Survival Following Surgery with or without Adjuvant Chemotherapy for Stage I–IIIA Non-Small Cell Lung Cancer: An East Asian Population-Based Study

ZHONG-ZHE LIN,^{a,b,c} WEN-YI SHAU,^d YU-YUN SHAO,^b YEN-YUN YANG,^e RAYMOND NIEN-CHEN KUO,^{e,f} JAMES CHIH-HSIN YANG,^{b,g} MEI-SHU LAI^{e,f,h}

^aDepartment of Oncology, National Taiwan University Hospital Yun-Lin Branch, Yunlin, Taiwan;

^bDepartment of Oncology, National Taiwan University Hospital, Taipei, Taiwan; ^cDepartment of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan; ^dDivision of Health Technology Assessment, Center for Drug Evaluation (Taiwan), Taipei, Taiwan; ^eCenter for Comparative Effectiveness Research, Clinical Trial Center, National Taiwan University Hospital, Taipei, Taiwan; ^fTaiwan Cancer Registry, Taipei, Taiwan; ^gGraduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan; ^hInstitute of Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

Key Words. Non-small cell lung cancer • Adjuvant chemotherapy • Asian ethnicity • Survival • Comparative effectiveness

Disclosures: The authors indicated no financial relationships.

ABSTRACT

Background. Asian ethnicity is associated with a distinct molecular etiology, treatment response, and survival outcome among patients with non-small cell lung cancer (NSCLC). This study examines the survival impact of platinum-based adjuvant chemotherapy for Asian patients with stage I–IIIA NSCLC.

Methods. This study recruited patients aged ≥ 18 years with histologically proven stage IA–IIIA NSCLC registered in the Taiwan Cancer Registry database in January 2004 to December 2007. Platinum-containing adjuvant chemotherapy had to be started within 90 days of the primary surgery. Kaplan–Meier survival curves, log-rank tests, and the Cox proportional hazards regression model were used to assess the influence of various risk factors on survival time.

Results. This study included 2,231 patients with stage IA–IIIA NSCLC who underwent primary surgery with a

clear surgical margin. The percentages of all causes of death were significantly lower for the chemotherapy group for both stage II and stage IIIA patients. Multivariate analysis identified platinum-based adjuvant chemotherapy as an independent prognostic factor for the overall survival outcome of stage II (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.39–0.94; $p = .024$) and IIIA (HR, 0.71; 95% CI, 0.52–0.96; $p = .029$) patients. Among these patients, those who received adjuvant chemotherapy had a superior overall survival outcome for both genders, for the subgroup of patients aged ≥ 70 years, and for those with adenocarcinoma.

Conclusion. Platinum-based adjuvant chemotherapy should be considered in the treatment plan for Asian patients with resected stage II and stage IIIA NSCLC. *The Oncologist* 2012;17:1294–1302

INTRODUCTION

Despite undergoing potentially curative surgery, patients with stage I, II, or IIIA non-small cell lung cancer (NSCLC) are at

substantial risk for recurrence and death. Patients with stage IA disease have a 5-year survival rate of 67%. Survival rates are lower with more advanced disease and patients with stage IIIA

Correspondence: James Chih-Hsin Yang, M.D., Ph.D., Department of Oncology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 10002, Taiwan. Telephone: 886-2-23123456-62858; Fax: 886-2-23711174; e-mail: chihyang@ntu.edu.tw; Mei-Shu Lai, M.D., Ph.D., Institute of Preventive Medicine, College of Public Health, National Taiwan University, 17 Hsuehshan Road, Taipei 10055, Taiwan. Telephone: 886-2-33668018; Fax: 886-2-23920456; e-mail: mslai@cph.ntu.edu.tw Received February 25, 2012; accepted for publication June 25, 2012; first published online in *The Oncologist Express* on July 23, 2012. ©AlphaMed Press 1083-7159/2012/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2012-0082>

disease have a 5-year survival rate of only 23% [1, 2]. Because treatment failure following potentially curative surgery is frequently encountered [3], adjuvant systemic therapy has become a rational approach to reduce the risk for recurrence and improve overall survival (OS) outcomes.

The Non-Small Cell Lung Cancer Collaborative Group meta-analysis demonstrated that adjuvant chemotherapy with a cisplatin-based regimen could provide a 5-year survival advantage of 5% for patients with resected NSCLC [4]. This meta-analysis prompted interest in the application of adjuvant chemotherapy for resected NSCLC. The benefit of platinum-based adjuvant chemotherapy for patients with stage I–III NSCLC was demonstrated in three prospective randomized trials in western countries [5–7]. To confirm the survival benefit resulting from adjuvant chemotherapy, a large meta-analysis (Lung Adjuvant Cisplatin Evaluation [LACE]) [8] combined the data of individual patients from five large adjuvant trials: the International Adjuvant Lung Cancer Trial (IALT) [5], European Big Lung Trial [9], Adjuvant Lung Project Italy (ALPI) [10], Adjuvant Navelbine International Trialist Association (ANITA) trial [6], and National Cancer Institute of Canada JBR.10 trial [7]. The LACE study enrolled 4,584 patients with completely resected NSCLC and showed that adjuvant chemotherapy is associated with a 5.4% lower risk for death at 5 years than with surgery alone (hazard ratio [HR] for death, 0.89; 95% confidence interval [CI], 0.82–0.96; $p = .005$). The survival benefit was statistically significant for patients with stage II and IIIA disease (HR, 0.83). For patients with stage IB disease, the survival benefit did not reach statistical significance (HR, 0.93). Conversely, adjuvant chemotherapy was found to be associated with a worse survival outcome for patients with stage IA disease (HR, 1.40). Based on these available data, guidelines from Cancer Care Ontario and the American Society of Clinical Oncology recommended cisplatin-based adjuvant chemotherapy for patients with completely resected stage II or IIIA NSCLC [11].

Asian ethnicity has been demonstrated to be an independent favorable prognostic factor for OS outcomes among NSCLC patients [12]. In addition, Asian patients with NSCLC may differ in their response to cytotoxic chemotherapy, compared with white patients [13]. The positive results of landmark studies [5–7] published in 2004–2006 prompted expansion of the clinical application of adjuvant chemotherapy for resected NSCLC in both western and Asian countries [14]. However, the efficacy of adjuvant chemotherapy for Asian patients with completely resected NSCLC has yet to be validated. Therefore, we conducted this retrospective population-based analysis of the Taiwan Cancer Registry (TCR) database to examine the survival benefit of adjuvant chemotherapy for Asian patients with stage I–IIIA NSCLC.

PATIENTS AND METHODS

Data Sources

The study cohort comprised patients registered in the TCR, a population-based cancer registry managed by the Bureau of Health Promotion (BHP), Department of Health in Taiwan. Hospitals with >50-bed capacity in Taiwan were requested to

participate in reporting all newly diagnosed malignant neoplasms to the TCR database, which represents ~80% of new cancer patients in Taiwan [15–17]. To verify the vital status, each selected case was linked with the database of death registry up to the end of 2010. Patient data were also linked with the claims database of Taiwan's National Health Insurance (NHI) for 2003–2009 to determine whether patients received cisplatin or carboplatin as part of their adjuvant chemotherapy. The NHI program is a mandatory health insurance system covering >98% of the Taiwanese population. The study protocol was approved by the Research Ethics Committee of the College of Public Health, National Taiwan University (protocol #990205) and the Data Release Review Board of the BHP.

Study Population

This study identified cases registered in the TCR database in January 2004 to December 2007. As shown in supplemental Figure A1, eligible patients had to be aged ≥ 18 years and have histologically proven NSCLC (International Classification of Disease for Oncology [18] codes 339–349 and morphology codes 8010, 8012–8013, 8022, 8032–8033, 8046, 8050, 8052, 8070–8072, 8082–8083, 8140, 8200, 8211, 8230, 8240, 8246, 8249–8250, 8252–8255, 8260, 8310, 8320, 8323, 8333, 8430, 8480–8481, 8490, 8550, 8560, 8711, 8890 and 8972). The cohort was carefully examined to exclude possible duplicate reported cases from different hospitals. When duplication was identified, the earlier date of diagnosis was used for the survival analysis. Eligible patients had to have stage IA–IIIA disease according to the American Joint Cancer Committee on Cancer system (Sixth Edition) [19] and receive a curative operation with a clear surgical margin. Adjuvant chemotherapy started within 90 days of the primary surgery had to include cisplatin or carboplatin as part of the therapeutic regimen. All cases with second primary malignancies and those receiving anticancer treatment prior to surgery were excluded.

Statistical Considerations

The characteristics of patients undergoing adjuvant chemotherapy were compared with those of patients receiving surgery alone using χ^2 statistics for categorical variables and t -tests for continuous variables to identify potential differences between the two groups. Survival time was defined as the period from the date of diagnosis of NSCLC to the date of death or the last date for which NHI claim or TCR data were available (December 31, 2010). Kaplan–Meier survival curves were created and log-rank tests were used to compare the survival curves between the groups of patients. A Cox proportional hazards regression model was used to assess the univariate and multivariate effects of the various risk factors on survival time. All statistical analyses were performed using SAS software (version 9.1.3; SAS Institute Inc., Cary, NC) and two-sided $p \leq .05$ was considered statistically significant.

Table 1. Characteristics of patients with stage IA–IIIA non-small cell lung cancer receiving primary surgery with or without adjuvant chemotherapy

Characteristic	Stage IA			Stage IB			Stage II			Stage IIIA		
	OP n (%)	OP+CT n (%)	p-value	OP n (%)	OP+CT n (%)	p-value	OP n (%)	OP+CT n (%)	p-value	OP n (%)	OP+CT n (%)	p-value
Total	689 (97.2)	20 (2.8)		758 (88.3)	100 (11.7)		222 (68.9)	100 (31.1)		134 (39.2)	208 (60.8)	
Gender			.649			.007			.038			.603
Male	311 (45.1)	8 (40.0)		484 (63.9)	50 (50.0)		155 (69.8)	58 (58.0)		76 (56.7)	112 (53.9)	
Female	378 (54.9)	12 (60.0)		274 (36.1)	50 (50.0)		67 (30.2)	42 (42.0)		58 (43.3)	96 (46.2)	
Age, yrs			.130			<.001			<.001			<.001
Median (range)	64 (19–89)	58 (43–81)		69 (20–89)	60 (33–82)		68 (27–92)	59 (35–81)		68 (31–90)	60 (32–82)	
18–69	456 (66.2)	15 (75.0)		391 (51.6)	78 (78.0)		118 (53.2)	80 (80.0)		74 (55.2)	164 (78.9)	
≥70	233 (33.8)	5 (25.0)		367 (48.4)	22 (22.0)		104 (46.8)	20 (20.0)		60 (44.8)	44 (21.2)	
Histology			.504			.087			.002			.005
Adenocarcinoma	533 (77.4)	14 (70.0)		447 (59.0)	64 (64.0)		97 (43.7)	63 (63.0)		78 (58.2)	148 (71.2)	
Squamous cell carcinoma	77 (11.2)	2 (10.0)		225 (29.7)	20 (20.0)		99 (44.6)	25 (25.0)		43 (32.1)	35 (16.8)	
Others	79 (11.5)	4 (20.0)		86 (11.3)	16 (16.0)		26 (11.7)	12 (12.0)		13 (9.7)	25 (12.0)	
Surgery type			.277			.943			.408			.698
Wedge resection	114 (16.5)	6 (30.0)		72 (9.5)	9 (9.0)		13 (5.9)	1 (1.0)		9 (6.7)	10 (4.8)	
(Bi)lobectomy ^a	572 (83.0)	14 (70.0)		674 (88.9)	89 (89.0)		197 (88.7)	97 (97.0)		114 (85.1)	183 (88.0)	
Pneumonectomy	3 (0.4)	–		12 (1.6)	2 (2.0)		12 (5.4)	2 (2.0)		11 (8.2)	15 (7.2)	
All cause of death	79 (11.5)	4 (20.0)	.278	208 (27.4)	21 (21.0)	.171	122 (55.0)	27 (27.0)	<.001	79 (59.0)	92 (44.2)	.008

^a(Bi)lobectomy includes lobectomy and bilobectomy.

Abbreviations: OP, surgery alone; OP+CT, surgery followed by adjuvant chemotherapy.

RESULTS

Baseline Characteristics of Patients

In total, 30,069 patients with lung cancer were reported to the TCR in 2004–2007. After excluding patients with other cancers, duplicate reported cases, and patients aged <18 years, 24,957 patients in total with newly diagnosed primary NSCLC were selected. In total, 2,231 patients with stage IA–IIIA NSCLC met all eligibility criteria. Among them, 428 patients (19.2% of the study population) received platinum-based adjuvant chemotherapy. The characteristics of the patients receiving primary surgery with or without adjuvant chemotherapy are summarized in Table 1. For stage IA disease, the differences in gender, age, and tumor histology of patients with and without adjuvant chemotherapy were not statistically significant. Stage IB and stage II patients receiving adjuvant chemotherapy were more likely to be women—50.0% versus 36.1% ($p = .007$) and 42.0% versus 30.2% ($p < .001$), respectively. Stage II and stage IIIA patient receiving adjuvant chemotherapy were more likely to have adenocarcinoma—63.0% versus 43.7% ($p = .002$) and 71.2% versus 58.2% ($p = .005$), respectively. Patients with stage IB, stage II, and stage IIIA disease receiving adjuvant chemotherapy tended to be younger (all p -values <.001).

Survival Analysis

One hundred forty-four (33.6%) of the 428 patients receiving adjuvant chemotherapy and 488 (27.1%) of the 1,803 patients in the control group died. As shown in Table 1, the percentages of all causes of death were significantly lower for the chemo-

therapy group for stage II (27.0% versus 55.0%; $p < .001$) and stage IIIA (44.2% versus 59.0%; $p = .008$) patients. The survival rates for patients receiving adjuvant chemotherapy and those for the control group were not significantly different for stage IA and IB disease (Fig. 1A, 1B). Meanwhile, the survival rates were significantly higher for the chemotherapy group for stage II (HR, 0.47; 95% CI, 0.31–0.71; $p = .0004$) (Fig. 1C) and stage IIIA (HR, 0.62; 95% CI, 0.46–0.83; $p = .0017$) (Fig. 1D) disease. For the chemotherapy group, the 2-year survival rates were 80.0%, 90.0%, 82.0%, and 76.4% for stage IA, IB, II, and IIIA patients, respectively (Fig. 1). For the control group, the 2-year survival rates were 96.2%, 85.8%, 64.4%, and 57.5% for stage IA, IB, II, and IIIA patients, respectively (Fig. 1).

Multivariate Analysis

As shown in Table 2, Cox regression analysis identified adjuvant chemotherapy as an independent prognostic factor for the OS outcome of patients with stage II (HR, 0.61; 95% CI, 0.39–0.94; $p = .024$) and stage IIIA (HR, 0.71; 95% CI, 0.52–0.96; $p = .029$) disease. Male gender was identified as an independent risk factor for mortality among patients with stage IA ($p = .002$), stage IB ($p = .005$), and stage IIIA ($p = .011$) disease. Advanced age was found to be independently associated with a worse OS outcome among patients with all stages of disease (all p -values $\leq .001$) (Table 2). Compared with adenocarcinoma, squamous cell carcinoma was significantly associated with a worse survival outcome among patients with stage IB ($p < .001$) and stage IIIA ($p = .010$) disease. Compared with

Figure 1. Overall survival of patients with resectable stage IA (A), IB (B), II (C), and IIIA (D) non-small cell lung cancer receiving primary surgery with or without adjuvant chemotherapy.

Abbreviations: CI, confidence interval; HR, hazard ratio; OP, surgery alone; OP+CT, surgery followed by adjuvant chemotherapy.

wedge resection, lobectomy, bilobectomy ($p = .001$), and pneumonectomy ($p = .049$) were associated with a better OS outcome among patients with stage IB disease (Table 2).

Subgroup Analysis for Stage II and IIIA Patients

Because gender, age, and tumor histology were all potential prognostic factors for OS outcomes, we conducted an exploratory analysis to determine whether or not platinum-based adjuvant chemotherapy provided patients in stage II and stage IIIA subgroups with a survival advantage. As shown in Figure 2 and Figure 3, patients receiving adjuvant chemotherapy had a consistently better OS outcome in different subgroups. For stage II disease, the survival advantage afforded by adjuvant chemotherapy reached statistical significance in the subgroups of male gender (HR, 0.51; 95% CI, 0.31–0.84; $p = .0086$) (Fig. 2A), female gender (HR, 0.45; 95% CI, 0.21–0.99; $p = .0454$) (Fig. 2A), age ≥ 70 years (HR, 0.28; 95% CI, 0.11–0.70; $p = .0064$) (Fig. 2B), and adenocarcinoma histology (HR, 0.42; 95% CI, 0.23–0.78; $p = .0057$) (Fig. 2C). For stage IIIA disease, the survival advantage provided by adjuvant chemotherapy was statistically significant for both genders (female: HR, 0.55; 95% CI, 0.33–0.92; $p = .0237$; male: HR, 0.63; 95% CI, 0.44–0.92; $p = .0165$) (Fig. 3A) and among pa-

tients aged ≥ 70 years (HR, 0.44; 95% CI, 0.26–0.76; $p = .0030$) (Fig. 3B).

DISCUSSION

In this population-based study of East Asian patients with resectable NSCLC undergoing curative operations, the use of platinum-based adjuvant chemotherapy was associated with a better OS outcome for patients with stage II (HR, 0.61; $p = .024$) and stage IIIA (HR, 0.71; $p = .029$) disease. The 2-year survival rates were significantly higher for patients receiving adjuvant chemotherapy than for those receiving surgery alone for stage II (82.0% versus 64.4%) and stage IIIA (76.4% versus 57.5%) disease. An exploratory analysis revealed that patients with stage II and stage IIIA disease (in subgroups of different genders, ages, and tumor histologies) receiving adjuvant chemotherapy had a consistently better OS outcome than their counterparts receiving surgery alone, particularly for patients aged ≥ 70 years and those with adenocarcinoma.

After the 1995 Non-Small Cell Lung Cancer Collaborative Group meta-analysis, six landmark prospective randomized clinical trials (the IALT, JBR.10 trial, ANITA trial, ALPI trial, Big Lung Trial, and CALGB 9633 trial [20]) and one large meta-analysis (LACE) were published, in which the current

Table 2. Cox proportional hazards models for patients with stage IA–IIIA non-small cell lung cancer

Characteristic	Stage IA			Stage IB			Stage II			Stage IIIA		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Treatment												
OP	1.00			1.00			1.00			1.00		
OP+CT	2.40	0.86–6.65	.093	1.23	0.78–1.95	.381	0.61	0.39–0.94	.024	0.71	0.52–0.96	.029
Gender												
Female	1.00			1.00			1.00			1.00		
Male	2.11	1.31–3.41	.002	1.59	1.15–2.21	.005	1.35	0.89–2.02	.155	1.57	1.11–2.22	.011
Age, yrs												
Continuous	1.05	1.03–1.08	<.001	1.04	1.02–1.05	<.001	1.03	1.01–1.05	.001	1.03	1.01–1.04	.001
Histology												
Adenocarcinoma	1.00			1.00			1.00			1.00		
Squamous cell carcinoma	1.06	0.59–1.90	.841	1.79	1.33–2.41	<.001	1.04	0.71–1.53	.826	1.66	1.13–2.45	.010
Other	1.18	0.61–2.28	.628	1.65	1.10–2.48	.016	1.35	0.80–2.26	.260	1.66	1.03–2.68	.039
Surgery type												
Wedge resection	1.00			1.00			1.00			1.00		
(Bi)lobectomy ^a	0.78	0.47–1.31	.347	0.54	0.38–0.77	.001	0.55	0.29–1.04	.065	1.14	0.59–2.20	.701
Pneumonectomy	—	—	—	2.22	1.01–4.89	.049	0.93	0.38–2.27	.879	1.40	0.61–3.18	.427

^a(Bi)lobectomy includes lobectomy and bilobectomy.

Abbreviations: CI, confidence interval; HR, hazard ratio; OP, surgery alone; OP+CT, surgery followed by adjuvant chemotherapy.

clinical application of adjuvant platinum-based chemotherapy for NSCLC in 2003–2008 (Table 3) was defined. Although the six trials recruited patients with different stages of disease and different clinical characteristics, two common trends were observed: (a) none of the trials demonstrated any significant survival advantage for adjuvant chemotherapy among stage I patients and (b) a significant survival benefit with adjuvant chemotherapy was demonstrated for stage II (the JBR.10 and ANITA trials) and stage IIIA (the IALT and ANITA trials) patients. The LACE meta-analysis, aggregating the results of five adjuvant trials (the IALT trial, JBR.10 trial, ANITA trial, ALPI trial, and Big Lung Trial), confirmed that the survival benefit varied considerably according to NSCLC stage, with potential detrimental effects for patients with stage IA disease, an insignificant trend toward benefit for stage IB patients, and a significant benefit for patients with stage II and IIIA NSCLC. As shown in Table 2 and Table 3, our results are consistent with those of the LACE study, supporting the use of platinum-based adjuvant chemotherapy for patients with stage II (HR, 0.61; 95% CI, 0.39–0.94; $p = .024$) and stage IIIA (HR, 0.71; 95% CI, 0.52–0.96; $p = .029$) NSCLC. However, our results raise questions regarding the use of adjuvant chemotherapy for patients with stage IA (HR, 2.40; 95% CI, 0.86–6.65; $p = .093$) and stage IB (HR, 1.23; 95% CI, 0.78–1.95; $p = .381$) disease.

This population-based study has several unique strengths. Compared with data from clinical trials, in which young patients with a good performance status tend to be enrolled, population-based studies are more likely to represent all patients encountered in daily practice. In addition, our data were obtained from a cancer registry estimated to encompass >80% of

all cancer cases in Taiwan [16]. Thus, the population in this study provides a diverse patient cohort of sufficient sample size to draw meaningful conclusions. However, this study also suffers from several limitations. First, the baseline characteristics of the chemotherapy group and those of the control group were imbalanced. Patients receiving adjuvant chemotherapy tended to be younger (Table 1); therefore, a selection bias may have caused survival outcomes to favor the chemotherapy groups. Nevertheless, in the multivariate analysis, adjuvant chemotherapy remained an independent factor associated with a lower risk for death for patients with stage II and stage IIIA disease. In addition, the survival advantage for patients receiving adjuvant chemotherapy was consistent among different age groups (Figs. 2B, 3B). Second, we were unable to assess a number of important prognostic factors, such as performance status and patient comorbidities. Physicians are more willing to recommend adjuvant chemotherapy for patients with a better performance status and fewer comorbidities, which may further bias the survival outcome in favor of chemotherapy. Nonetheless, we believe that information related to age partly accounted for the influence of performance status and comorbidities.

To the best of our knowledge, this is the first report evaluating the application of adjuvant chemotherapy for East Asian patients with resectable NSCLC. NSCLC in the East Asian population differs from that found among whites in the aspects of etiology, drug response, and survival time [21, 22]. Mutation in the gene encoding epidermal growth factor receptor (*EGFR*) is highly correlated with treatment response to *EGFR* tyrosine kinase inhibitors, and the East Asian population has the highest frequency of *EGFR* mutation in the world. The me-

Figure 2. Effects of gender (A), age (B), and tumor histology (C) on the survival advantage provided by adjuvant chemotherapy among patients with stage II non-small cell lung cancer.
Abbreviations: CI, confidence interval; HR, hazard ratio; OP, surgery alone; OP+CT, surgery followed by adjuvant chemotherapy.

Figure 3. Effects of gender (A), age (B), and tumor histology (C) on the survival advantage provided by adjuvant chemotherapy among patients with stage IIIA non-small cell lung cancer.

Abbreviations: CI, confidence interval; HR, hazard ratio; OP, surgery alone; OP+CT, surgery followed by adjuvant chemotherapy.

Table 3. Representative studies of adjuvant chemotherapy with platinum-based regimens for resectable non-small cell lung cancer

Study	n of patients	Stage	Population	Stage IA	Stage IB	Stage II	Stage IIIA
Prospective trials							
IALT [5]	1,867	I–III	Global	NS	NS	NS	Beneficial
NCIC JBR.10 [7]	482	IB–II	North America	Not tested	NS	Beneficial	Not tested
ANITA [6]	840	IB–IIIA	Europe, America, South Africa	Not tested	NS	Beneficial	Beneficial
ALPI [10]	1,209	I–IIIA	Europe	NS	NS	NS	NS
Big Lung Trial [9]	381	I–IIIA	UK	NS	NS	NS	NS
CALGB 9633 [18]	344	IB	USA	Not tested	NS	Not tested	Not tested
Meta-analyses							
LACE [8]	4,584	I–III	Global	NS	NS	Beneficial	Beneficial
Current study	2,231	I–IIIA	Asia (Taiwan)	NS	NS	Beneficial	Beneficial

Abbreviations: ALPI, Adjuvant Lung Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; CALGB, Cancer and Leukemia Group B; LACE, Lung Adjuvant Cisplatin Evaluation; NCIC, National Cancer Institute of Canada; NS, not significant.

dian survival time of Asian patients receiving combination chemotherapy exceeds that of white patients with similar clinical characteristics and who have undergone similar treatments. For example, a 3-month difference in the median survival time was demonstrated between Japanese and white patients undergoing the same paclitaxel plus carboplatin regimen [23]. In a randomized study comparing gemcitabine plus cisplatin with pemetrexed plus cisplatin, the HR for OS among East Asian versus white patients was 0.65 [24]. Nevertheless, our data suggest that platinum-based adjuvant chemotherapy provides a survival advantage for East Asian patients at least equal to that afforded white patients. These findings support the applicability to Asian populations of the current guidelines related to adjuvant chemotherapy based mainly on data from western countries.

CONCLUSIONS

Adjuvant chemotherapy including a platinum-based regimen should be considered in the treatment plan for patients with resected stage II and stage IIIA NSCLC. The lower risk for death provided by platinum-based adjuvant chemotherapy among the Asian population is comparable with that found in the lit-

erature, which is based mainly on data from white patients. Future research should explore biomarkers to identify patient subgroups most likely to benefit from adjuvant chemotherapy in both Asian and western countries.

ACKNOWLEDGMENTS

This study was supported by the Bureau of Health Promotion, Department of Health, Taiwan (Taiwan Cancer Registry Project) and by grants from the Science and Technology Unit, Department of Health, Taiwan (DOH99-TD-B-111-001, DOH100-TD-B-111-001).

AUTHOR CONTRIBUTIONS

Conception/design: Zhong-Zhe Lin, Chih-Hsin Yang, Mei-Shu Lai
Financial and administrative support: Chih-Hsin Yang, Mei-Shu Lai
Provision of study material or patients: Chih-Hsin Yang, Mei-Shu Lai
Collection and/or assembly of data: Zhong-Zhe Lin, Wen-Yi Shau, Yu-Yun Shao, Yen-Yun Yang, Raymond Nien-Chen Kuo
Data analysis and interpretation: Zhong-Zhe Lin, Wen-Yi Shau, Yu-Yun Shao, Yen-Yun Yang, Raymond Nien-Chen Kuo, Chih-Hsin Yang, Mei-Shu Lai
Manuscript writing: Zhong-Zhe Lin, Wen-Yi Shau, Chih-Hsin Yang, Mei-Shu Lai
Final approval of manuscript: Zhong-Zhe Lin, Wen-Yi Shau, Yu-Yun Shao, Yen-Yun Yang, Raymond Nien-Chen Kuo, Chih-Hsin Yang, Mei-Shu Lai

REFERENCES

- Bordoni R. Consensus conference: Multimodality management of early- and intermediate-stage non-small cell lung cancer. *The Oncologist* 2008;13:945–953.
- Chhatwani L, Cabebe E, Wakelee HA. Adjuvant treatment of resected lung cancer. *Proc Am Thorac Soc* 2009;6:194–200.
- Immerman SC, Vanecko RM, Fry WA et al. Site of recurrence in patients with stages I and II carcinoma of the lung resected for cure. *Ann Thorac Surg* 1981;32:23–27.
- Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995;311:899–909.
- Arriagada R, Bergman B, Dunant A et al.; International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351–360.
- Douillard JY, Rosell R, De Lena M et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A randomised controlled trial. *Lancet Oncol* 2006;7:719–727.
- Winton T, Livingston R, Johnson D et al.; National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;352:2589–2597.
- Pignon JP, Tribodet H, Scagliotti GV et al.; LACE Collaborative Group. Lung Adjuvant Cisplatin Evaluation: A pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008;26:3552–3559.
- Waller D, Peake MD, Stephens RJ et al. Chemotherapy for patients with non-small cell lung cancer: The surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004;26:173–182.
- Scagliotti GV, Fossati R, Torri V et al.; Adjuvant Lung Project Italy/European Organisation for Research Treatment of Cancer-Lung Cancer Cooperative Group Investigators. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 2003;95:1453–1461.
- Pisters KM, Evans WK, Azzoli CG et al.; Cancer Care Ontario; American Society of Clinical Oncology.

- Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIa resectable non-small-cell lung cancer guideline. *J Clin Oncol* 2007;25:5506-5518.
12. Ou SH, Ziegler A, Zell JA. Asian ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. *J Thorac Oncol* 2009;4:1083-1093.
13. Lin CC, Hsu HH, Sun CT et al. Chemotherapy response in East Asian non-small cell lung cancer patients harboring wild-type or activating mutation of epidermal growth factor receptors. *J Thorac Oncol* 2010;5:1424-1429.
14. Selvaggi G, Scagliotti GV. Perspectives in adjuvant chemotherapy in NSCLC. *Expert Rev Respir Med* 2007;1:99-110.
15. Taiwan Cancer Registry. Introduction. Available at <http://tcr.cph.ntu.edu.tw/main.php?Page=N1>, accessed July 12, 2012.
16. Parkin DM, Whelan SL, Ferlay J et al. *Cancer Incidence in Five Continents, Volume VIII, No. 155*. Lyon, France: IARC Scientific Publications, 2002.
17. Chiang CJ, Chen YC, Chen CJ et al. Cancer trends in Taiwan. *Jpn J Clin Oncol* 2010;40:897-904.
18. Fritz A, Percy C, Jack A et al. *International Classification of Diseases for Oncology (ICD-O)*. 3rd ed. Geneva, Switzerland: World Health Organization, 2000.
19. Green FL, Page DL, Fleming ID et al. Liver including intrahepatic bile ducts. In: *AJCC Cancer Staging Handbook, Sixth Edition*. New York: Springer, 2002; 131-144.
20. Strauss GM, Herndon JE 2nd, Maddaus MA et al. 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. *J Clin Oncol* 2008;26:5043-5051.
21. Yang CH. EGFR tyrosine kinase inhibitors for the treatment of NSCLC in East Asia: Present and future. *Lung Cancer* 2008;60(suppl 2):S23-S30.
22. Lin ZZ, Yang CH. Current roles and future perspectives of epidermal growth factor receptor tyrosine kinase inhibitors in advanced non-small-cell lung cancer. *Eur J Clin Med Oncol* 2010; vol. 2, issue 3.
23. Gandara DR, Kawaguchi T, Crowley J et al. Japanese-US common-arm analysis of paclitaxel plus carboplatin in advanced non-small-cell lung cancer: A model for assessing population-related pharmacogenomics. *J Clin Oncol* 2009;27:3540-3546.
24. Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543-3551.

See www.TheOncologist.com for supplemental material available online.