Adjuvant Platinum-Based Chemotherapy *vs* Observation in Non-Small Cell Lung Cancer: Meta-analysis of Trials with Intermediate- and Long-Term Follow-Up

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Abstract: Largely, earlier data of adjuvant chemotherapy following complete resection of non-small cell lung cancer (NSCLC) showed survival advantage. However, recent data with longer follow-up demonstrated conflicting results. The aim of this meta-analysis is to test whether the early positive survival advantage remains or fades with time. Included were 4 randomized clinical trials each with a follow-up of more than 6 years and involving 3,529 patients (1,750 and 1,779 patients in the adjuvant chemotherapy and observation arms, respectively). Patients' median age ranged from 59 to 61 years and they were mostly males (65% to 87%). The analysis showed that adjuvant chemotherapy reduced mortality by 14% (HR = 0.86; 95% CI, 0.79 to 0.94; $P = 0.0001$). The overall survival (OS) benefit remained after adjustment for known prognostic variables. The OS advantage was shown for patients with stage II (HR = 0.80; 95% CI, 0.68 to 0.94, $P = 0.008$) and stage III (HR = 0.80; 95% CI, 0.69 to 0.92; $P = 0.002$) indicating 20% reduction in the risk of dying in those stages. On the other hand, no benefit was shown for patients with stage I (HR = 0.98; 95% CI, 0.85 to 1.14; $P = 0.82$). Similarly, chemotherapy significantly prolonged disease-free survival (DFS) as compared with observation with a risk reduction of 17% (HR = 0.83; 95% CI, 0.75 to 0.90; $P < 0.0001$). Analysis of DFS according to disease stage was limited due to lack of adequate data. Adjuvant chemotherapy was not associated with excessive non-lung cancer mortality (HR = 1.16; 95% CI, 0.93 to 1.45; $P = 0.18$). Only one trail reported adequate data on the pattern of recurrence with significant reduction in local (HR = 0.74; 95% CI, 0.61 to 0.90; $P = 0.002$) and distant (HR = 0.84; 95% CI, 0.72 to 0.98; $P = 0.02$) relapse. In stage IB disease, adjuvant chemotherapy improved OS (HR = 0.68; 90% CI, 0.51 to 0.90; $P = 0.02$) and DFS HR = 0.69; 90% CI, 0.49 to 0.97; $P = 0.035$) only for those with primary tumor size of ≥ 4 cm. The current meta-analysis that was based on large patient population followed-up for an appropriate intermediate and long duration have provided significant clinical conclusions concerning the benefits of adjuvant chemotherapy for resected NSCLC. In the future, other meta-analyses with even longer-term follow up may be necessary.

Keywords: Non-small cell lung cancer, adjuvant chemotherapy, prognosis, meta-analysis.

INTRODUCTION

Lung cancer is the leading cause of cancer death for men and women in most industrialized countries [1]. Surgical resection offers the best chance for cure for patients with non-small cell lung cancer (NSCLC) who are diagnosed with early disease, however, about 30-70% of patients with early stage disease will suffer from recurrence and die from the disease [2]. Most of the earlier trials utilizing adjuvant chemotherapy were small and underpowered to detect a modest survival benefit. In 1995 a large meta-analysis from the NSCLC Collaborative Group comparing surgery with surgery plus chemotherapy revealed 13% reduction in the risk of death, equivalent to an absolute benefit of 5% at 5 years in favor of the patients who received chemotherapy [3]. In 2004 the International Adjuvant Lung trial (IALT) also reported a significant survival advantage with adjuvant chemotherapy. There was a significant 4% increase in 5-year survival in the adjuvant chemotherapy arm *vs* observation [4]. Subsequently, a few multi-institutional large randomized trials have been conducted and they reported a survival advantage with the use of cisplatin-based adjuvant chemotherapy in patients with resected NSCLC [5-7].

The long-term follow-up data from these trials began to emerge. The recent, long-term, updates of some of these trials showed a notable loss of the efficacy of the adjuvant therapy in terms of loss of the associated significant survival benefits. Notably, in The Cancer and Leukemia Group B (CALGB) 9633, the preliminary results in 2004 reported significant improvement in overall survival (OS) and disease-free survival (DFS) in favor of the adjuvant chemotherapy arm. Yet, in the final analysis at a median follow up of 74 months the reported survival benefit was non-significant [8]. The IALT original report in 2004 revealed a significant improvement in OS. But the reported efficacy of adjuvant chemotherapy in the IALT report was also lost in their updated report after a longer follow-up [4, 9]. On the other hand, the long-term update from the North American Intergroup JBR.10 trial showed that the early significant survival benefit associated with their adjuvant chemotherapy did remain statistically significant with a median follow-up of 112 months [6, 10].

These conflicting data raised the question of whether the significant survival advantage from chemotherapy fades with

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time [11, 12]. Such discordant results in the adjuvant settings call for a longer follow-up data to avoid premature conclusions. Trials of other cancers clearly underscored the value of long-term follow up in the adjuvant setting. For instance in the adjuvant ATLAS (Adjuvant Tamoxifen, Longer Against Shorter) trial in breast cancer, while earlier data suggested a lack of benefit from longer duration of adjuvant tamoxifen [13], more recent data challenged that conclusion [14].

The objective of this meta-analysis is to provide an answer to the question whether the early positive survival advantage reported with the use of adjuvant chemotherapy in patients with resected NSCLC remains or fades with time. We pooled data from randomized, peer-reviewed clinical trials that has reported a median follow up of > 6 years to evaluate the pooled long-term results.

METHODS

Literature Search

A comprehensive search of citations was performed from PubMed, proceedings of the main oncology conferences, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Review of Effectiveness. The search was limited to randomized, peer-reviewed clinical studies and reviews in English language. Our initial search through each resource used queries with the medical subject headings (MeSH) terms: "lung cancer", "lung neoplasm", "chemotherapy", "adjuvant chemotherapy", "cisplatin", "carboplatin", "prognosis", "recurrence", "survival", and "mortality" in various combinations. The search strategy also used several text terms to identify relevant information. Reference lists from relevant primary studies and review articles were also examined to find other additional publications.

Selected for the analyses were only those randomized, peer-reviewed clinical studies published in English language investigated the effect of platinum-based adjuvant chemotherapy *vs* observation in completely resected NSCLC. We only included studies with a reported median follow-up of ≥ 72 months (6 years).

Statistical Methods

Before performing the analyses, data of each published study were carefully checked and verified for coherence with the original publications. Data were entered in a computer database for transfer and statistical analysis in Review Manager Version 5.0.17 (Cochrane Collaboration, Software Update, Oxford, United Kingdom) and Comprehensive Meta Analysis Version 2.2.048 (New Jersey, USA). For trials included in this meta-analysis, if log hazard ratio (HR) and its variance were not presented explicitly, the method reported by Parmar *et al*., was used to extract estimates of these statistics [15].

To analyze the effects of adjuvant chemotherapy, only the updated data of eligible studies were used. In this meta-analysis, both fixed and random effect models were tested where appropriate [16, 17]. X^2 tests were used to study heterogeneity between trials. I^2 statistic was used to estimate the percentage of total variation across studies, due to heterogeneity rather than chance. If the *P* value was ≤0.1, the assumption of homogeneity was deemed invalid, and the random-effects model was reported after exploring the causes of heterogeneity [18]. A two-tailed *P* value of <0.05 was considered statistically significant. Findings of the meta-analysis are depicted in classical Forest plots, with point estimates and 95% CIs – unless otherwise specified - for each trial and overall; size of the squares is proportional to effect size. In some of the reported Forest plots, the earlier data of some of the studies were displayed for illustration purpose only, however, only the mature updated data were used for the analyses.

RESULTS

One potentially eligible study was excluded as the study was terminated early due to a slow accrual; moreover, the length of follow-up was not reported [19]. Three more studies including the Big Lung Trial were excluded because the reported follow-up was shorter than the predefined required median follow-up duration of ≥ 72 months [5, 7, 20-22].

Four RCTs met the inclusion criteria and were included in this meta-analysis [4, 6, 8-10, 23]. There were a total of 3,529 patients (1,750 and 1,779 patients in the adjuvant chemotherapy and observation arms, respectively). The median follow-up ranged from 74 to 112 months. Tables **1** and **2** depict summary of the earlier and updated data of the included studies. As shown in Table **1**, the median age ranged from 59 to 61 years and most patients were males (65% to 87%). The disease stages of included patients were IA to IIIB, while only few patients had stage IIIB. Table **3** shows abridgment of the earlier and follow-up outcome data of the included trials.

Potential efficacy of adjuvant chemotherapy was analyzed and reported as HR and 95% CI. However, forced by the slow accrual, investigators of the CALGB study converted the trial hypothesis to one-sided testing ($\alpha = 0.05$), and therefore reported CIs as two-sided 90%, which best correspond to one-tailed *P* values [8].

Analysis of OS

Using the updated data of included studies showed that adjuvant chemotherapy reduced mortality by 14% (HR = 0.86; 95% CI, 0.79 to 0.94; *P* = 0.0001) (Fig. **1**). The result of the test for heterogeneity of the treatment effect was not significant (*P* = 0.54). Three studies (IALT, JBR.10, and ANITA) [9, 10, 23], reported OS benefit adjusted by Cox model for known prognostic variables. Fig. (**2**) showed that the adjusted analysis demonstrated a similar benefit with a 15% reduction in mortality (HR = 0.85; 95% CI, 0.78 to 0.93; *P* = 0.0006). The result of the test for heterogeneity of the treatment effect was not significant (*P* = 0.21).

Analysis of OS according to disease stage is shown in Fig. (**3**). For stage I or IB the difference in OS was not statistically significant (HR = 0.98; 95% CI, 0.85 to 1.14; *P* = 0.82), however, an OS advantage was shown for stage II and III with 20% (HR = 0.80; 95% CI, 0.68 to 0.94; *P* = 0.008), and 20% (HR = 0.80; 95% CI, 0.69 to 0.92; *P* = 0.002) reduction in mortality, respectively. The result of the test for heterogeneity of the treatment effect was not significant (*P* = 0.19).

Table 1. Baseline Characteristics of the Randomized Patients

Study & Description	Inclusion Stage	Year Launched (Median FU in mo, Range)	Chemotherapy			Stage (%)						Observation			Stage %					
			No.	Median Age -y (range)	Males %	IA	IB	IIA	IIB	IIIA	IIIB	No.	Median Age -y (Range)	Males %	IA	IB	IIA	IIB	IIIA	IIIB
IALT 2004 [4] RCT to 3-4 cycles of cisplatin-based CTX *vs* observation	I-IIIB	1995 (56, 0-89)	932	59 (27-77)	80.7	10.3	25.4	4.3	20.4	38.3	1.1	935	59 (32-75)	80.2	9.3	27.9	4.3	19.5	37.3	1.8
IALT 2010[9]		(90, 0-123)																		
JBR.10 2005 [6] RCT of cisplatin for 4 cycles every 4 weeks and vinorelbine weekly for 16 weeks *vs* observation	IB-II	1994 (61, 18-112) CTX (64, 5-108) Obs.	242	61 (35-82)	64		46	16	38			240	61 (34-78)	64		45	13	42		
JBR.10 2010 [10]		(112, 38-166)																		
CALGB 2008 [8] RTC to paclitael and carboplatin for 4 cycles *vs* observation	IB	1996 (74, range NR)	173	61 (34-78)	65		100					171	62 (40-81)	63		100				
ANITA 2006 [23] RCT of cisplatin for 4 cycles every 4 weeks and vinorelbine weekly for 16 weeks *vs* observation	IB-IIIB	1994 (76, 43-113)	407	59 (32-75)	85		36	22 (stage II)		41	<1	433	59 (18-75)	87		36	26 (stage II)		37	<1

Abbreviations: ANITA; Adjuvant Navelbine International Trialist Association, CALGB; Cancer and Leukemia Group B protocol 9633CTX, chemotherapy, FU; follow-up, IALT; International Adjuvant Lung Trial, JBR.10; National Cancer Institute of Canada Clinical Trial Group, NR; not reported, RCT; randomized controlled trial.

Analysis of DFS

Similarly, chemotherapy significantly prolonged DFS as compared with observation with a risk reduction of 17% (HR = 0.83; 95% CI, 0.75 to 0.90, $P < 0.0001$) (Fig. **4**). The result of the test for heterogeneity of the treatment effect was not significant ($P = 0.44$). Fig. (**5**) shows that the DFS benefit was only suggestive for patients with stage III (HR = 0.85; 95% CI 0.72 to 1.01; $P = 0.05$), while those with stage I (HR = 0.88; 95% CI 0.74 to 1.04; $P = 0.14$) or stage II (HR = 0.87; 95% CI 0.69 to 1.09; $P = 0.23$) showed no benefit. Test for the overall effect adjusted for disease stage, however, remained significant (HR = 0.87; 95% CI 0.78 to 0.86; $P = 0.007$). The result of the test for heterogeneity of the treatment effect according to stage was not significant ($P = 0.89$). That data should be interpreted with caution as analysis of DFS based on disease stage was only available from the IALT [9] and the CALGB [8] studies, and the latter study only included patients with stage IB.

Analysis of Non-Lung Cancer Mortality

Adequate data to evaluate non-lung cancer mortality were available from the CALGB, IALT, and JBR.10 studies [8-10]. The overall HR for non-lung cancer death in the chemotherapy groups was 1.16 (95% CI, 0.93 to 1.45; $P = 0.18$), indicating lack of significant excessive mortality (Fig. **6**). The AILT also reported that death HR was not different according to age (data not shown).

Table 2. Additional Baseline Characteristics of the Randomized Patients

Study	Performance Status (%)			Surgery (%)			Histology (%)			Planned Radio-therapy	% Received Radio-therapy
	0	1	2	Pneumonectomy	Lobectomy	Other	Squamous	Adenocarcinoma	Other		
IALT 2004 [4]										N1 or N2	
Chemotherapy	54	38	8	35	64	1	46	41	13		22.7
Observation	53	40	7	35	64	1	48	40	12		27.5
JBR.10 2005 [6]										None	
Chemotherapy	50	50	0	25	66	9	37	53	10		0
Observation	49	51	0	22	71	7	38	53	9		0
ANITA 2006 [23]										Optional	
Chemotherapy	48	47	3	38	57	4	59	40	1		22
Observation	52	44	3	36	58	5	58	41	2		33
CALGB 2008 [8]										None	
Chemotherapy	56	44	1	12	88	0	35	54	12		0
Observation	58	41	1	11	89	0	34	49	16		0

Table 3. Summary of Overall and Disease-Free Survival of the Randomized Patients

Study	Overall Survival			Disease-Free Survival		
	Chemotherapy	Observation	*P* Value	Chemotherapy	Observation	*P* Value
IALT 2004 [4]						
Survival (%)	49.6	46.1	< 0.03	44.4	38.3	< 0.003
2-year survival (%)	70.3	66.7	-	61	55.5	-
5-year survival (%)	44.5	40.4	-	39.4	34.3	-
IALT 2010 [9]						
Survival (%)	38	36.9	0.10	35	32.5	0.02
Median survival (mo)	54	45	-	-	-	-
JBR.10 2005 [6]						
Survival (%)	64	53.8	-	57.3	50.4	0.003
Median survival – all stages (mo)	94	73	0.04	Not reached	46.7	<0.001
Median survival – stage II (mo)	80	41	0.004	-	-	-
5-year survival (%)	69	54	0.03	61	49	0.08
JBR.10 2010 [10]						
Survival (%)	48.2	40.4	0.04	-	-	-
5-yaer survival (%)	67	56	-	-	-	-
Median survival – stage IB (mo)	132	117.6	0.87	-	-	-
Median survival – stage II (mo)	81.6	43.2	0.01	-	-	-
ANITA 2006 [23]						
Survival (%)	49	42	-	40	34	-
Median survival (mo)	65.7	43.7	0.017	36.3	20.7	0.002
5-year survival – stage IB (%)	62	64	-	-	-	-
5-year survival – stage II (%)	52	42	-	-	-	-
5-year survival – stage III (%)	42	26	-	-	-	-
CALGB 2008 [8]						
Survival (%)	57.2	52.6	0.125	63	46	0.065
Median survival (mo)	95	79	-	89	56	-
2-year survival (%)	90	84	0.053	75	68	0.048
5-year survival (%)	60	58	0.190	52	48	0.117

Missing data were not available in the published papers.

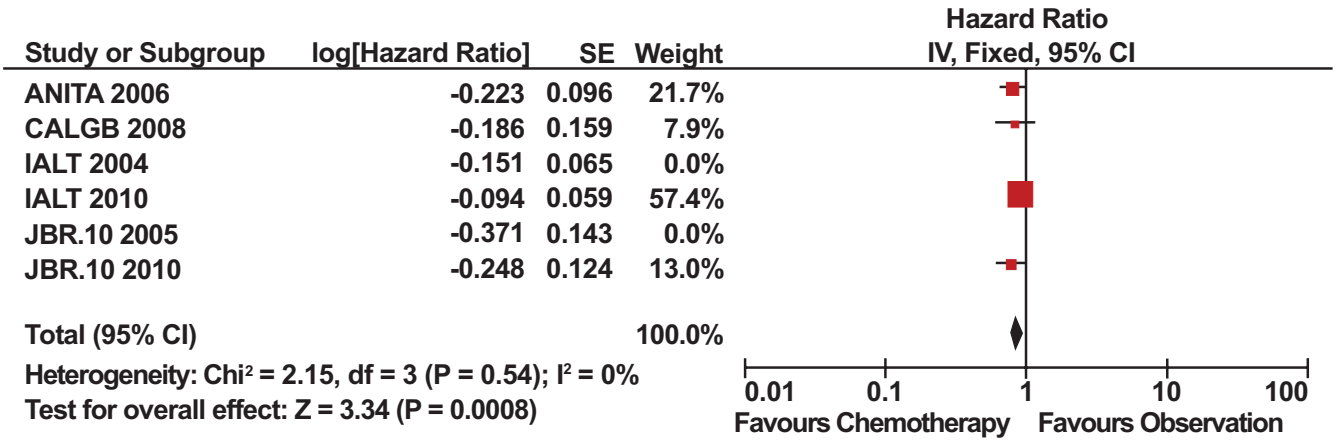

Fig. (1). Overall survival: hazard ratio of death with chemotherapy *vs* observation. Earlier data of the IALT and JBR.10 studies were included for illustration purpose only but were not included in estimating treatment effect.

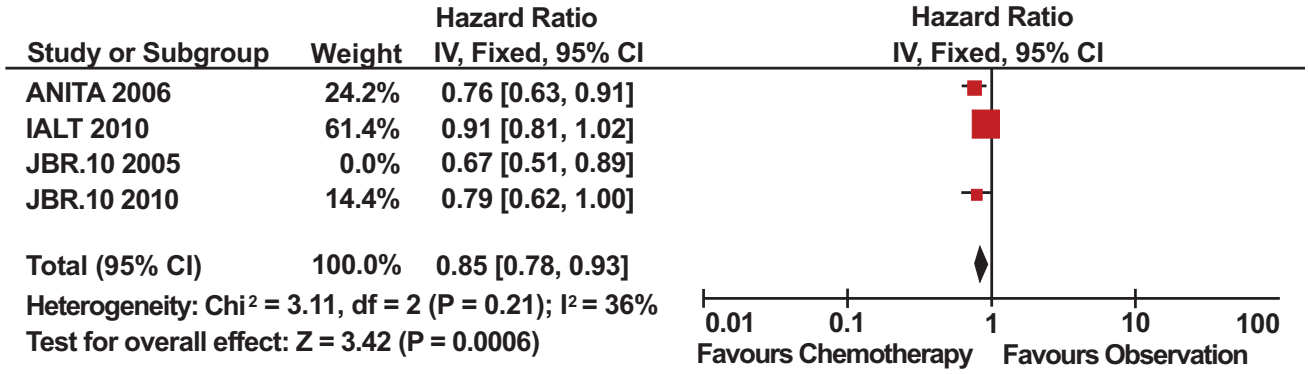

Fig. (2). Overall survival: hazard ratio of death with chemotherapy *vs* observation adjusted for known prognostic variables. Earlier data of the JBR.10 study were included for illustration purpose only but were not included in estimating treatment effect.

Analysis of the Pattern of Recurrence

The HR for disease recurrence was only available from the IALT study [9]. In the later study, adjuvant chemotherapy significantly reduced both local (HR = 0.74; 95% CI, 0.61 to 0.90; $P = 0.002$) and distant (HR = 0.84; 95% CI, 0.72 to 0.98; $P = 0.02$) recurrence. In the ANITA study [23], while HR was not reported, relapse was lower in the chemotherapy group than in the observation group (local relapse, 49 [12%] patients *vs* 76 [18%] patients, $P = 0{\cdot}025$; distant relapse, 101 [25%] *vs* 122 [28%], $P = 0{\cdot}27$). In both groups, the lung was the most common site of relapse (chemotherapy, 91 [22%] *vs* control, 123 [28%]; $P = 0{\cdot}004$).

Survival Analysis as Function of the Size of the Primary Tumor in Stage IB

The CALGB [8] and JBR.10 [10] studies reported on the potential benefit of adjuvant chemotherapy on OS according to the size of the primary tumor in stage IB disease, where a significant total effect advantage was shown (HR = 0.68; 95% CI, 0.51 to 0.90; $P = 0.02$) only for tumors that ≥ 4 cm (Fig. **7**). The result of the test for heterogeneity of the treatment effect on OS, however, was significant ($P = 0.04$). Similarly, in the CALGB study, chemotherapy achieved DFS advantage only for tumors that ≥ 4 cm (HR = 0.69; 90% CI, 0.49 to 0.97; $P = 0.035$).

Survival Analysis by Time Periods Using 5 Years as the Follow-Up Cutoff Point

The analysis was only available from the updated IALT study [9]. The HR for OS was 0.86 (95% CI 0.76 to 0.97; $P < 0.01$) for the first 5 years of follow-up and 1.45 (95% CI 1.02 to 2.07; $P < 0.04$) for the following years. The test of interaction for differences between the two periods was highly significant ($P < 0.006$). The HR for DFS was 0.85 (95% CI 0.75 to 0.95; $P < 0.006$) for the first 5 years and 1.33 (95% CI 0.89 to 2.0; $P < 0.16$) after 5 years of follow-up.

The test of interaction for differences between the two periods was also significant ($P < 0.04$).

DISCUSSION

This meta-analysis of recent large adjuvant trials of cisplatin-based chemotherapy in completely resected stage IB-IIIA NSCLC confirms the statistically significant intermediate and long term effect of chemotherapy with 14% reduction in the risk of dying and 16% reduction in the risk of death or disease relapse. There has been at least 5 meta-analyses published investigating the effect of adjuvant chemotherapy in NSCLC [3,24-28]. However, these meta-analyses extracted data from relatively short follow up of

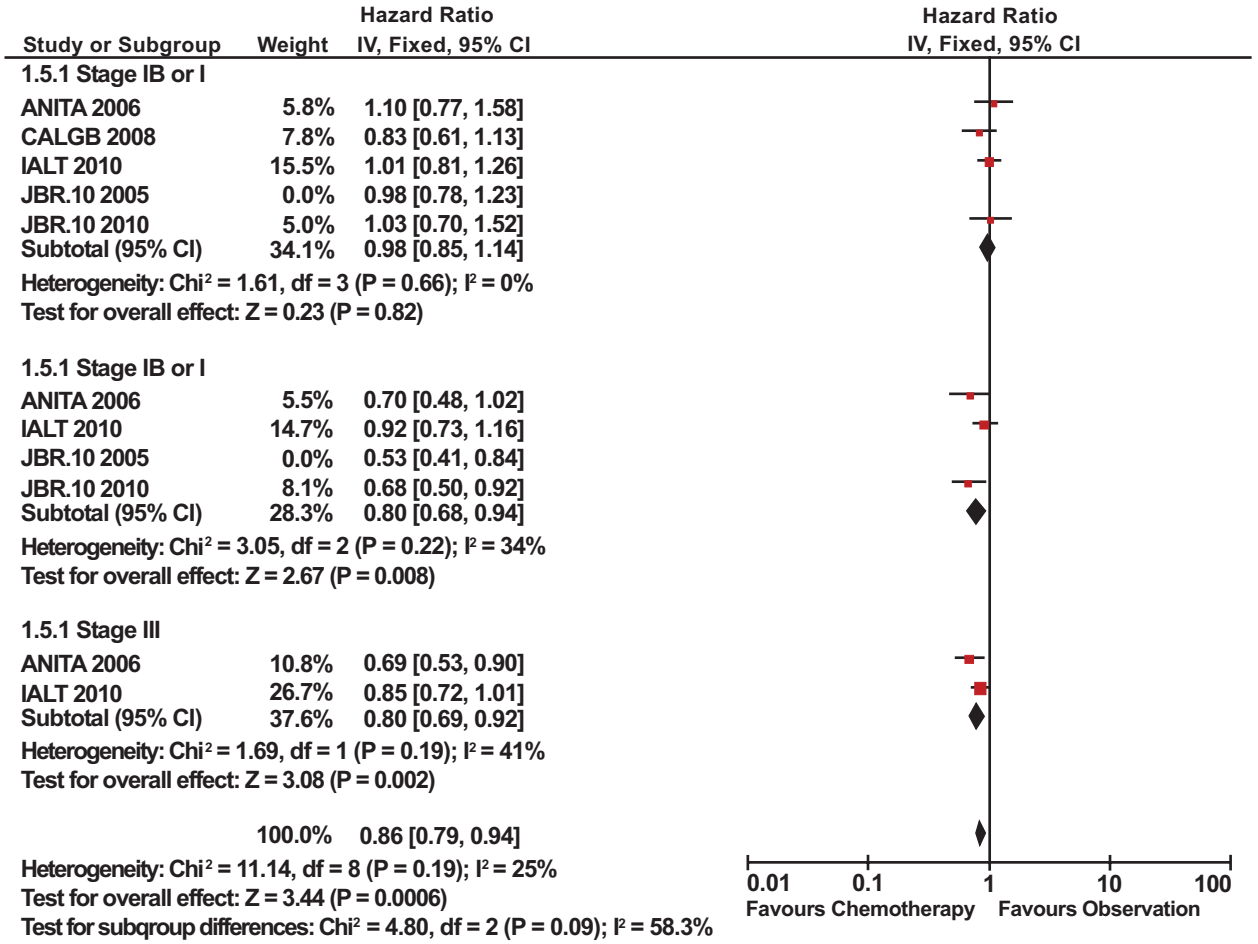

Fig. (3). Overall survival: hazard ratio of death with chemotherapy *vs* observation by disease stage. Earlier data of the IALT and JBR.10 studies were included for illustration purpose only but were not included in estimating treatment effect.

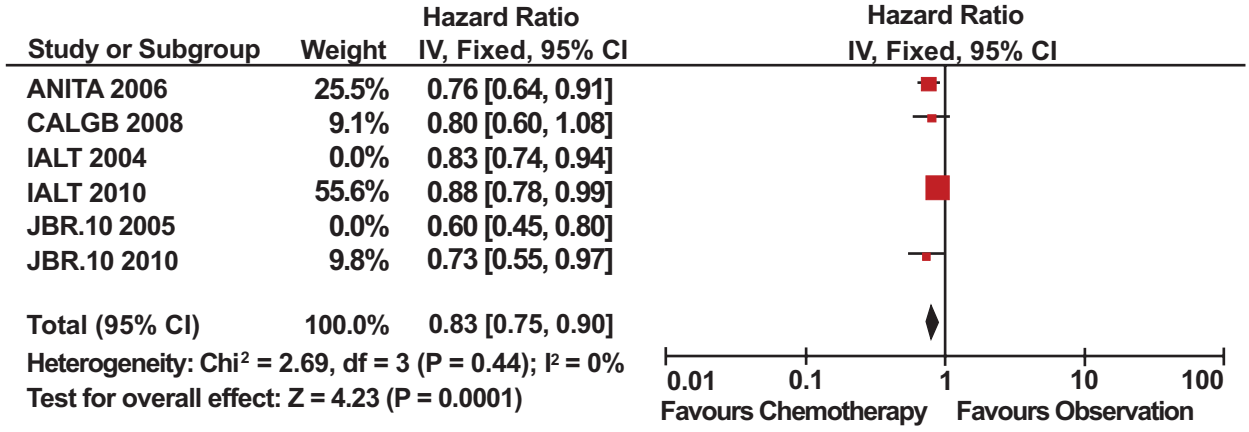

Fig. (4). Disease-free survival: hazard ratio of recurrence or death with chemotherapy *vs* observation. Earlier data of the IALT and JBR.10 studies were included for illustration purpose only but were not included in estimating treatment effect.

patients in individual trials. For example, the recent meta-analysis of 5 trials [28], reported results with a median follow up of 5.2 years, with only one trial that had a median follow up more than 6 years [23]. A more recent meta-analysis of the subgroup of patients who received cisplatin and vinorelbine in 5 trials have been recently published [29]. All trials included in this meta-analysis had median follow up of less than 6 years (average 5.1 years). In their updated report, the authors of the IALT study acknowledge that the difference in results beyond 5 years of follow up underscores the need for long-term follow up [9].

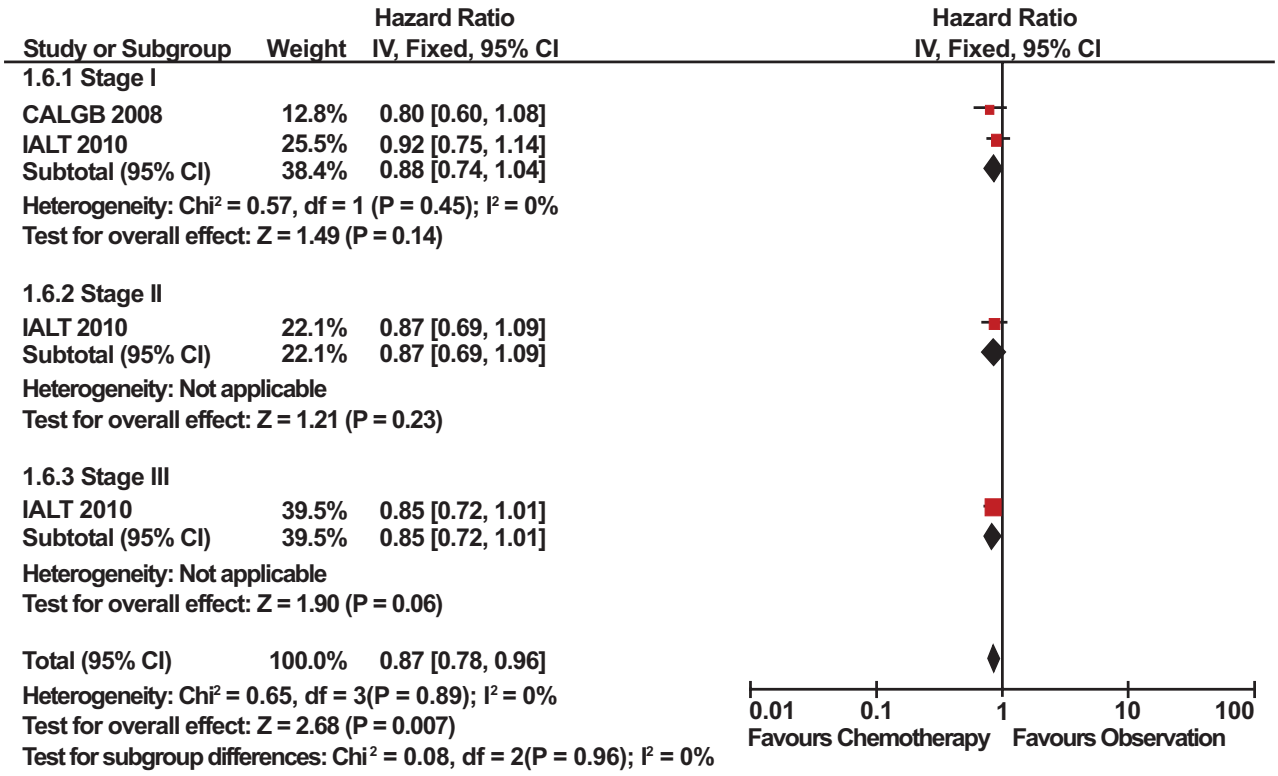

Fig. (5). Disease-free survival: hazard ratio of recurrence or death with chemotherapy *vs* observation by disease stage.

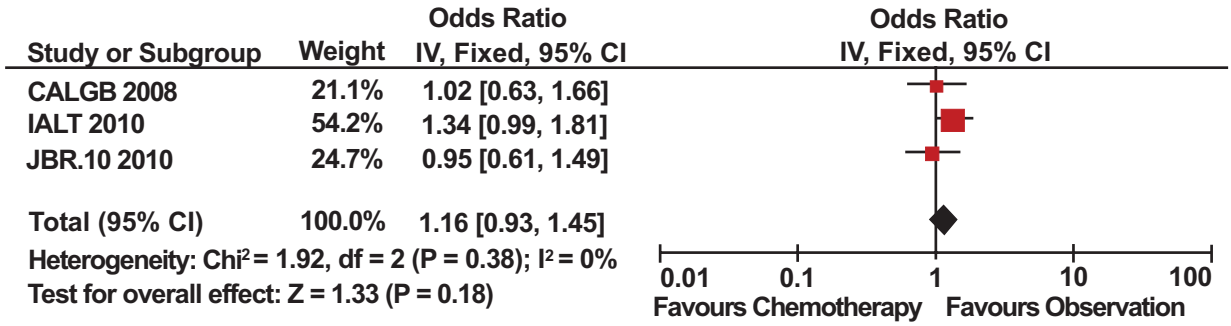

Fig. (6). Overall survival: hazard ratio of non-lung cancer death with chemotherapy *vs* observation.

It is clear from the above discussion that there is need to reevaluate the effect chemotherapy beyond 5 years of follow up. Hence, we adopted minimum follow up of 6 years as a cut off. This will provide intermediate and long-term follow-up and allow the inclusion of 4 trials for the evaluation to have statistical power and probably clinical impact.

Each of the 5 trials in the recent LACE meta-analysis included patients with stage I, II and III disease. The analysis showed 11% reduction in risk of death with the use of adjuvant chemotherapy [28]. Notably, in that meta-analysis both the ALPI [5, 7] and the Big lung trial [22] were included and both were negative. Based on our inclusion criteria, the ALPI and BLT studies were not included in our meta-analysis due to relatively short median follow up of 5.37 and 4.9 years, respectively. Our meta-analysis includes 2 different negative studies; CALGB [8] and the updated IALT [9]. Nevertheless, we have been able to demonstrate a 14% death reduction.

Results of OS analysis according to disease stage confirmed the lack of benefit from chemotherapy in stage I disease. This is in line with the findings in LACE and the most recent vinorelbine subgroup meta-analyses [28, 29]. The Non-small Cell Lung Cancer Collaborative Group meta-analysis investigated the effect of cisplatin-based regimens according to stage [3]. However, they grouped stage I and II together precluding comparison with our findings. On the other hand, chemotherapy improved OS significantly by 20% in each of stage II or III individually. That benefit was comparable to the 17% OS improvement reported by LACE for either of stage II or III [28]. On the other hand, in the later meta-analysis, patients who received vinorelbine achieved more OS gain (stage II 26% and stage III 34%). It

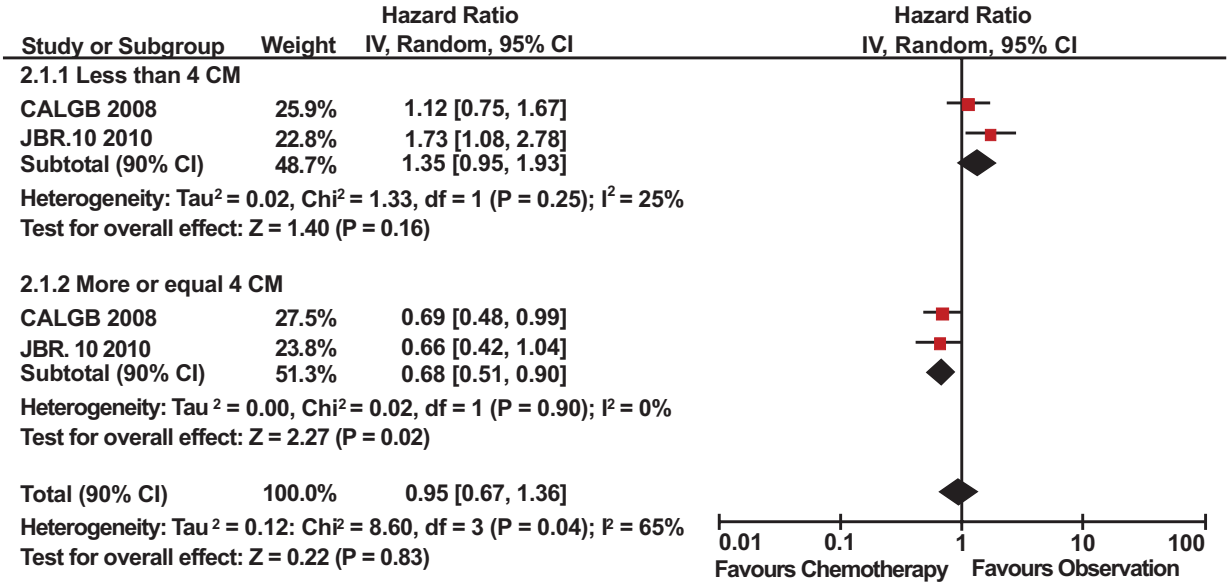

Fig. (7). Overall survival: hazard ratio of death with chemotherapy *vs* observation in stage IB by the size of the primary tumor (< 4 cm *vs* ≥ 4 cm).

is probable that cisplatin-vinorelbine offers the best outcome compared with other combinations [12].

Our meta-analysis suggested that for stage IB patients, only those with tumor ≥ 4 cm showed significant survival advantage from chemotherapy. While that might be expected based on the reported outcomes, the results need to be interpreted with caution as they were derived from only two studies (CALGB [8] and JBR.10 [10]), moreover, none of these trials stratified patients with stage IB disease according to tumor size.

The current meta-analysis confirmed a significant improvement in DFS by 17% in chemotherapy arms. This is not different from the 16% improvement in DFS reported in the LACE meta-analysis [28]. Analysis of DFS according to disease stage, only suggested a potential benefit for patients with stage III. That data should be interpreted with caution as that analysis was based on data derived from 2 trials only, i.e. IALT [9] and the CALGB [8], moreover, in the latter study only patients with stage IB were included.

From the available data, there was no evidence of significant increase in non-lung cancer death in the chemotherapy groups. While, the updated IALT analysis raised questions about potential negative long-term adverse effects of adjuvant chemotherapy, our analysis could not demonstrate significant increase in that risk. On the other hand, the LACE meta-analysis found more non-lung cancer death for chemotherapy (HR = 1.36; 95% CI 1.10 to 1.69; P = 0.004). Although LACE meta-analysis was individual patient data analysis, it did not provide information on intermediate and long-term non-lung cancer death, which may be due to recognized long-term chemotherapy toxicities as cardiovascular and pulmonary side effects, and deaths from second malignancies.

In conclusion, while we did not conduct individual patient data analysis, we believe that our analyses that were based on large patient population followed-up for an appropriate intermediate and long duration have provided significant clinical conclusions concerning the benefits of adjuvant chemotherapy for resected NSCLC. Investigators are encouraged to report long term updates of adjuvant NSCLC trials. In the future, other meta-analyses with even longer-term follow up may be necessary.

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