, overall survival was also analyzed using the random effects model. This resulted in the same HR of 0.82 (95% CI, 0.69–0.97), as would be expected with a set of very homogeneous trials.

Sensitivity Analysis for Overall Survival

The overall hazard ratio (HR = 0.82) was very similar to the hazard ratios of the two largest included RCTs (Depierre et al.,[22] HR = 0.83; SWOG S9900,[29] HR = 0.84). To ensure that the result of the meta-analysis was not being driven entirely by the results of these two RCTs, a sensitivity analysis was undertaken whereby these two RCTs were taken out of the analysis. The hazard ratio for the remaining RCTs was 0.79 (95% CI, 0.59–1.08) (Figure 3), which is reasonably similar to the hazard ratio for the overall result, and almost reached statistical significance, but the confidence intervals were wider, as there were fewer patients.

Overall Survival by Chemotherapy Type

As prespecified in the protocol, an analysis grouping trials according to the type of chemotherapy given was also performed. All patients received a platinum-based chemotherapy—either cisplatin or carboplatin—that was combined with other agents. These other agents were split into the following three groups, according to the way the chemotherapy works: platinum plus vinca alkaloid/etoposide, platinum plus taxane, and other platinum regimen. The results are shown in Figure 4. The three groups all have very similar hazard ratios, and no individual group is significant. The test for interaction ($\chi^2_{[1]} = 0.12$, $p = 0.99$) indicates no clear evidence of a difference of treatment effect shown by chemotherapy group.

Overall Survival by Postoperative Treatment

Five of the seven trials reported that patients also received postoperative treatment, which was either radiotherapy or chemotherapy. An analysis could be performed at trial level to detect any difference in the effect of neoadjuvant treatment between the two groups of trials receiving additional radiotherapy or chemotherapy (i.e., was the observed effect of preoperative chemotherapy influenced or moderated by the postoperative therapy) (Figure 5). Where radiotherapy was given postoperatively,[23,27,32] it was given to patients on

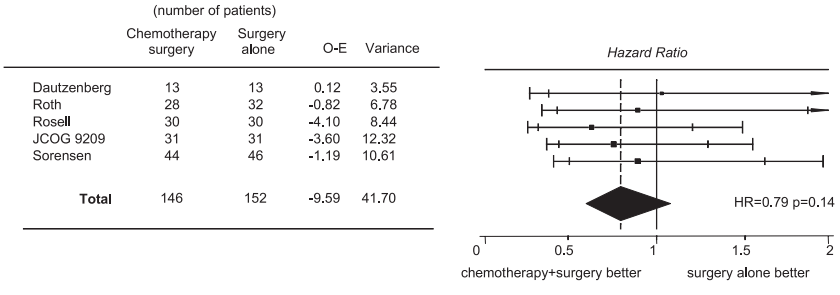


FIGURE 3. Hazard ratio plot for sensitivity analysis for overall survival.

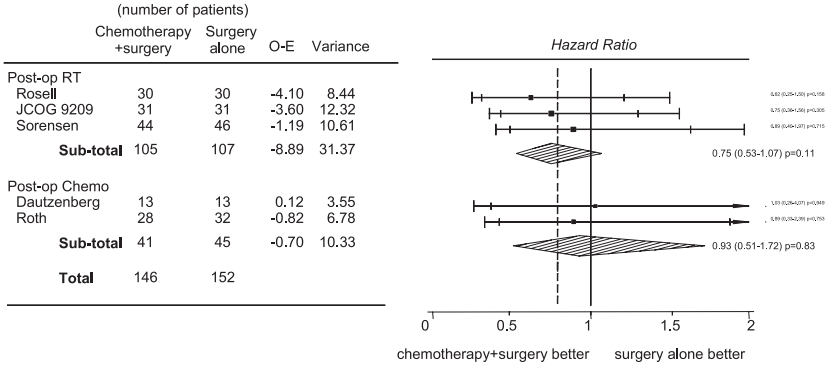


FIGURE 4. Hazard ratio plot for overall survival by chemotherapy grouping.

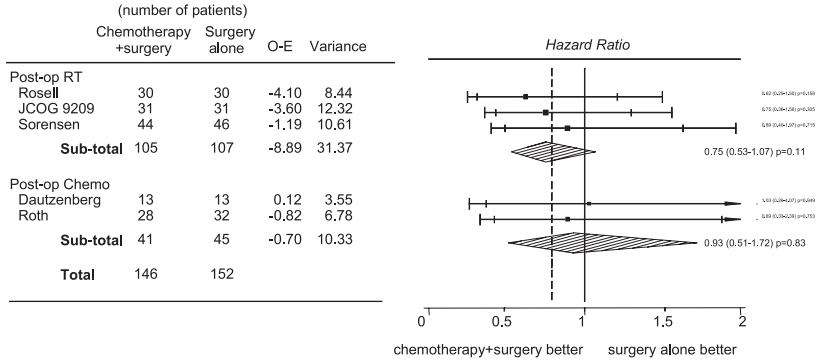


FIGURE 5. Hazard ratio plot for overall survival by postoperative treatment.

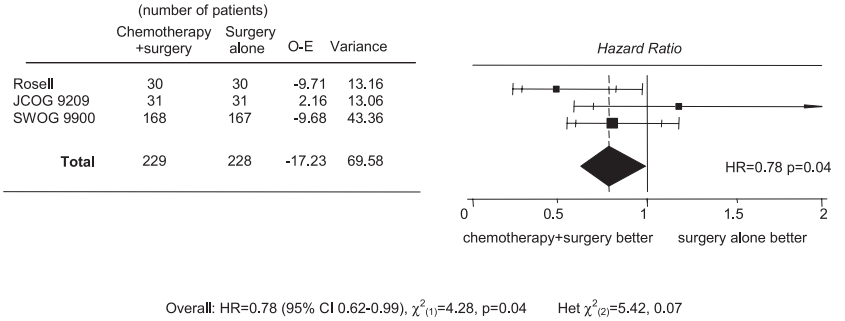


FIGURE 6. Hazard ratio plot for disease-free survival.

both arms. However, when chemotherapy was given postoperatively,[19,31] it was only given to those patients on the preoperative chemotherapy arm. Because of this inconsistency, and because of the small numbers of patients included, this analysis should be viewed as exploratory.

The test for interaction ($\chi^2_{[1]} = 0.31$, $p = 0.58$) indicates no clear evidence of a difference in the effectiveness of preoperative chemotherapy, between those trials that gave radiotherapy postoperatively and those that gave further chemotherapy postoperatively.

Analysis of Other Outcomes

Of the prespecified additional outcomes, only disease-free survival had sufficient data reported to allow analyses. For this endpoint, data could be extracted from the publications of three RCTs[23,29,32] (457 patients). Results (Figure 6) showed a significant increase in disease-free survival associated with the use of preoperative chemotherapy ($p = 0.04$). The hazard ratio of 0.78 (95% CI, 0.52–0.99) represents an overall 22% relative reduction in the risk of progression of disease or death on preoperative chemotherapy. There was some evidence of statistical heterogeneity, ($\chi^2_{[2]} = 5.42$, $p = 0.07$), and the I^2 of 63% further suggested variability between the trial results. However, it is difficult to draw conclusions from this analysis, as it is based on only three trials and 457 patients (35% of eligible data). The results are undoubtedly being driven by the results of the largest RCT,[29] which accounts for three-quarters of the patients included in this analysis.

Toxicity and Quality-of-Life Assessment

Quality of life was not assessed in any of the seven trials. There was, however, some information about toxicity of the treatment. Three of the trials reported leukopenia, anemia, alopecia, and nausea and vomiting to be common mild side effects of the chemotherapy given. One further trial reported that there were "no major toxic effects" associated with chemotherapy. As these side effects were not reported as severe, chemotherapy appears to have been well tolerated by patients.

Tests for Publication Bias

A formal test for publication bias was carried out (Figures 7 and 8). The *p* value from Begg's test was 0.29 and the *p* value from Egger's test was 0.94, both suggesting there was no significant publication bias. Begg's funnel plot is fairly symmetrical, with no clear indication that small negative studies are missing and thus does not suggest publication

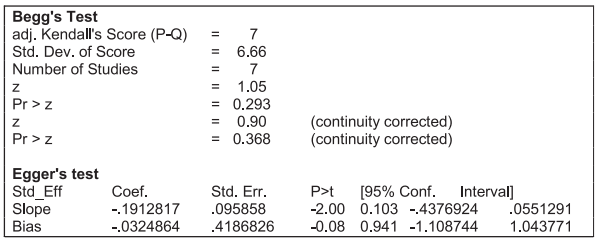


FIGURE 7. Begg's and Egger's tests for publication bias.

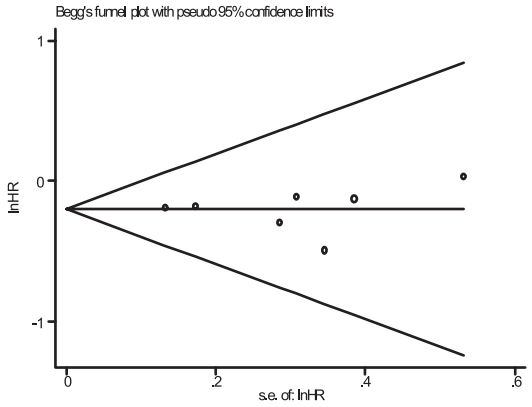


FIGURE 8. Begg's graph for publication bias.

bias. In fact, the plot might suggest that small studies in favor of preoperative chemotherapy are missing. However, as the number of trials included in this analysis is only seven, which is less than the minimum recommended number of 10 trials,[33] this analysis is likely to be unreliable. Also, we are already aware that some trials (i.e., the five eligible but excluded RCTs that have already been identified) are missing from the analysis. Because these RCTs cannot be added to the test for publication bias (as there are no results for them), it is not clear where these would fit on Begg's graph. However, from this limited analysis, there is no indication of significant publication bias among the included RCTs.

DISCUSSION

At the outset of this project, the question of whether chemotherapy should be given before surgery in NSCLC had not been formally addressed in a systematic review. Because of the presence of large, ongoing trials or very recently closed trials, it was decided that a systematic review and meta-analysis of the published data should be carried out as a means of summarizing current evidence on the effectiveness of this intervention.

Unfortunately, the limitations of a systematic review based on data extracted from published RCTs meant that despite finding 12 eligible RCTs that included 1310 patients, the meta-analysis was limited to data from only seven RCTs. Of the five RCTs that could not be included, four RCTs did not present relevant statistics or survival curves in the trial report and one RCT could not be included, as the patients who received preoperative chemotherapy were not reported independently from those patients who were treated with postoperative chemotherapy. The seven remaining RCTs included 988 patients and represented 75% of the known randomized evidence.

For the main endpoint of overall survival, the meta-analysis showed a significant benefit to chemotherapy given before surgery over surgery alone. This is equivalent to an absolute benefit of 6% at 5 years. Although all trials randomized patients to chemotherapy and surgery versus surgery alone, there was a wide range of treatments given postoperatively, sometimes in both arms, sometimes only in the chemotherapy arm. There is no suggestion that preoperative chemotherapy is more or less effective depending on whether chemotherapy or radiotherapy was given after surgery (test for interaction, $\chi^2_{[1]} = 0.31$; $p = 0.58$). However, data were only available for five of seven trials and included only 298 patients; therefore, this result has low power, is limited, and should be interpreted extremely cautiously. There was also no suggestion that patients performed better or worse depending on which type of chemotherapy they were given preoperatively ($p = 0.99$).

There was no suggestion of statistical heterogeneity ($p = 0.98$, $I^2 = 0$) or publication bias (Begg's test, $p = 0.29$; Egger's test, $p = 0.94$) in the results for overall survival. There was more heterogeneity reported for disease-free survival ($p = 0.07$, $I^2 = 63$), but this analysis is very limited because of the small number of RCTs and patients included.

No meaningful patient level subgroup analyses (e.g., whether the treatment is greater or less effective in early- versus late-stage disease) could be performed on the basis of the data reported in the publications. This illustrates the difficulty of trying to explore patient-level characteristics using aggregate data. The RCTs included in this review reported patient-level characteristics in a number of different ways, making comparisons between the trials impossible. The only practical way to explore these patient subgroups is by using individual patient data.

No formally measured quality-of-life data were reported in any of the RCT publications; therefore, no conclusions could be drawn beyond a description of the toxicity reported that may have impacted on the patient's quality of life. There did not appear to be any serious toxicity associated with chemotherapy from the information reported.

Eight of the 12 RCTs initially identified and six of the seven RCTs included in this systematic review stopped early. If recruitment to trials is stopped because of significant differences between treatments or a "random high," this can lead to excessive false-positive results,[34] but this problem can be overcome to some extent by collecting extra follow-up data. Two RCTs[20,21] that stopped because of an observed significant benefit on the preoperative chemotherapy arm reported their results twice, both in 1994, then in 1998[31] and 1999.[32] In both cases, the treatment effect lessened over time, and in one case,[20,31] the p value changed from $p < 0.01$ to $p = 0.06$. The use of IPD would allow for the collection of additional follow-up and the ongoing IPD meta-analysis may go some way toward balancing this potential problem.

In August of 2005, when the literature searches were carried out for a second time, a systematic review, by Berghmans et al., of preoperative chemotherapy and surgery versus surgery alone was identified.[35] It reported six RCTs and 590 patients. It did not include two of the trials in this review.[27,29] However, it did include one additional trial[36] that had been deemed ineligible for inclusion in this review. This additional trial randomized patients to receive chemotherapy followed by surgery plus chemotherapy versus surgery followed by radiotherapy. This comparison was therefore confounded by the inclusion of radiotherapy in just one arm so that it is not possible to say whether any difference between arms is

TABLE 4. Comparison of Trials Included in Reviews by Berghmans et al. and Burdett et al.

Berghmans et al.	Burdett et al.
Dautzenberg et al.[19]	Dautzenberg et al.[19]
Rosell et al.[32]	Rosell et al.[32]
Roth et al.[31]	Roth et al.[31]
Depierre et al.[21]	Depierre et al.[22]
JCOG 9209[23]	JCOG 9209[23]
Pass et al.[36]	SWOG 9900[29]
	Sorensen et al.[27]

attributable to the addition of chemotherapy or radiotherapy (Table 4). The overall fixed effect hazard ratio (calculated by the Parmar method[16]) for the review by Berghmans is 0.69 (95% CI, 0.06–0.84), which is significantly in favor of treatment. This is a more extreme result than the result of this review (HR = 0.82; 95% CI, 0.69–0.97), with some heterogeneity ($p = 0.07$). Because this review was completed after the review by Berghmans et al., data have been included that were made public in May of 2005, an inclusion of a further 398 patients.

Two further large RCTs have recently closed but are not yet reported, and one large RCT is ongoing. One large RCT[29] included in this systematic review has only recently been reported as an abstract. It is hoped that these RCTs will be included in the ongoing IPD meta-analysis.

IPD meta-analyses are not reliant on published information, and the ongoing IPD meta-analysis will allow the inclusion of recently closed and ongoing trials. This will bring the total number of RCTs that can potentially be included to 15. IPD meta-analyses allow a more reliable estimate and the collection of additional follow-up, which may go some way toward addressing the potential problems of RCTs that have stopped early. It will also allow other outcomes such as disease-free survival to be investigated further.

CONCLUSIONS

Although the systematic review reported here is limited, it represents a comprehensive and up-to-date systematic review of the published data and suggests a significant survival benefit for patients with NSCLC who receive preoperative chemotherapy compared with those who do not. The value of this treatment will be assessed further through the ongoing IPD meta-analysis.

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ERRATUM

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