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ORIGINAL REPORT

Adjuvant Paclitaxel Plus Carboplatin Compared With Observation in Stage IB Non–Small-Cell Lung Cancer: CALGB 9633 With the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups

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ABSTRACT

Purpose
Adjuvant chemotherapy for resected non–small-cell lung cancer (NSCLC) is now accepted on the basis of several randomized clinical trials (RCTs) that demonstrated improved survival. Although there is strong evidence that adjuvant chemotherapy is effective in stages II and IIIA NSCLC, its utility in stage IB disease is unclear. This report provides a mature analysis of Cancer and Leukemia Group B (CALGB) 9633, the only RCT designed specifically for stage IB NSCLC.

Patients and Methods
Within 4 to 8 weeks of resection, patients were randomly assigned to adjuvant chemotherapy or observation. Eligible patients had pathologically confirmed T2N0 NSCLC and had undergone lobectomy or pneumonectomy. Chemotherapy consisted of paclitaxel 200 mg/m^2 intravenously over 3 hours and carboplatin at an area under the curve dose of 6 mg/mL per minute intravenously over 45 to 60 minutes every 3 weeks for four cycles. The primary end point was overall survival.

Results
Three hundred-forty-four patients were randomly assigned. Median follow-up was 74 months. Groups were well-balanced with regard to demographics, histology, and extent of surgery. Grades 3 to 4 neutropenia were the predominant toxicity; there were no treatment-related deaths. Survival was not significantly different (hazard ratio [HR], 0.83; CI, 0.64 to 1.08; $P = .12$). However, exploratory analysis demonstrated a significant survival difference in favor of adjuvant chemotherapy for patients who had tumors ≥ 4 cm in diameter (HR, 0.69; CI, 0.48 to 0.99; $P = .043$).

Conclusion
Because a significant survival advantage was not observed across the entire cohort, adjuvant chemotherapy should not be considered standard care in stage IB NSCLC. Given the magnitude of observed survival differences, CALGB 9633 was underpowered to detect small but clinically meaningful improvements. A statistically significant survival advantage for patients who had tumors ≥ 4 cm supports consideration of adjuvant paclitaxel/carboplatin for stage IB patients who have large tumors.

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INTRODUCTION

The use of adjuvant chemotherapy in non–small-cell lung cancer (NSCLC) has changed dramatically in recent years. Until the report of the International Adjuvant Lung Trial (IALT) in 2003,[1] there was little convincing evidence that adjuvant chemotherapy improved outcome in NSCLC. Since then, five randomized trials reported that adjuvant chemotherapy improves survival in resected NSCLC.[2-6]

In 2004, we reported preliminary results of Cancer and Leukemia Group B (CALGB) 9633, a randomized clinical trial (RCT) designed to study adjuvant paclitaxel/carboplatin in stage IB NSCLC. Preliminary results indicated that adjuvant chemotherapy improved overall survival (OS) and disease-free survival (DFS).[5] Indeed, accrual to CALGB 9633 was stopped early by the Data and Safety Monitoring Board after a planned interim analysis in November 2003 demonstrated that OS

had crossed a prespecified stopping boundary for efficacy. The hazard ratio (HR) for OS was the lowest reported in any RCT (HR, 0.62; 90% CI, 0.44 to 0.89; $P = .014$, one tailed).

When CALGB 9633 was under development in the early 1990s, our objective was to study adjuvant chemotherapy in high-risk, stage I NSCLC. We hoped to define high risk on the basis of a number of clinicopathologic and molecular markers. However, we concluded that it was not then possible to utilize clinical/molecular markers to define risk in a uniform and reproducible manner.

Accordingly, we defined high risk on the presence of T2N0 disease. In stage I NSCLC, large tumor size has been the most consistent determinant of survival. Among nine series that included greater than 2,000 patients with T2N0 disease, 5-year survival after resection ranged from 45% to 68%.[7] On the basis of such data, the International Staging System subdivided stage I into A and B subcategories in 1997, which defined stage IB NSCLC as T2N0M0.[8]

We chose paclitaxel/carboplatin on the basis of two phase II studies that indicated response rates of 62% in advanced NSCLC.[9,10] Although superiority to other combinations was not confirmed in subsequent RCTs[11-13] or meta-analyses,[14,15] paclitaxel/carboplatin remains one of the most widely used regimens in the United States. Moreover, toxicity compares favorably to cisplatin-based doublets, and no standard chemotherapy regimen had been established in the adjuvant setting.[16]

Although our 2004 presentation demonstrated considerable efficacy in stage IB NSCLC, median follow-up then was only 34 months. In addition, survival comparisons were based on only 57% (88 of 155) of deaths required for final analysis.[5]

Since 2004, three larger trials with broader inclusion criteria (ie, IALT, National Cancer Institute of Canada Clinical Trials Group [NCIC-CTG] JBR10 trial, and Adjuvant Navelbine International Trialists Association [ANITA]) each reported significant OS advantages with cisplatin-based doublets, but they failed to demonstrate improved survival in stage IB subsets.[2,4,6] In addition, Lung Adjuvant Cisplatin Evaluation (LACE), a pooled analysis of five RCTs that included 4,584 patients, also showed a significant OS advantage for all patients, but it failed to demonstrate efficacy for the 30% who had stage IB disease.[17] The objective of this report is to provide a mature analysis for CALGB 9633.

METHODS

Study Design

Random assignment was performed within 4 to 8 weeks of resection and was stratified on the basis of histology (squamous *v* nonsquamous), tumor differentiation (poor *v* others), and mediastinoscopy (performed v not performed). Participants were randomly assigned to adjuvant chemotherapy or observation. Chemotherapy consisted of paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ) 200 mg/m^2 intravenously over 3 hours and carboplatin (Paraplatin; Bristol-Myers Squibb), at an area under the curve (AUC) dose of 6 mg/mL per minute intravenously over 45 to 60 minutes. Treatment was repeated every 3 weeks for four cycles. CALGB 9633 was approved by institutional review boards in accordance with Department of Health and Human Services regulations.

Eligibility

Eligibility required age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1; histologically proven NSCLC; T2 tumor; pathologically negative lymph nodes at mediastinoscopy and/or surgery; and resection that consisted of lobectomy or pneumonectomy.

Statistical Analysis

The primary objective of the study was to determine if adjuvant chemotherapy improved OS after resection of stage IB NSCLC. Secondary objectives were to assess the impact of chemotherapy on DFS and to assess toxicities of adjuvant paclitaxel and carboplatin.

On the basis of available literature, we projected 50% 5-year survival for surgery alone in stage IB NSCLC. The study was designed in 1996 to determine whether adjuvant chemotherapy resulted in a 13% absolute improvement in 5-year survival (from 50% to 63%), with 80% power and with a two-tailed log-rank test conducted at the .05 significance level. With an assumption that survival was exponentially distributed, this improvement corresponded to an HR of 0.67. Although the accrual target was initially 500 patients, accrual was less than 50% of expected. As an alternative to protocol termination, we elected to reduce the accrual target from 500 to 384 patients in 2000. We reasoned that slow accrual allowed longer observation times for each patient. Although the protocol originally was designed for two-sided hypothesis testing, it was converted to one-sided testing ($\alpha = .05$) to maintain feasibility and statistical power when the sample size was reduced. The magnitude of effect size that we were seeking with 80% power did not change when the required number of deaths was reduced from 200 to 155.

OS and DFS were calculated by using the Kaplan-Meier life-table method. OS was defined as time from random assignment to death from any cause. DFS was defined as time from random assignment to recurrence or death. Subgroup comparisons of OS and DFS were performed by using the log-rank test and the Cox proportional hazards model. Exploratory analyses were conducted with the Cox model to explore the effect of tumor size on OS and DFS and to determine whether treatment differences were consistent between men and women and among ethnicities.

Accordingly, all *P* values reported herein are one-sided (unless otherwise specified). Reported confidence intervals are two-sided 90% confidence intervals, which best correspond to one-tailed *P* values. Analyses reflect the CALGB database as of April 6, 2007.

Descriptive statistics were tabulated and summarized with SAS software (Version 9.1; SAS Institute, Cary, NC). Survival analysis was performed with S-Plus (Version 3.3; Statistical Sciences, Seattle, WA) software. Analyses were performed by using the intent-to-treat principle, which included all eligible, ineligible, and canceled patients.

Interim Monitoring and Early Stopping

In accordance with CALGB policy, the study was reviewed semiannually by an independent data safety monitoring board (DSMB). Early termination was considered if the *P* value of the log-rank test was less than a nominal significance level calculated with the use of the Lan–DeMets α spending

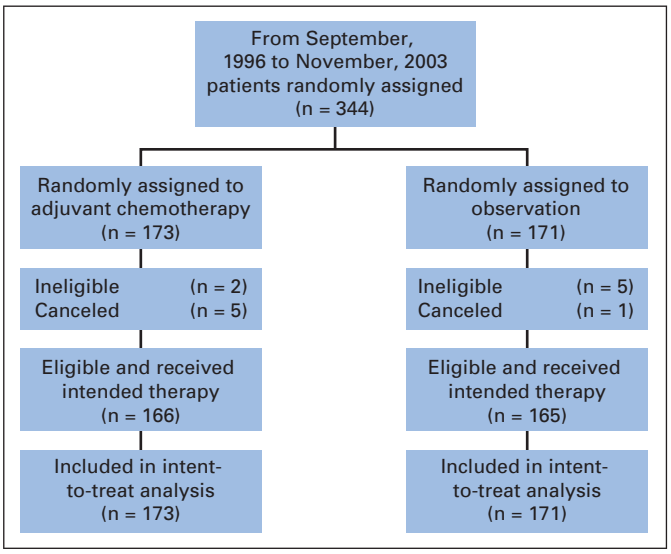

Fig 1. Consort diagram.

Table 1. Baseline Patient Characteristics

Variable	Chemotherapy (n = 173) No.	%	Control (n = 171) No.	%	P*
Sex					
Male	112	65	108	63	.76
Female	61	35	63	37	
Age, years					
Median	61		62		.40
Range	34-78		40-81		
Age distribution, years					.24
30-39	3	2	0	0	
40-49	27	16	20	12	
50-59	48	28	56	33	
60-69	56	32	62	36	
≥ 70	39	23	33	19	
Ethnicity					
White	157	91	150	88	.36
Nonwhite	16	9	21	12	
Performance status					
0	94	56	98	58	.84
1	74	44	70	41	
2	1	1	1	1	
Unknown	2	1	4	2	
Weight loss, %					
< 5	125	80	126	80	.77
5-10	20	13	22	14	
> 10	11	7	10	6	
Unknown	0	0	1	1	
Symptoms present					
No	39	23	45	26	.47
Yes	131	77	126	74	
Symptom duration, months					
< 3	101	67	94	64	
3-6	31	21	30	21	.82
> 6	19	13	22	15	
Tumor diameter, cm†					
Mean	4.59		4.50		.69
Median	4.0		4.0		
Range	0-14		1-12		
Histology					
Adenocarcinoma	90	54	84	49	.47
Squamous	58	35	58	34	
Other	20	12	28	16	
Tumor differentiation					
Well or moderate	86	50	85	50	.99
Poor	87	50	86	50	
Mediastinoscopy					
Yes	139	80	135	79	.75
No	34	20	36	21	
Surgical procedure					
Thoracotomy	158	95	157	93	.48
Thoracoscopy	8	5	11	7	
Extent of resection					
Lobectomy	146	88	151	89	.34
Pneumonectomy	19	12	18	11	

*P values are two-sided.
†Statistics for tumor diameter are based on 162 and 168 patients in chemotherapy and control groups, respectively.

function[18,19] with O'Brien–Fleming boundaries.[20] Accrual was stopped in November 2003, when survival results were less than the prespecified stopping boundary.

RESULTS

Participants

The protocol was activated on September 5, 1996 and was closed on November 26, 2003 (Fig 1). At closure, 344 patients had been enrolled, which represented 90% of target accrual. One hundred seventy-three patients were randomly assigned to chemotherapy, and 171 were randomly assigned to observation.

Among 344 patients, seven were retrospectively determined to be ineligible (two in the chemotherapy and five in the observation group), and six were cancelled and never received treatment (five in the chemotherapy and one in the observation group). Two patients were ineligible because they did not have NSCLC, and five were because they did not have stage IB disease. Thus, 331 patients were eligible and received their intended treatment. However, all 344 patients are included in the intent-to-treat analysis.

Demographics

As listed in Table 1, groups were well balanced with regard to age, sex, PS, symptoms at diagnosis, tumor size, histology, and extent of resection. Median follow-up was 74 months. Patients in both groups were predominantly white men who had a PS of 0.

The mean tumor diameter was 4.59 cm and 4.50 cm in the experimental and control groups, respectively. The median tumor diameter was 4.0 cm in both groups. (This apparent discrepancy is based on the fact that there were 51 patients whose tumor diameters were coded as 4.0 cm.) Overall, 59% of participants had tumors $\geq$ 4.0 cm in diameter.

The predominant histology was adenocarcinoma, which represented 51% of tumors. Preoperative mediastinoscopy was performed on 80%. Resection consisted of lobectomy in 89% and pneumonectomy in 11%.

Toxicity and Delivery of Chemotherapy

Toxicity data are available on 158 (91%) of 173 patients who received chemotherapy. Chemotherapy was well tolerated, and there were no treatment-related toxic deaths. The predominant toxicity was grade 3 to 4 neutropenia, which was observed in 35% (Table 2).

Data are available on 136 (79%) of 173 patients regarding delivery of chemotherapy. Eighty-six percent (117 of 136) received all four cycles of adjuvant chemotherapy. Among those given four cycles, 66% (77 of 117) received full-dose chemotherapy, and 34% (40 of 117) required a dose reduction at some point. Fifty-seven percent (77 of 136) received four cycles of chemotherapy at full dose.

OS, DFS, and Competing Risk Analysis

Table 3 includes data on OS and DFS for all 344 patients. With 74 deaths in the chemotherapy arm and 81 in the control arm, the difference in OS was not statistically significant (HR, 0.83; 90% CI, 0.64 to 1.08; $P = .125$; Fig 2A). The median survival times were 95 months and 78 months in chemotherapy and observation groups, respectively. Lack of differences were consistent between men and women ($P = .29$) and among ethnicity groups ($P = .28$).

The difference in DFS did not reach statistical significance (HR, 0.80; 90% CI, 0.62 to 1.02; $P = .065$; Fig 2B). The median DFS times were 89 months and 56 months in chemotherapy and observation groups, respectively. Lack of treatment differences were consistent between men and women ($P = .64$) and between white and nonwhite ethnicities ($P = .17$).

Cumulative incidence models were used to estimate the probability of death from lung cancer versus death as a result of other causes. As listed in Table 4, there was a 28% reduction in mortality as a result

Table 2. Toxicity of Adjuvant Chemotherapy

	Toxicity Grade					
	3 (severe)		4 (life-threatening)		5 (lethal)	
Toxicity	No.	%	No.	%	No.	%
Neutropenia	18	11	38	24	0	0
Thrombocytopenia	9	6	0	0	0	0
Anemia	4	3	0	0	0	0
Nausea and vomiting	9	6	0	0	0	0
Infection	9	6	0	0	0	0
Hyperglycemia	23	15	1	1	0	0
Myalgias/arthralgias	9	6	0	0	0	0
Malaise/fatigue	5	3	1	1	0	0
Sensory neuropathy	8	5	0	0	0	0
Anorexia	2	1	0	0	0	0
Dyspnea	5	3	2	1	0	0
Hypotension	0	0	1	1	0	0
Phlebitis	1	1	1	1	0	0
Pain	7	4	0	0	0	0
Weight loss	1	1	0	0	0	0
Maximum toxicity	64	41	45	28	0	0

NOTE. Data were available on 158 of 173 patients randomly assigned to adjuvant chemotherapy.

Table 3. Overall and Disease-Free Survival for All Patients Stratified by Tumor Size

Survival Outcome	Survival Analyses: Overall — Adjuvant Chemotherapy	Overall — Control	Overall — *P*	Overall — HR	Overall — 90% CI	Disease-Free — Adjuvant Chemotherapy	Disease-Free — Control	Disease-Free — *P*	Disease-Free — HR	Disease-Free — 90% CI
Intent-to-treat analysis of all randomly assigned patients										
No. of patients	173	171				173	171			
Recurrence or death			.125	0.83	0.64 to 1.08			.065	0.80	0.62 to 1.02
No.	74	81				81	92			
%	43	47				47	54			
1-year										
%	94	94	.50			85	81	.079		
90% CI, %	91 to 98	91 to 97				80 to 90	75 to 87			
2-year										
%	90	84	.053			75	68	.048		
90% CI, %	86 to 95	79 to 90				68 to 81	62 to 76			
3-year										
%	80	73	.020			67	58	.0048		
90% CI, %	74 to 86	65 to 79				60 to 74	51 to 66			
4-year										
%	70	62	.045			60	54	.060		
90% CI, %	63 to 77	55 to 70				53 to 68	47 to 62			
5-year										
%	60	58	.190			52	48	.117		
90% CI, %	52 to 68	51 to 66				45 to 61	41 to 57			
6-year										
%	55	53	.353			51	46	.094		
90% CI, %	48 to 64	45 to 62				43 to 59	38 to 54			
Tumor size $\geq$ 4 cm in diameter										
No. of patients	99	97				99	97			
Recurrence or death										
No.	37	53	.042	0.69	0.48 to 0.99	42	53	.035	0.69	0.49 to 0.97
%	38	55				42	55			
1-year										
%	94	92	.284			82	76	.182		
90% CI, %	90 to 98	87 to 97				74 to 90	68 to 85			
2-year										
%	90	81	.047			71	67	.259		
90% CI, %	85 to 95	75 to 88				63 to 81	58 to 77			
3-year										
%	78	71	.126			66	56	.085		
90% CI, %	71 to 85	64 to 79				57 to 76	47 to 67			
4-year										
%	71	64	.141			63	54	.105		
90% CI, %	60 to 79	56 to 73				53 to 73	44 to 65			
5-year										
%	64	61	.355			59	51	.141		
90% CI, %	56 to 73	53 to 70				49 to 70	41 to 62			
6-year										
%	60	54	.197			55	47	.137		
90% CI, %	52 to 70	45 to 64				46 to 67	37 to 59			
Tumor size $<$ 4 cm in diameter										
No. of patients	63	71				63	71			
Recurrence or death										
No.	34	33	.32	1.12	0.75 to 1.67	36	38	.49	1.01	0.69 to 1.48
%	54	46				57	54			
1-year										
%	94	97	.165			89	86	.308		
90% CI, %	89 to 99	94 to 100				81 to 97	78 to 94			

(continued on following page)

Table 3. Overall and Disease-Free Survival for All Patients Stratified by Tumor Size (continued)

Survival Outcome	Survival Analyses									
	Overall					Disease-Free				
	Adjuvant Chemotherapy	Control	*P*	HR	90% CI	Adjuvant Chemotherapy	Control	*P*	HR	90% CI
2-year										
%	90	87	.280			79	70	.119		
90% CI, %	84 to 97	91 to 94				70 to 90	60 to 82			
3-year										
%	81	73	.141			66	60	.234		
90% CI, %	73 to 89	64 to 82				55 to 79	50 to 73			
4-year										
%	67	62	.272			56	55	.477		
90% CI, %	58 to 78	53 to 73				45 to 70	45 to 69			
5-year										
%	52	54	.392			40	46	.278		
90% CI, %	42 to 64	45 to 65				29 to 55	35 to 59			
6-year										
%	45	52	.221			40	44	.353		
90% CI, %	35 to 58	43 to 63				29 to 55	33 to 58			

Abbreviation: HR, hazard ratio.

of lung cancer (HR, 0.72; 90% CI, 0.50 to 1.02). However, this difference was not significant ($P = .059$). Death as a result of other causes was similar (HR, 1.02; 90% CI, 0.68 to 1.53; $P = .47$).

Exploratory Analysis: Relationship Between Adjuvant Chemotherapy and Tumor Size

Because tumor size is so well established as a prognostic factor in stage I NSCLC, we conducted an exploratory analysis to determine whether patients who had large tumors derived benefit from adjuvant chemotherapy. We chose to dichotomize at 4.0 cm because of mounting evidence that 4.0 cm represents a better threshold than the traditional 3.0 cm cutoff for subdividision of stage I patients into prognostically meaningful groups.[21-24]

Tumor size was available in 96% (330 of 344) of patients. Fifty-nine percent (196 of 330) had tumors ≥ 4.0 cm in diameter (Table 3). Among those with larger tumors, the mean tumor diameters were 5.77 cm and 5.80 cm in chemotherapy and control groups, respectively (median diameter, 5.0 cm in both groups). In this subgroup, there

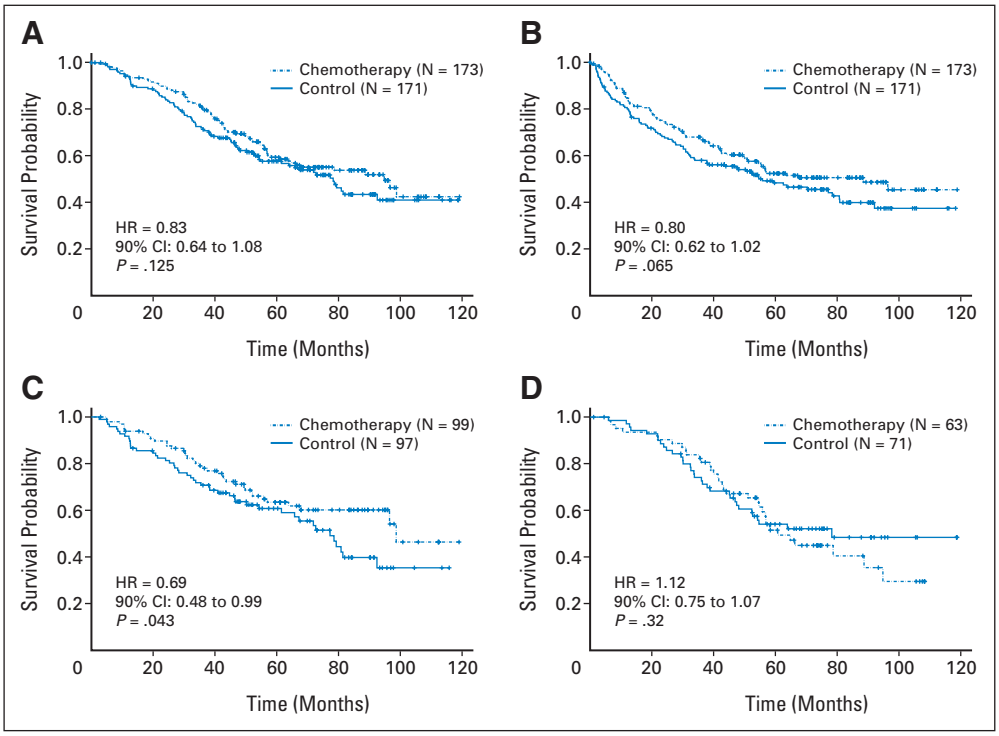

Fig 2. Kaplan-Meier estimates of survival among patients who received adjuvant paclitaxel and carboplatin and those who underwent observation alone. (A) Overall survival, all patients; (B) disease-free survival, all patients; (C) tumor size ≥ 4 cm in diameter; and (D) tumor size < 4 cm in diameter.

Table 4. Competing Risk Analysis

Cause of Death	Treatment Group: Adjuvant Chemotherapy (n = 173) No.	%	Control (n = 171) No.	%	Analysis P	HR	90% CI
Lung cancer	39	22.5	50	29.2	.059	0.72	0.50 to 1.02
Other	35	20.2	31	18.1	.47	1.02	.68 to 1.53
All	74	42.7	81	47.4	.125	0.83	0.64 to 1.08

Abbreviation: HR, hazard ratio.

were significant advantages in OS and DFS for adjuvant chemotherapy. There was a 31% reduction in risk of death, as measured by OS analysis, among those with tumors ≥ 4 cm (HR, 0.69; 90% CI, 0.48 to 0.99; $P = .043$; Fig 2C) who received chemotherapy. Median survival times were 99 months and 77 months in chemotherapy and control groups, respectively. There was also a significant, 31% improvement in DFS that favored the chemotherapy group (HR, 0.69; 90% CI, 0.49 to 0.97; $P = .035$) in the median DFS times of 96 and 63 months, respectively.

Forty-one percent (134 of 330) had tumors less than 4.0 cm in diameter (Table 3). Among patients who had tumors less than 4.0 cm, mean tumor diameters were 2.73 cm and 2.71 cm in chemotherapy and control groups, respectively (median, 3.0 cm in both groups). In this subgroup (Fig 2D), there was a trend toward inferior OS in the chemotherapy group (HR, 1.12; 90% CI, 0.75 to 1.67; $P = .32$). Median survivals were 61 months and 78 months in chemotherapy and controls groups, respectively. There was no difference in DFS (HR, 1.01; 90% CI, 0.69 to 1.48; $P = .49$), as median DFS times were 55 months and 53 months in chemotherapy and control groups, respectively.

DISCUSSION

The last 5 years have seen a dramatic shift in the standard of care regarding adjuvant chemotherapy of NSCLC. Beginning with the report of a significant survival difference from IALT, five multi-institutional RCTs have been reported that demonstrate statistically significant survival advantages associated with adjuvant chemotherapy for early-stage NSCLC.

These five positive RCTs include the preliminary 2004 report of CALGB 9633.[1] This was the only RCT designed specifically for stage IB NSCLC. However, stage IB patients were eligible to participate in each trial. Although mature results of CALGB 9633 no longer demonstrate a significant OS advantage for adjuvant chemotherapy across the entire cohort, the other four RCTs have retained significance in the entire study population. Because stage IB patients were eligible to participate in each positive trial, one question is whether sufficient evidence exists to routinely recommend adjuvant chemotherapy for patients with stage IB NSCLC, despite the results reported here. The answer would appear to be no.

Three of these four RCTs utilized a cisplatin-based doublet as the adjuvant chemotherapy. In IALT, patients were randomly assigned either to observation or to three or four cycles of cisplatin (Platinol; Bristol-Myers Squibb) combined with either vinorelbine (Navelbine; GlaxoSmithKline, Research Triangle Park, NC), vinblastine (Velban; Eli Lilly & Co, Indianapolis, IN), vindesine, or etoposide (Vepesid; Bristol-Myers Squibb). All resectable patients (including stages IA to IIIB) were eligible to participate in IALT.[2]

In both NCIC-CTG-JBR-10 and ANITA, patients were randomly assigned either to observation or to four cycles of cisplatin/vinorelbine. Eligibility in NCIC-CTG-JBR-10 included stages IB and II NSCLC,[4] whereas stagesIB, II, and IIIA were eligible in in ANITA.[6] The fourth RCT was the Japan Lung Cancer Research Group (JLCRG) study, in which patients with stage IA or IB lung adenocarcinoma were randomly assigned to 2 years of adjuvant chemotherapy with oral uracil/tegafur (UFT) or observation.[3]

Although each study showed a significant OS advantage for chemotherapy, no cisplatin-based RCT demonstrated a significant OS advantage for the stage IB subset. In IALT, there was no survival advantage among 681 stage I patients (HR, 0.95; 95% CI, 0.74 to 1.23), 73% of whom had stage IB NSCLC.[2,25] ANITA demonstrated a significant OS advantage for adjuvant cisplatin/vinorelbine among all patients and among patients in the stages II and IIIA subsets, although not in the stage IB subset (HR, 1.10; 95% CI, 0.76 to 1.67).[6] Similarly, NCIC-CTG-JBR-10 demonstrated a significant OS advantage for adjuvant cisplatin/vinorelbine in all patients and in the stage II subset.[4] However, there was no survival advantage in stage IB disease ($P = .79$).

The only other multi-institutional RCT that did show benefit in stage IB disease is JLCRG, which utilized adjuvant UFT in stage I lung adenocarcinoma. Results indicate a significant survival improvement for all 979 patients with stage IA or IB disease (HR, 0.71; 95% CI, 0.52 to 0.98).[3] Among the 27% of participants with stage IB disease, there was a significant survival advantage (HR, 0.48; 95% CI, 0.29 to 0.81). In contrast, there was no benefit for UFT within the much larger stage IA subset (HR, 0.97; 95% CI, 0.64 to 1.46). There is no experience with adjuvant UFT outside Japan, and this agent is not available in Europe or North America for NSCLC.

The only other data that supports efficacy for adjuvant chemotherapy in stage IB NSCLC comes from a small, single-institutional RCT from Italy.[26] In this trial, 140 stage IB patients were randomly assigned after resection to six cycles of adjuvant cisplatin/etoposide or observation. Results demonstrate large and significant OS/DFS advantages in the adjuvant arm. Five-year, 10-year, and median survivals were 62%, 44%, and 84.8 months versus 42%, 20%, and 41.6 months, respectively ($P = .02$). Although impressive, the small sample size and the large effect size introduce questions about the reproducibility of these findings.

Accordingly, results of CALGB 9633 remain highly relevant to the question of the effect of adjuvant chemotherapy in stage IB NSCLC. Unfortunately, with longer follow-up, our encouraging preliminary findings have not been sustained. Nonetheless, the HR of 0.83 reported in our current analysis is similar to overall HRs observed in several positive trials. For example, in IALT and in ANITA, statistically significant survival advantages for adjuvant chemotherapy indicate HRs of 0.86, and 0.80, respectively. Moreover, LACE, a pooled analysis of five RCTs, reports a significant modest OS advantage (HR, 0.89; 95% CI, 0.82 to 0.96).[17]

Accordingly, the 17% reduction in risk of death observed in updated results from our study is similar in magnitude to survival advantages observed in several positive trials. However, with only 344 participants, CALGB 9633 is considerably smaller than any of the other RCTs. Given the smaller sample size and the lower event rates, our study had only 31% power to demonstrate a significant survival difference with HR = 0.83. Similarly, the 28% reduction in lung cancer mortality would suggest a benefit for adjuvant chemotherapy, although with only 89 deaths as a result of lung cancer, there was insufficient power to show a statistically significant difference.

Clearly, our results do not support routine use of adjuvant chemotherapy as standard of care in stage IB NSCLC. Recent American Society of Clinical Oncology guidelines assert that "adjuvant chemotherapy is not recommended for routine use for patients with completely resected stage IB NSCLC,"[27] a conclusion with which we concur.

Nonetheless, CALGB 9633 does demonstrate a trend in favor of use of adjuvant chemotherapy. Moreover, exploratory analysis suggests that the adjuvant chemotherapy significantly improves survival for patients who had tumors $\geq$ 4.0 cm.

Although the analysis on the basis of on tumor size represents an unplanned subgroup analysis, the finding that adjuvant chemotherapy is effective for stage IB patients with large tumors is biologically plausible,[21-24] and, if confirmed, would represent an observation that could substantially impact clinical practice. In this regard, after our updated 2006 presentation,[28] investigators from NCIC-CTG-JBR-10 analyzed their data and also found a significant survival advantage for stage IB patients with greater than 4-cm tumors (Frances Shepherd, personal communication, April 19, 2007). We currently are participating in a pooled analysis in the context of an expanded LACE analysis in which this observation will be further explored.

We believe that our results support consideration for adjuvant chemotherapy in stage IB patients for those who had tumors $\geq$ 4.0 cm, which comprised 59% of patients in our study. The finding of a significant 31% mortality reduction provides a basis for considering adjuvant treatment in this subgroup, despite the fact that this was not an a priori objective of our trial. Indeed, the vast majority of such patients would be classified as having stage II tumors on the basis of a proposed new staging system for NSCLC.[23,24]

In terms of treatment regimen, our results suggest that adjuvant paclitaxel/carboplatin was at least comparable to cisplatin-based combinations for stage IB disease.[29] Although LACE reported a significant survival advantage for all treated patients (HR, 0.89; 95% CI, 0.82 to 0.96) and in stage II and III patients (HR, = 0.83; 95% CI, 0.73 to 0.95), there was no significant advantage in stage IB NSCLC (HR, 0.93; 95% CI, 0.78 to 1.10).[17]

It also should be emphasized that adjuvant paclitaxel plus carboplatin was well tolerated, and there were no chemotherapy-related toxic deaths. Although compliance with adjuvant chemotherapy has been difficult in all RCTs, it was less problematic in CALGB 9633 than in cisplatin-based trials.[30,31] Accordingly, paclitaxel plus carboplatin could be considered as a treatment option in selected stage IB patients who had tumors $\geq$ 4.0 cm in diameter. We believe that our results support the need to at least discuss the potential role of adjuvant chemotherapy with stage IB patients who have large tumors.

At this time, our study indicates that routine use of adjuvant chemotherapy is not justified for all patients with stage IB NSCLC. Nonetheless, results of CALGB 9633 (and confirmatory findings from NCIC-CTG-JBR-10) support consideration for adjuvant chemotherapy in stage IB patients who have tumors $\geq$ 4.0 cm in diameter.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

