Survival Benefit of Neoadjuvant Chemotherapy in Non-small Cell Lung Cancer

An Updated Meta-Analysis of 13 Randomized Control Trials

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Introduction: The survival effectiveness of neoadjuvant chemotherapy in non-small cell lung cancer (NSCLC) is still unclear based on the study of most up-to-date literatures. This article contributes to this problem by conducting an updated meta-analysis.

Methods: Based on Burdett et al's (*J Thorac Oncol* 2006;1:611–621) systematic review, this meta-analysis was conducted. Articles were searched electrically. The possible survival benefit of neoadjuvant chemotherapy was assessed by hazard ratio (HR) in terms of overall survival. A subgroup meta-analysis with only stage III NSCLC was also conducted. The software of Review Manager was used for data management.

Results: Thirteen randomized control trials, 6 of which were new ones, were included into this meta-analysis. The overall survival of NSCLC patients in neoadjuvant chemotherapy arm were improved significantly, comparing with those in surgery-alone arm (combined HR = 0.84; 95% confidence interval, 0.77–0.92; $p = 0.0001$). When only patients with stage III NSCLC were considered, the result was similar (combined HR = 0.84; 95% confidence interval, 0.75–0.95; $p = 0.005$).

Conclusion: Neoadjuvant chemotherapy, as an addition of surgery, would significantly improve the overall survival of operable NSCLC patients, including patients with stage III NSCLC.

Key Words: Non-small cell lung cancer, Neoadjuvant chemotherapy, Surgery, Survival, Randomized control trial, Meta-analysis.

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In 2006, Burdett et al.[1] published a systematic review to clarify the effectiveness of neoadjuvant chemotherapy in patients with non-small cell lung cancer (NSCLC). In their review, they conducted a meta-analysis (quantitative assessment) and discovered a survival benefit of neoadjuvant chemotherapy in operable NSCLC patients. Their results strengthened neoadjuvant chemotherapy as a strategic treatment choice for operable NSCLC patients for the sake of long-time survival. Nevertheless, the data supporting their conclusion seemed a little weak in respect that there were only seven eligible trials included in that analysis and that most of those included trials were small-scale ones.

In the following years, researchers from different parts of the world published several articles with different conclusions on neoadjuvant chemotherapy in NSCLC. For example, in 2007, Gilligan et al.[2] reported a multicenter randomized trial (named as MRC LU22) with results indicating that neoadjuvant chemotherapy might not benefit NSCLC patients in terms of long-time survival. MRC LU22 was a large-scale randomized control trial (RCT) performed by researchers of several different European countries, with totally 519 eligible NSCLC patients enrolled. Follow at heel, in 2008, in the Meeting of American Society of Clinical Oncology (ASCO), Scagliotti et al.[3] reported another large-scale RCT with totally 270 eligible patients, and their results supported neoadjuvant chemotherapy as an beneficial addition of surgery in NSCLC. In addition, researchers from China had also reported their results on this subject in recent years, and different conclusions were reached.

Because the conclusions of those newly reported trials were inconsistent, it seemed still confusing whether neoadjuvant chemotherapy would benefit NSCLC patients in view of long-time survival. Therefore, we believed that there was a need to conduct an updated meta-analysis of neoadjuvant chemotherapy to clarify it, and here, based on Burdett et al.'s meta-analysis, an updated meta-analysis was performed.

METHODS

Trials Search and Criteria of Eligibility

All those seven eligible trials[4–12] analyzed in Burdett et al.'s meta-analysis were taken into this updated meta-analysis. In addition, we also performed a search work for the following: (1) eligible trials published/reported in English or Chinese, which were not included in Burdett et al.'s meta-analysis; and

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(2) articles with updated data for trials that had been analyzed. Trial search was performed in April 2009, using the keywords of "lung cancer + neoadjuvant/induction/preoperative chemotherapy" on PubMed (online, 2005–2009), Chinese Biomedical Disc (1978–2009), and ASCO Annual Meeting abstracts (2006–2008). References in reviews concerning neoadjuvant chemotherapy for NSCLC were also read to search for eligible trials.[13–17]

Criteria of eligibility for every eligible trial included (1) to investigate the survival effects of neoadjuvant chemotherapy, as an addition of surgery, in NSCLC patients; (2) to be RCT or phase III randomized study, published as full-length article or abstract; (3) to be published/reported in English or Chinese publicly.

Data Extraction and Statistical Methods

Before data extraction, all the authors had read every eligible article completely, and a quality assessment of every article was performed according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[18]

Hazard ratio (HR) was used to measure the survival effects of neoadjuvant chemotherapy in NSCLC patients. The individual HR of every trial was recorded directly if available. Otherwise, the individual HR for a specific trial was calculated with the following formula:

$$\ln(\mathrm{HR}) = (O - E)/V$$

where O refers to observed number of deaths in the neoadjuvant chemotherapy arm; E refers to log-rank expected number of deaths in the neoadjuvant chemotherapy arm; and V refers to variance of $(O - E)$.

The values of $(O - E)$ and V could be calculated from the total number of deaths and the reported log-rank statistic or its p value, as described by Parmar et al.[19,20] The Kaplan-Meier survival curve would be used for estimation of survival data, if needed.

The calculation of individual HR and combined HR were performed with the software of Review Manager (Computer program, version 5.0; from The Nordic Cochrane Center, Copenhagen, Denmark). When there was no significant heterogeneity among included trials, the combined HR was calculated by using a fix-effect model; otherwise, a random-effect model would be used. A HR value of less than 1.0 would imply a survival advantage in the neoadjuvant chemotherapy arm. The value of HR would be considered as a statistically significant result if its 95% confidence interval (95% CI) did not overlap 1.0.

Heterogeneity across eligible trials was tested by two ways: (1) χ^2 test, in which a p value of more than 0.1 would indicate the absence of heterogeneity; and (2) I^2 test, in which $I^2 = 100\% \times (\chi^2 - \mathrm{n} + 1)/\chi^2$, and an I^2 value of less than 50% would suggest a low possibility of heterogeneity.

RESULTS

A total of 247 new trials, designed as clinical trials studying on the neoadjuvant chemotherapy in NSCLC, were found out. However, only nine[2,3,21–26] of them were RCTs or phase III randomized trials and were identified as potential eligible trials for this updated study. The other 238 trials were ruled out. After a careful discussion, one trial, reported by Pass et al.[21] was excluded because postoperative radiation therapy was added only in the surgery arm; another trial, reported by Felip et al.,[26] was also excluded because of an absence of survival data. As a result, a total of six new trials were identified to meet the criteria of inclusion for our study.

Finally, together with those 7 trials that had been included in Burdett et al.'s meta-analysis, a total of 13 trials were included into this study. Among them, six trials[2–4,6,9,11] were reported from Europe, five[10,22–25] from Asia, and two[8,12] from North America. Nine eligible trials[2–4,6,8–12] were published in English and four[22–25] in Chinese. All these 13 eligible trials were RCTs. The total number of randomized patients in these trials was 3224, with 1637 in the neoadjuvant chemotherapy arm and 1587 in the surgery-alone arm. Platinum-based regimens of neoadjuvant chemotherapy were used in all eligible trials. Characteristics of these eligible trials are given in Table 1. Table 2 illustrates the methodological quality of 13 eligible RCTs.

It is of note that there were four Chinese trials[22–25] included into this meta-analysis. Those four Chinese trials were completed by different lung cancer centers of China, and they were all RCTs, and most of them were large-scale trials. Although the publication years of those trails were very close to each other (2001–2004), the details of their study designs, such as chemotherapy regimens and basic characteristics of included patients, were not always the same. We also noticed that the conclusions of those Chinese trails were not consistent to each other, three of them supporting the addition of neoadjuvant chemotherapy, but one not.

All eligible articles were reported in the form of full-length articles, with exceptions of three trials (S9900, Sorensen et al.'s, and CH.E.S.T.), which had been reported in the form of abstracts in the ASCO meeting. There were totally 17 articles (abstracts) serving as data sources of this study, because updated articles (abstracts) were reported for 4 trials.[3,5–8,12,27,28] We extracted the information of the study design for a specific trial from the primary article (abstract), which usually described the study design in detail, whereas survival data were extracted from the updated article (abstract) that was reported after a longer follow-up time.

Overall Survival Analysis

Individual HRs of every eligible trial of neoadjuvant chemotherapy, in terms of overall survival, were shown in Figure 1. The individual HRs of nine trials[3,6,8,9,11,22,24,25,28] were in favor of neoadjuvant chemotherapy plus surgery (individual HR <1.0), whereas those of other four trials[2,4,10,23] were in favor of surgery alone (individual HR >1.0). Although the difference between the largest and the smallest individual HRs was as large as 0.69 (95% CI, 1.19–0.50), significant heterogeneity between the 13 trials was not found ($p = 0.20$, $I^2 = 24\%$). Therefore, a fixed-model effect was used in this analysis. Eventually, the combined HR of these trials was 0.84 (95% CI, 0.77–0.92), which was a statistically significant result ($p = 0.0001$) and, as a whole, was in favor of neoadjuvant chemotherapy.

TABLE 1. General Characteristics of 13 Eligible Trials

References	Recruitment	Stage	No. Patients	Histological Types	Chemotherapy Regimen	*p*
Dautzenberg et al.[4]	1985–1987	I–III	26	Sq: 21; ad: 4; large: 1	VCP × 2	0.85
Roth et al.[7,8]	1987–1993	IIIa	60	Sq: 22; ad: 30; large: 6; others: 2	CEP × 3	0.056
Rosell et al.[5,6]	1989–1991	IIIa	60	Sq: 42; ad: 14; large: 4	MIP × 3	0.005
Zhou et al.[22]	1990–2001	III	624	Sq: 321; ad: 207; others: 96	BAI (21)/MVP (68)/CAP (36)/EP (67)/VIP (30)/GP (30)/NP (32)/TP (10)/TN (30) × 2	<0.01
Depierre et al.[9]	1991–1997	I–III	355	Sq: 263; ad: 60; large: 32	MIP × 2	0.15
Liao et al.[23]	1995–1997	I–IIIa	211	Unavailable	MVP/MAP × 2	0.53
Li et al.[25]	1990–1995	III	137	Sq: 110; ad: 21; others: 6	CAP/EP × 1	>0.05
JCOG[10]	1993–1998	IIIa	62	Sq: 15; ad: 41; others: 6	VP × 3	0.074
Yao et al.[24]	1990–2002	III	456	Sq: 252; ad: 169; others: 35	GP (47)/NP (35)/MVP (86)/EP (66) × 2	<0.01
Sorensen et al.[11]	1998–2004	Ib–IIIa	90	Unavailable	TP × 3	0.715
S9900[12,28]	1999–2004	Ib–IIIa	336	Sq: 127; ad: 107; others: 102	TP × 3	0.19
MRC LU22[2]	1997–2005	I–III	519	Sq: 256; ad: 138; others: 125	MVP (70)/MIP (41)/NP (216)/PC (2)/DC (69)/GP (130) × 3	0.86
Ch.E.S.T.[3,27]	2000–2004	Ib–IIIa	270	Sq: 111; ad: 85; others: 74	GP × 3	0.005

BAI, bronchial artery infusion; CAP, cyclophosphamide + adriamycin + cisplatin; CEP, etoposide + cyclophosphamide + cisplatin; DC, docetaxel + carboplatin; EP, etoposide + cisplatin; GP, gemcitabine + cisplatin; MAP, mitomycin + adriamycin + cisplatin; MIP, mitomycin + ifosfamide + cisplatin; MVP, mitomycin + vindesine + cisplatin; NP, navelbine + cisplatin; TP, taxol + carboplatin; TN, paclitaxel + navelbine; VCP, vindesine + cyclophosphamide + cisplatin; VIP, vindesine + ifosfamide + cisplatin; VP, vindesine + cisplatin; sq, squamous carcinoma; ad, adenocarcinoma; large, large cell carcinoma; *p*, *p* value on survival comparison.

TABLE 2. Assessment of Methodological Quality of 13 Eligible RCTs

References	Patients Inclusion Criteria	Randomization Method	Allocation Concealment Method	Stratification Factors	Rate of Drop Out (%)	Analyses Methods	Outcomes Assessed	Intent-To-Treat Approach
Dautzenberg et al.[4]	Available	No details	NR	NR	0.0	Log-rank test	OS; DFS; MST	NR
Roth et al.[7,8]	Available	Lists, blocks	Data center	NR	3.3	Log-rank test; Wilcoxon test; Cox model	OS; MST	Yes
Rosell et al.[5,6]	Available	No details	Central telephone	NR	4.76	Kaplan-Meier; Log-rank test	OS; DFS	No
Zhou et al.[22]	Available	Random number	NR	NR	4.17	Kaplan-Meier	OS	Yes
Depierre et al.[9]	Unavailable	No details	Central telephone	Stage; N_2	4.83	Kaplan-Meier; log-rank test; Cox model	OS; DFS; MST	No
Liao et al.[23]	Available	Envelope randomization	NR	Stage	8.66	Kaplan-Meier; log-rank test; Cox model	OS; MST	No
Li et al.[25]	Available	No details	NR	NR	11.7	Kaplan-Meier; log-rank test	OS	Yes
JCOG[10]	Available	No details	NR	Completed resection; chemotherapy response	0.0	Kaplan-Meier; log-rank test	OS; DFS; MST	NR
Yao et al.[24]	Available	Random number	NR	NR	NR	Kaplan-Meier; log-rank test	OS	NR
Sorensen et al.[11]	Unavailable	No details	NR	NR	NR	Kaplan-Meier; log-rank test	OS; MST	NR
S9900[12,28]	Unavailable	No details	NR	NR	5.37	Kaplan-Meier; log-rank test	OS; DFS; MST	NR
MRC LU22[2]	Available	No details	Central telephone	NR	NR	Kaplan-Meier; log-rank test	OS; DFS; MST	NR
Ch.E.S.T.[3,27]	Unavailable	No details	NR	NR	NR	Kaplan-Meier; log-rank test	OS	NR

NR, not recorded; OS, overall survival; DFS, disease-free survival; MST, median survival time; N_2, ipsilateral mediastinal lymph node involvement; RCT, randomized control trails.

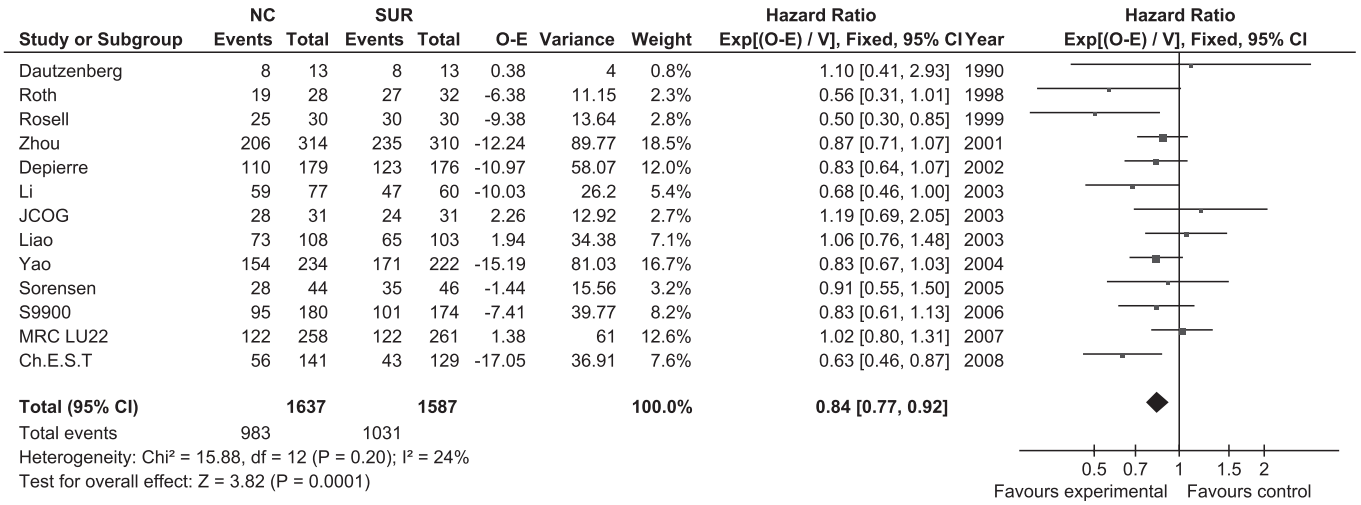

FIGURE 1. HR plot for overall survival. The combined HR was obtained using a fixed-effect model. By definition, a HR <1 implies a survival advantage for neoadjuvant chemotherapy in operable NSCLC. Combined HR = 0.84 (95% CI, 0.77–0.92; $p = 0.0001$). NSCLC, non-small cell lung cancer; NC, neoadjuvant chemotherapy arm; SUR, surgery alone arm; HR, hazard ratio; CI, confidence interval.

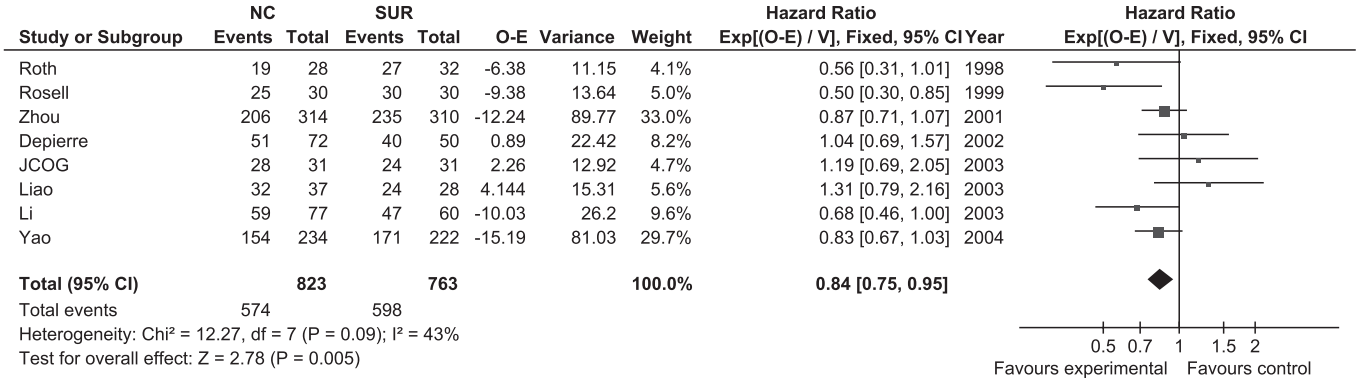

FIGURE 2. HR plot for overall survival in only stage III NSCLC. The combined HR was obtained using a fixed-effect model. By definition, a HR <1 implies a survival advantage for neoadjuvant chemotherapy in operable stage III NSCLC. Combined HR = 0.84 (95% CI, 0.75–0.95; $p = 0.005$). NSCLC, non-small cell lung cancer; NC, neoadjuvant chemotherapy arm; SUR, surgery alone arm; HR, hazard ratio; CI, confidence interval.

Sensitivity Analysis

It was obvious that the weights of two trials (Zhou et al.[22] and Yao et al.[24]) were the largest, and the individual HRs of them were similar to the combined HR (Figure 1). To ensure that the combined HR was not severely driven by the two trials, we conducted a sensitivity analysis by taking them out. After the removal, the combined HR for the remaining 11 trials, in terms of overall survival, was 0.83 (95% CI, 0.75–0.93), which was in favor of neoadjuvant chemotherapy significantly too ($p = 0.001$).

To our knowledge, the four Chinese[22–25] trials were included into the meta-analysis for the first time. To test whether the combined result was swayed by them or not, another sensitivity analysis was preformed by taking all Chinese trials out of the meta-analysis. Finally, a combined HR of 0.83 (95% CI, 0.73–0.93) with nine English trials was obtained, and it also indicated a significant survival benefit of neoadjuvant chemotherapy in those NSCLC patients ($p = 0.002$).

Subgroup Analysis

Stage III NSCLC patients were included in all the 13 trials. However, survival data of those patients were presented in only 8 trials,[6,8–10,22–25] with 1586 eligible patients. With the purpose of understanding the possible survival benefits of neoadjuvant chemotherapy in stage III NSCLC patients, a subgroup meta-analysis was performed. With those eight trials, a subgroup combined HR of neoadjuvant chemotherapy in stage III NSCLC patients was obtained as 0.84 (95% CI, 0.75–0.95; Figure 2), which illustrated that neoadjuvant chemotherapy benefited stage III NSCLC patients significantly ($p = 0.005$). Because survival data of patients with stages I to II NSCLC were available in only one trial (reported by Liao et al.[23]), we could not conduct a subgroup analysis for those patients. However, according to Liao et al.'s trial, it seemed that neoadjuvant chemotherapy would not benefit those patient with stage I disease (HR = 0.99, 95% CI, 0.56–1.76, $p = 0.97$) and may even be

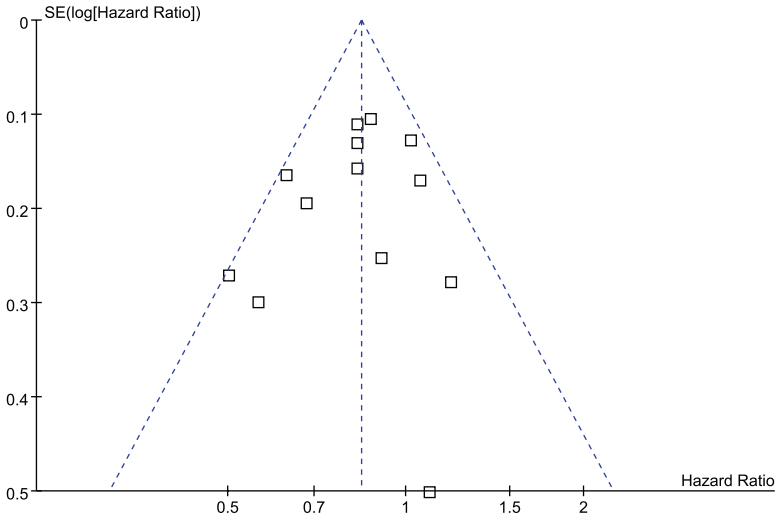

FIGURE 3. Funnel plot for publication bias test. The funnel plot is symmetrical and indicates no obvious publication bias.

detrimental in those with stage II disease (HR = 2.35, 95% CI, 1.03–5.38, $p = 0.042$). Note that the numbers of eligible patients with stage I disease and those with stage II disease were 99 and 47, respectively.

Publication Bias Test

The possible publication bias among these 13 eligible trials was tested by funnel plot. As shown in Figure 3, the funnel plot was symmetrical, indicating that no obvious publication bias occurred.

DISCUSSION

Although there have been arguments on neoadjuvant chemotherapy for a long time, our study supported neoadjuvant chemotherapy to be beneficial for operable NSCLC patients in terms of overall survival. Theoretically, effective neoadjuvant chemotherapy would facilitate operation by shrinking the primary tumors and reducing possibly involved lymph nodes and, thus, improve resectability.[29–31] Neoadjuvant chemotherapy may also reduce or eradicate so-called "residual tumor cells"[32–34]and "micrometastatic lesions,"[35–37] which are now considered to be related to postoperative recurrence and metastases.

In this analysis, a combined HR value of 0.84 was obtained according to overall survival, indicating that overall survival of operable NSCLC patients in the neoadjuvant chemotherapy arm was improved. This was a significant result (95% CI, 0.77–0.92) and suggested a nearly 16% reduction of death risk in the neoadjuvant arm, comparing with the surgery-alone arm. It was similar to that of Burdett et al.'s[1] meta-analysis, in which a combined HR of 0.82 (95% CI, 0.69–0.97) was obtained. Because bias test and sensitivity analysis showed no obvious publication bias or imbalance among these eligible trials, we believe that this result was reliable.

When only patients with stage III NSCLC were considered, the combined HR of neoadjuvant chemotherapy in terms of overall survival was 0.84 (95% CI, 0.75–0.95), which was nearly the same to the combined HR for all operable NSCLC patients (stages I–III), indicating that no more or less survival benefits occur in stage III NSCLC patients. This result was

TABLE 3. Trials Included in Different Meta-Analyses

Bergman et al.[13]	Nakamura et al.[15]	Burdett et al.[1]	This Study
Dautzenberg et al., 1990		Dautzenberg et al., 1990	Dautzenberg et al., 1990
Pass et al., 1992	Pass et al., 1992		
Roth et al., 1998	Roth et al., 1998	Roth et al., 1998	Roth et al., 1998
Rosell et al., 1999	Rosell et al., 1999	Rosell et al., 1999	Rosell et al., 1999
Depierre et al., 2002	Depierre et al., 2002	Depierre et al., 2002	Depierre et al., 2002
JCOG, 2003	JCOG, 2003	JCOG, 2003	JCOG, 2003
		S9900, 2006	S9900, 2007
		Sorensen et al., 2005	Sorensen et al., 2005
			MRC LU22, 2007
			Zhou et al., 2001
			Liao et al., 2003
			Li et al., 2003
			Yao et al., 2004
			Ch.E.S.T., 2008

similar to the results reported by Berghmans et al.[13] and Nakamura et al.,[15] even though the latter two studies both failed to get any statistically significant result because of too small number of eligible patients (n = 331 in Nakamura et al.'s and n = 337 in Berghmans et al.'s study).

As for the role of neoadjuvant chemotherapy in those patients with stage I and II disease, we think it is too early to draw any conclusion, because corresponding data were yet not sufficient by now. This meta-analysis was an updated study of Burdett et al.'s meta-analysis,[1] with the same purpose of assessing the effectiveness of neoadjuvant chemotherapy in NSCLC patients. In Burdett et al.'s study, eligible trials were searched in November 2004 and August 2005 by searching MEDLINE (1966–2005), the Cochrane Library, large international meeting of oncology, and reference lists of relevant publications and book chapters. The methodological aspect of each trial was assessed by the CONSORT statement. Their meta-analysis included only seven RCTs, all of which were published or reported in English. In this study, we adopted the similar search methodology and inclusion criteria of eligible trials as Burdett et al.'s meta-analysis. We updated their study by extending the searching years (up to April 2009) and language (both English and Chinese), adding six eligible trials, and using new ways of data extraction and statistical management.

In this study, nearly half of these 13 eligible trials were large-scale ones,[2,3,9,22–24,28] among which more than 100 eligible patients were enrolled in each study arm. Comparing to Burdett et al.'s and other previously published meta-analyses[1,13,15] concerning neoadjuvant in NSCLC, the number of eligible trials in this study was the most, as presented in Table 3.

However, this meta-analysis is still far from perfect. First, it is not an individual patient data analysis, and therefore, it precludes a more comprehensive analysis such as adjusting for baseline factors and other differences that exist between the trials from which the data were pooled. Furthermore, we could not discover the possible survival benefits of neoadjuvant chemotherapy in different NSCLC patient groups with different histologic types, detailed stages, ages, general conditions, etc., of patients, because of inadequateness of corresponding data in these eligible trials. Among these 13 eligible trials of this study, there was none that was designed to choose regimens of neoadjuvant chemotherapy individually for every eligible patient according to their personal characteristics, in view of individual treatment.[38–42] Although all these eligible trials used platinum-based neoadjuvant chemotherapy, the exact regimens among these trials were multitudinous. Our study could not answer that which regimens would be the best choice. Conversely, it might be a design defect in some trials when some stage III NSCLC patients were randomized into the surgery-alone arm, because the standard of care for patients with stage III lung cancer, independent of surgery, is to treat them with chemotherapy with or without radiation therapy. Therefore, future studies should avoid this. Also, our study could not answer whether neoadjuvant chemotherapy is more beneficial than postoperative adjuvant chemotherapy,[43] which has been taken as a standard treatment for most of operable patients.[44,45]

In summary, this is an updated meta-analysis of 13 eligible RCTs on neoadjuvant chemotherapy in operable NSCLC patients. According to its result, neoadjuvant chemotherapy is a beneficial addition of surgery for operable NSCLC patients, in terms of overall survival, comparing with surgery alone. When only stage III NSCLC patients were concerned, the result is similar. Because of data insufficiencies, the role of neoadjuvant chemotherapy in stage I and II is inconclusive yet. At the same time, further studies are expected to locating neoadjuvant chemotherapy in a proper role in the treatment strategy of NSCLC as a whole.

REFERENCES

1. Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *J Thorac Oncol* 2006;1:611–621.
2. Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet* 2007;369:1929–1937.
3. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. A phase III randomized study of surgery alone or surgery plus preoperative gemcitabine-cisplatin in early-stage non-small cell lung cancer (NSCLC): Follow-up data of Ch.E.S.T. *J Clin Oncol* 2008;26:LAB7508.
4. Dautzenberg B, Benichou J, Allard P, et al. Failure of the perioperative PCV neoadjuvant polychemotherapy in resectable bronchogenic non-small cell carcinoma. Results from a randomized phase II trial. *Cancer* 1990;65:2435–2441.
5. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994;330:153–158.
6. Rosell R, Gomez-Codina J, Camps C, et al. Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. *Lung Cancer* 1999;26:7–14.
7. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 1994;86:673–680.
8. Roth JA, Atkinson EN, Fossella F, et al. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Lung Cancer* 1998;21:1–6.
9. Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol* 2002;20:247–253.
10. Nagai K, Tsuchiya R, Mori T, et al. A randomized trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer (JCOG 9209). *J Thorac Cardiovasc Surg* 2003;125:254–260.
11. Sorensen HR, Ravn J, Hansen O, et al. Scandinavian phase III trial of neoadjuvant chemotherapy in NSCLC stages IB-IIIA/T3. *J Clin Oncol* 2005;23:LAB7146.
12. Pisters K, Vallieres E, Bunn P, et al. A phase III trial of surgery alone or surgery plus pre-operative (pre-op) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Preliminary results. *Proc Am Soc Clin Oncol* 2006;24:LBA7012 (Abstract).
13. Berghmans T, Paesmans M, Meert AP, et al. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. *Lung Cancer* 2005;49:13–23.
14. Felip E, Rosell R. Neoadjuvant chemotherapy in non-small cell lung cancer. *Curr Med Chem* 2002;9:893–898.
15. Nakamura H, Kawasaki N, Taguchi M, Kabasawa K. Role of preoperative chemotherapy for non-small-cell lung cancer: a meta-analysis. *Lung Cancer* 2006;54:325–329.

16. Brahmer JR, Ettinger DS. Non-small cell lung cancer: adjuvant and neo-adjuvant chemotherapy. *Respirology* 2007;12:320–325.
17. Santo A, Genestreti G, Sava T, et al. Neo-adjuvant chemotherapy in non-small cell lung cancer (NSCLC). *Ann Oncol* 2006;17:55–61.
18. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996; 276:637–639.
19. Parmar M, and Machi D. *Survival Analysis: Practical Approach*. Chichester: Wiley; 1995.
20. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815–2834.
21. Pass HI, Pogrebniak HW, Steinberg SM, Mulshine J, Minna J. Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. *Ann Thorac Surg* 1992;53:992–998.
22. Zhou QH, Liu XL, Li L, et al. A randomized clinical trial of preoperative neoadjuvant chemotherapy followed by surgery in the treatment of stage III non-small cell lung cancer. *Chin J Lung Cancer* 2001;4:251–256.
23. Liao ML, Zhou YZ, Ding JA, et al. The study of peri-operative chemotherapy in stage I-IIIa NSCLC. *Zhonghua Yi Xue Za Zhi* 2003; 83:962–966.
24. Yao K, Xiang MZ, Min JX, et al. A randomized clinical trial of preoperative neoadjuvant chemotherapy in the treatment of stage III non-small cell lung cancer. *J Clin Oncol China* 2004;31:611–613.
25. Li Q, Song YH, Zheng ZY, et al. Clinical evaluation of preoperative short course chemotherapy in treatment of stage III non-small cell lung cancer. *Chin J Cancer Prev Treat* 2005;10:505–507.
26. Felip E, Rosell R, Massuti B, et al. The NATCH trial: observations on the neoadjuvant arm. *Proc Am Soc Clin Oncol* 2007;25:LBA 7578 (Abstract).
27. Scagliotti GV; on behalf of Ch.E.S.T. Investigators. Preliminary results of Ch.E.S.T.: a phase III study of surgery alone or surgery plus pre-operative gemcitabine-cisplatin in clinical early stages non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2006;23:LBA7023 (Abstract).
28. Pisters K, Vallieres E, Bunn P, et al; Southwest Oncology Group. S9900: Surgery alone or surgery plus induction (ing) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): follow-up on a phase III trial. *J Clin Oncol* 2007;25:LAB7520.
29. De Marinis F, Gebbia V, De Petris L. Neoadjuvant chemotherapy for stage IIIA-N2 non-small cell lung cancer. *Ann Oncol* 2005;16:116–122.
30. Pujol JL, Le Chevalier T, Ray P, et al. Neoadjuvant chemotherapy of locally advanced non-small cell lung cancer. *Lung Cancer* 1995;12: 107–18.
31. Milroy R, Macbeth F. Neoadjuvant chemotherapy in stage IIIa non-small cell lung cancer. *Thorax* 1995;50:S25–S30.
32. Hosch SB, Scheunemann P, Izbicki JR. Minimal residual disease in non-small-cell lung cancer. *Semin Surg Oncol* 2001;20:278–281.
33. Lequaglie C, Conti B, Brega M, Giudice G. Unsuspected residual disease at the resection margin after surgery for lung cancer: fate of patients after long-term follow-up. *Eur J Cardiothorac Surg* 2003;23: 229–232.
34. Sawabata N, Keller SM, Matsumura A, et al. The impact of residual multi-level N2 disease after induction therapy for non-small cell lung cancer. *Lung Cancer* 2003;42:69–77.
35. Gu CD, Osaki T, Oyama T, et al. Detection of micrometastatic tumor cells in pN0 lymph nodes of patients with completely resected nonsmall cell lung cancer: impact on recurrence and survival. *Ann Surg* 2002;235: 133–139.
36. Castaldo G, Tomaiuolo R, Sanduzzi A, Ponticiello A, Marchetiello I, Salvatore F. Carcinoembryonic antigen mRNA analysis detects micrometastatic cells in blood from lung cancer patients. *Eur Respir J* 2003;22:418–421.
37. Huang JS, Dong QG, Bao GL, Han BH. Implication of micrometastatic cancer cells in the peripheral blood on prognosis of non-small cell lung cancer. *Zhonghua Zhong Liu Za Zhi* 2004;26:294–296.
38. Shigematsu H, Toyooka S, Suzuki M. The need for an individual approach to lung cancer treatment. *PLoS Med* 2006;3:e206.
39. Yuan P, Miao XP, Zhang XM, et al. XRCC1 and XPD genetic polymorphisms predict clinical responses to platinum-based chemotherapy in advanced non-small cell lung cancer. *Zhonghua Zhong Liu Za Zhi* 2006;28:196–199.
40. Smith S, Su D, Rigault L, Schwartz, P, et al. ERCC1 genotype and phenotype in epithelial ovarian cancer identify patients likely to benefit from paclitaxel treatment in addition to platinum-based therapy. *J Clin Oncol* 2007;25:5172–5179.
41. Vilmar A, Sorensen JB. Excision repair cross-complementation group 1 (ERCC1) in platinum-based treatment of non-small cell lung cancer with special emphasis on carboplatin: a review of current literature. *Lung Cancer* 2009;64:131–139.
42. Simon G, Sharma A, Li X, et al. Feasibility and efficacy of molecular analysis-directed individualized therapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2007;25:2741–2746.
43. Strauss GM. Adjuvant vs neoadjuvant chemotherapy in resectable NSCLC: is that the real question? *Oncology* 2009;23:534–538.
44. Betticher DC. Adjuvant and neoadjuvant chemotherapy in NSCLC: a paradigm shift. *Lung Cancer* 2005;50:9–16.
45. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-small cell lung cancer (v. 2.2009). Available at: http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf. Accessed February 5, 2009.