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Propensity-matched analysis of adjuvant chemotherapy for completely resected Stage IB non-small-cell lung cancer patients

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ABSTRACT

Background: The use of adjuvant chemotherapy (ACT) in completely resected stage IB non-small cell lung cancer (NSCLC) is still controversial. The divergent outcomes of prospective trials have created uncertainty as to the utility of ACT in stage IB NSCLC. This study assesses the effect of postoperative adjuvant chemotherapy in stage IB patients in clinical practice.

Methods: Patients with pT2aN0M0 stage IB NSCLC who underwent complete resection from 2004 to 2015 were identified from prospectively collected databases in two medical centers. The log-rank test was used to compare overall survival (OS) and disease free survival (DFS). Fine and Gray's competing risks regression model was built to identify predictors of cancer-specific survival. One to one propensity-score matching (PSM) was performed to reduce the selection bias and additional analyses were performed on these subgroups.

Results: Of 1005 patients identified for the study, 202 (20.1%) received ACT and 803 (79.9%) underwent surgery alone (observation group). Compared with the observation group, patients who underwent ACT were younger ($p < 0.001$), had larger tumors ($p = 0.004$), and had higher rates of squamous cell carcinoma ($p < 0.001$) and lymphovascular invasion ($p = 0.017$). After propensity score matching, 196 pairs of patients were 1:1 matched in the two groups and all baseline characteristics were well balanced. ACT was not associated with improved survival (including OS, DFS; all log-rank $p > 0.05$) in both unmatched and matched (196 pairs) cohorts. In subgroup analysis of the matched population, ACT was not associated with survival benefits for patients regardless of whether their tumors measured < 4 cm or ≥4 cm (both log-rank $p > 0.05$).

Conclusions: In patients with completely resected stage IB (T2aN0M0) NSCLC, ACT is not associated with improved prognosis. Further large multicenter studies are needed to confirm these findings.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide [1]. Surgical resection is the main treatment of choice for early-stage non-small cell lung cancer (NSCLC) [2,3]. Tumor recurrence is the major cause of treatment failure after resection [4,5]. Beginning with the report of a significant survival difference related to receipt of adjuvant chemotherapy (ACT) from the International Adjuvant Lung Cancer Trial (IALT) [6], five multi-institutional randomized controlled trials (RCTs) have demonstrated statistically significant survival advantages associated with ACT for patients with completely resected NSCLC [6–10]. Since then, ACT has become standard of care for resected stages II and III NSCLC patients. Because stage IB patients were also eligible to participate in each trial, one question is whether sufficient evidence exists to routinely recommend ACT for patients with stage IB NSCLC. The National Comprehensive Cancer Network (NCCN) guideline suggests consideration of ACT for stage IB patients with high-risk features, especially tumors larger than 4 cm [2]. The European Society for Medical Oncology (ESMO) guideline states that ACT can be considered in patients with resected stage IB disease and a primary tumor > 4 cm [11]. The American Society of Clinical Oncology (ASCO) guideline, however, differs in its recommendations and adjuvant cisplatin-based

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chemotherapy is not recommended for routine use in these patients [12].

The Cancer and Leukemia Group B (CALGB) 9633 trial is the only multi-institutional RCT designed specifically for stage IB NSCLC to date and demonstrated no benefit from postoperative ACT. Only a post-hoc subgroup analysis demonstrated a significant survival difference in favor of ACT for patients who had tumors ≥ 4 cm in diameter [10]. However, a point worthy of mention is the progressive increase in mortality hazard ratios [10,13,14]. An updated survival analysis of the National Cancer Institute of Canada Clinical Trials Group and the National Cancer Institute of the United States Intergroup Trial (JBR-10) with a median follow-up of 9.3 years showed a persistent benefit in survival for ACT. However, this benefit appeared to be confined to N1 patients [15]. Interestingly, the positive survival advantage reported in IALT first in 2004 was no longer evident after 90 months follow up [16]. Finally, the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis did not show any benefit of ACT for stage I NSCLC patients [17]. In addition to these trials, prior population-based studies have many biases, lack analyses of disease specific survival (DSS), and fail to include many important clinical data that may influence overall survival (OS) [18–20].

The purpose of our study was to evaluate further the role of platinum-based doublet ACT in patients with completely resected stage IB (T2aN0M0) NSCLC in a clinical setting by using data from prospectively collected databases in two medical centers in China.

2. Methods

2.1. Patients and adjuvant chemotherapy

Patients with pathologic stage IB (T2aN0M0) NSCLC who underwent complete resection (by either VATS or thoracotomy) from 2004 to 2015 were identified from prospectively collected databases in two medical centers in China. Pathologic staging was based on the American Joint Committee on Cancer (AJCC) seventh edition staging criteria [21]. Exclusion criteria were: neoadjuvant chemotherapy, positive surgical margins, death within 1 month after resection, or inadequate follow-up information. Only patients who received chemotherapy starting within 120 days from surgical resection were included [22].

The indication for platinum-based ACT in the two institutions was pathologic stage II-IV disease after surgical resection. The use of ACT and the regimens used for ACT in patients with stage IB disease were not randomized but took place according to physician recommendations based on patient and tumor conditions. Four cycles of platinum-based doublet chemotherapy were typically administered in the adjuvant setting.

2.2. Patient follow-up

Routine follow up after completing treatment included an outpatient department visit every 3 months for the first 2 years and at 6-

Table 1
Clinicopathological characteristics of patients before and after PSM.

Characteristic	Before PSM			After PSM		
	Observation (n = 803)	ACT (n = 202)	P value	Observation (n = 196)	ACT (n = 196)	P value
Age (years)	64.0 ± 10.1	59.6 ± 9.5	**< 0.001***	59.1 ± 11.0	60.0 ± 9.3	0.511
Sex			0.230			0.919
Male	459 (57.2)	106 (52.5)		105 (53.6)	104 (53.1)	
Female	344 (42.8)	96 (47.5)		91 (46.4)	92 (46.9)	
Comorbid conditions			0.602			0.746
No	525 (65.4)	136 (67.3)		134 (68.4)	131 (66.8)	
Yes	278 (34.6)	66 (32.7)		62 (31.6)	65 (33.2)	
Smoking status			0.723			0.605
Never	488 (60.8)	120 (59.4)		122 (62.2)	117 (59.7)	
Current or prior	315 (39.2)	82 (40.6)		74 (37.8)	79 (40.3)	
Tumor size (cm)	2.8 ± 1.0	3.1 ± 1.2	**0.004***	3.0 ± 1.1	3.1 ± 1.2	0.576
Histologic type			**< 0.001***			0.543
Adenocarcinoma	687 (85.6)	152 (75.3)		155 (79.1)	150 (76.5)	
Squamous cell carcinoma	116 (14.4)	50 (24.7)		41 (20.9)	46 (23.5)	
Differentiation			0.066			0.822
Well/moderate	611 (76.1)	141 (69.8)		142 (72.4)	140 (71.4)	
Poor (including neuroendocrine tumors)	192 (23.9)	61 (30.2)		54 (27.6)	56 (28.6)	
Visceral pleural invasion			0.372			0.725
No	228 (28.4)	51 (25.3)		47 (24.0)	50 (25.5)	
Yes	575 (71.6)	151 (74.7)		149 (76.0)	146 (74.5)	
Lymphovascular invasion			**0.017***			0.652
No	739 (92.0)	175 (86.6)		169 (86.2)	172 (87.8)	
Yes	64 (8.0)	27 (13.4)		27 (13.8)	24 (12.2)	
Extent of resection			0.975			0.863
Lobectomy	732 (91.2)	184 (91.1)		177 (90.3)	178 (90.8)	
Wedge resection	71 (8.8)	18 (8.9)		19 (9.7)	18 (9.2)	
Lymph node resection type			0.725			0.334
Lymph node dissection	754 (93.9)	191 (94.6)		189 (96.4)	185 (94.4)	
Lymph node sampling	49 (6.1)	11 (5.4)		7 (3.6)	11 (5.6)	
Postoperative complications			0.279			0.550
No	737 (91.8)	190 (94.1)		181 (92.4)	184 (93.9)	
Yes	66 (8.2)	12 (5.9)		15 (7.6)	12 (6.1)	

Continuous variables are reported as median (interquartile range) or mean ± standard deviation. Dichotomous variables are reported as number (%). *PSM*, propensity score matching; *ACT*, adjuvant chemotherapy; *SD*, standard deviation. Comorbid conditions include chronic obstructive pulmonary disease (COPD), cardiovascular diseases, diabetes, and renal insufficiency. Postoperative complications include arrhythmia, atelectasis, pneumonia, mechanical ventilation > 24 h, embolism and thrombosis, heart failure, and acute kidney injury in this study. Bold value, statistical significance.

month intervals thereafter. For patients who failed to present at follow up clinic, follow-up information was also obtained by telephone call. Follow-up evaluation included physical examination, chest CT scan, and blood tests including relevant tumor markers. When any symptom or sign of recurrence was observed, further examinations including chest and abdominal CT scans, brain magnetic resonance imaging, bone scintigraphy and positron emission tomography were also performed. We diagnosed recurrence based on a relevant physical examination and diagnostic imaging and confirmed the diagnosis histologically when clinically feasible. A secondary primary lung cancer was differentiated from recurrent NSCLC according to the criteria proposed by Girard and colleagues [23]. The duration of overall survival (OS) was defined as the interval between the date of surgical resection and the date of death from any cause. Time to recurrence (disease free survival [DFS]) was defined as the interval between the date of surgical resection and the date of the first event (locoregional or distant recurrence or death from any cause). Cancer-specific survival (CSS) was defined as the time from the date of initial surgery until the date of death from the initial lung cancer. Patients who had no documented evidence of events were censored at the date of last follow-up.

Table 2
Univariable and multivariable analyses of overall survival and disease-free survival.

	Univariate analysis			Multivariate analysis		
Variable	HR/SHR	95% CI	P value	HR/SHR	95% CI	P value
Overall survival						
Age	1.048	1.028–1.069	< **0.001**	1.035	1.015–1.055	< **0.001**
Female sex	0.423	0.284–0.630	< **0.001**	0.596	0.372–0.954	**0.031**
Comorbid conditions	1.511	1.061–2.152	**0.022**	1.243	0.858–1.801	0.249
Positive smoking history	1.976	1.380–2.828	< **0.001**	1.133	0.740–1.735	0.566
Size	1.452	1.243–1.697	< **0.001**	1.293	1.078–1.550	**0.006**
Squamous cell carcinoma	1.836	1.244–2.712	**0.002**	0.871	0.564–1.346	0.535
Poor differentiation	2.476	1.740–3.525	< **0.001**	1.905	1.319–2.752	**0.001**
Visceral pleural invasion	0.443	0.311–0.630	< **0.001**	0.751	0.493–1.146	0.184
Lymphovascular invasion	1.672	0.842–3.320	0.142			
Wedge resection	1.783	1.068–2.977	**0.027**	1.336	0.681–2.620	0.399
Lymph node sampling	2.560	1.556–4.213	< **0.001**	2.185	1.164–4.100	**0.015**
Postoperative complications	1.115	0.600–2.072	0.730			
Adjuvant chemotherapy	0.765	0.494–1.183	0.228			
Cancer-specific overall survival						
Age	1.039	1.016–1.062	**0.001**	1.031	1.009–1.054	**0.006**
Female sex	0.486	0.317–0.744	**0.001**	0.659	0.380–1.145	0.139
Comorbid conditions	1.268	0.852–1.887	0.242			
Positive smoking history	1.661	1.117–2.468	**0.012**	0.999	0.619–1.610	0.995
Size	1.504	1.272–1.777	< **0.001**	1.297	1.065–1.579	**0.010**
Squamous cell carcinoma	1.657	1.054–2.607	**0.029**	0.803	0.492–1.308	0.378
Poor differentiation	3.171	2.140–4.699	< **0.001**	2.509	1.649–3.818	< **0.001**
Visceral pleural invasion	0.446	0.301–0.660	< **0.001**	0.766	0.478–1.230	0.270
Lymphovascular invasion	2.096	1.047–4.193	**0.037**	1.517	0.740–3.112	0.255
Wedge resection	1.209	0.628–2.328	0.570			
Lymph node sampling	1.564	0.796–3.073	0.195			
Postoperative complications	1.476	0.776–2.810	0.236			
Adjuvant chemotherapy	0.801	0.505–1.272	0.347			
Disease-free survival						
Age	1.029	1.015–1.043	< **0.001**	1.023	1.010–1.037	**0.001**
Female sex	0.764	0.584–1.000	**0.050**	0.948	0.715–1.257	0.709
Comorbid conditions	1.076	0.820–1.413	0.597			
Positive smoking history	1.215	0.934–1.582	0.147			
Size	1.255	1.117–1.410	< **0.001**	1.174	1.026–1.344	**0.019**
Squamous cell carcinoma	1.248	0.906–1.718	0.175			
Poor differentiation	1.910	1.460–2.499	< **0.001**	1.667	1.266–2.197	< **0.001**
Visceral pleural invasion	0.647	0.493–0.849	**0.002**	0.880	0.641–1.208	0.429
Lymphovascular invasion	1.309	0.772–2.219	0.317			
Wedge resection	1.043	0.659–1.652	0.856			
Lymph node sampling	2.063	1.367–3.113	**0.001**	1.921	1.269–2.909	**0.002**
Postoperative complications	1.174	0.742–1.859	0.494			
Adjuvant chemotherapy	0.764	0.550–1.062	0.109			
Cancer-specific disease-free survival						
Age	1.022	1.008–1.037	**0.002**	1.019	1.004–1.033	**0.010**
Female sex	0.869	0.659–1.147	0.321			
Comorbid conditions	0.930	0.695–1.246	0.629			
Positive smoking history	1.049	0.789–1.394	0.742			
Size	1.249	1.109–1.405	< **0.001**	1.163	1.017–1.329	**0.027**
Squamous cell carcinoma	1.104	0.771–1.582	0.589			
Poor differentiation	2.090	1.574–2.773	< **0.001**	1.878	1.412–2.498	< **0.001**
Visceral pleural invasion	0.685	0.513–0.916	**0.011**	0.929	0.670–1.287	0.659
Lymphovascular invasion	1.455	0.850–2.490	0.172			
Wedge resection	0.721	0.412–1.262	0.252			
Lymph node sampling	1.422	0.870–2.322	0.160			
Postoperative complications	1.370	0.858–2.188	0.187			
Adjuvant chemotherapy	0.783	0.558–1.100	0.158			

HR, hazard ratio; *SHR*, subhazard ratio; *CI*, confidence interval; Bold value, statistical significance.

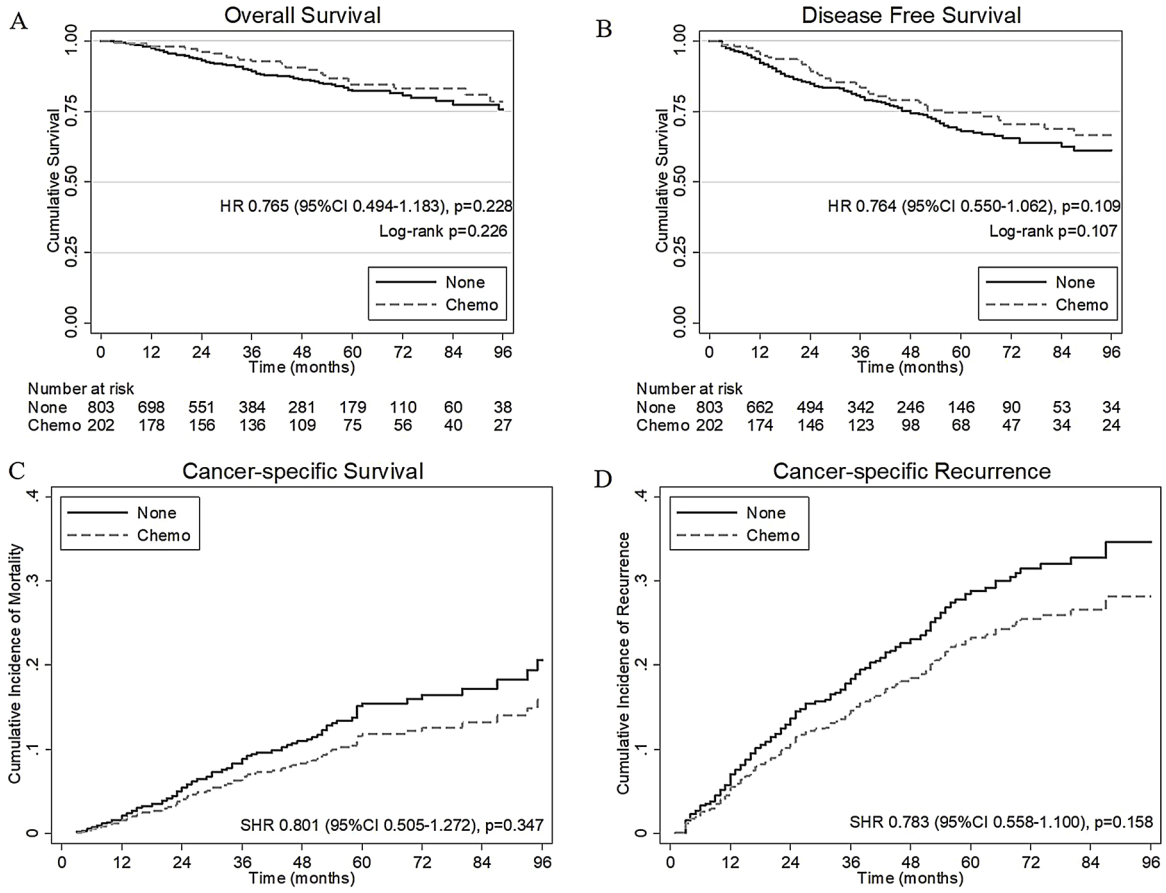

Fig. 1. Kaplan-Meier survival curves of OS (A) and DFS (B), and cumulative incidence of disease-specific death (C) and recurrence (D) for patients with adjuvant chemotherapy(Chemo) or not (None) before PSM.

2.3. Statistical analysis

Patients were divided into two cohorts: those who underwent ACT and those who did not (surgery only; observation group). Continuous variables were compared by using the Student's *t*-test and categorical variables were compared by using the Pearson's χ^2 test. The Kaplan-Meier method with log-rank test was performed to compare the survival curves for OS and DFS. Competing risks analysis was used to analyze cancer-specific OS (CS-OS), with any death not caused by lung cancer considered a competing event, and cancer-specific DFS (CS-DFS), with any death without recurrence considered a competing event. A Cox proportional hazards regression model was constructed to examine predictors of OS and DFS, while a competing risks regression model (Fine and Gray) [24] was built to identify predictors to cancer-specific survival. Multivariable regression models were constructed incorporating factors with $p < 0.10$ identified in univariate analyses.

Propensity score matching (PSM) was performed to reduce the potential effects of selection bias. A logistic regression model was established to calculate the propensity score based on the following covariates: age, sex, comorbid condition, smoking history, tumor size, histologic type, histologic grade, visceral pleural invasion, lymphovascular invasion, surgical procedures, and postoperative complication

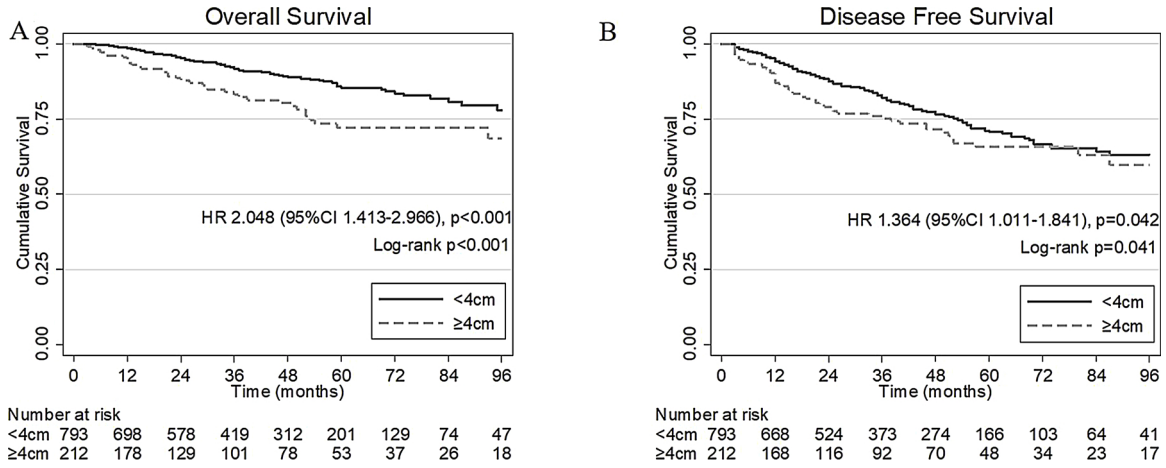

Fig. 2. Kaplan-Meier survival curves of OS (A) and DFS (B) for patients with different tumor sizes.

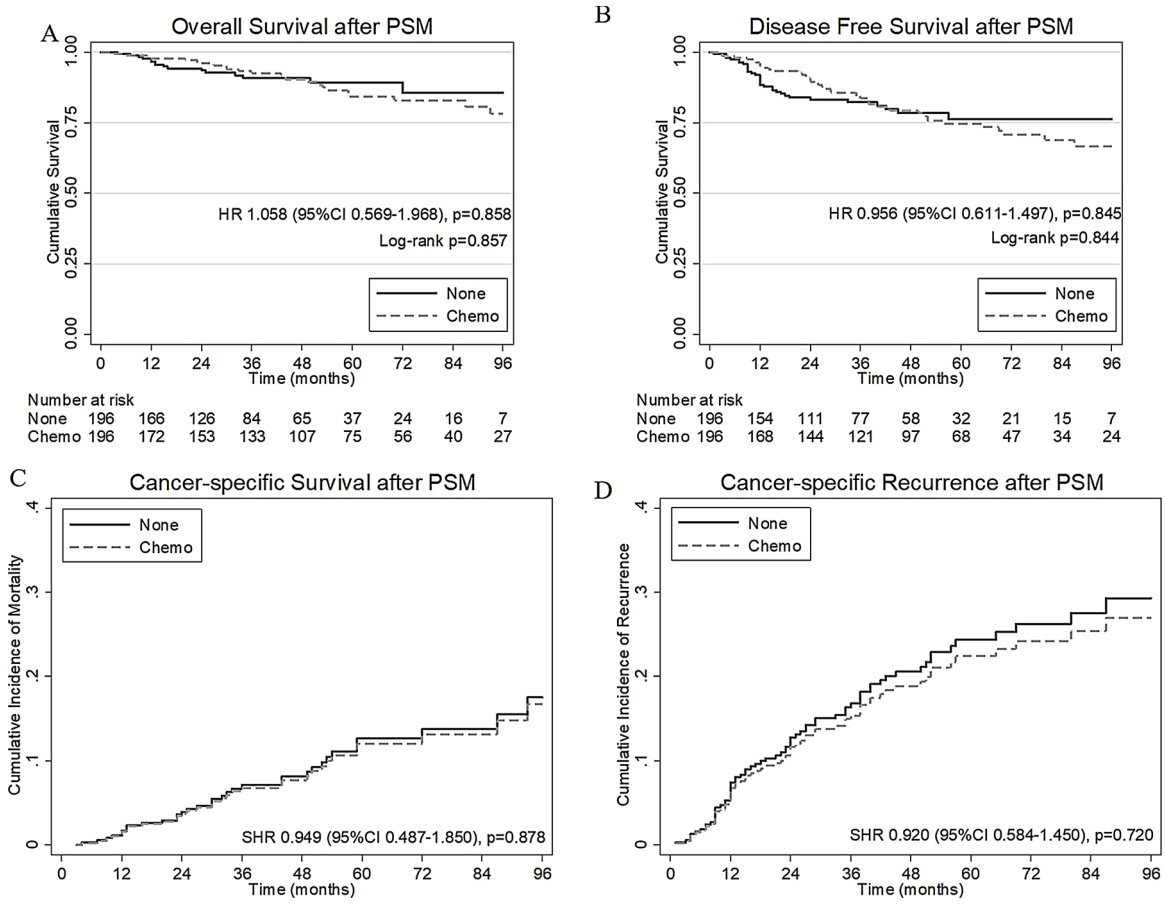

Fig. 3. Kaplan-Meier survival curves of OS (A) and DFS (B), and cumulative incidence of disease-specific death (C) and recurrence (D) for patients with adjuvant chemotherapy(Chemo) or not (None) after PSM.

condition. Patients who received ACT were matched with patients who underwent surgery only by a 1:1 greedy algorithm without replacement (caliper = 0.10).

Statistical analyses were performed using Stata/SE 14.0 for Windows (StataCorp, College Station, TX). All the statistical tests were two-sided and p values of 0.05 or less were considered statistically significant.

3. Results

3.1. Clinicopathological characteristics

Of 1005 patients identified in the study, 202 (20.1%) received ACT and 803 (79.9%) underwent surgery alone. Detailed information regarding adjuvant chemotherapy was available for 171 of 202 (84.7%) patients in the ACT group. The most commonly used regimens were pemetrexed plus cisplatin (54; 31.6%), paclitaxel plus carboplatin (43; 25.1%), gemcitabine plus cisplatin (35; 20.5%), pemetrexed plus carboplatin (17; 10.0%) and gemcitabine plus carboplatin (8; 4.7%). Other rarely used regimens included docetaxel plus cisplatin, paclitaxel plus cisplatin, and vinorelbine plus cisplatin. Five patients received only a single chemotherapeutic agent. Nearly 90% percent of ACT patients (153 in 171) received 3 or more cycles of adjuvant of chemotherapy.

The median follow up was 37 (range 3–164) months. Compared with the observation group, patients who underwent ACT were younger ($p < 0.001$), had larger tumors ($p = 0.004$), and had higher rates of squamous cell carcinoma ($p < 0.001$) and lymphovascular invasion ($p = 0.017$). There were no significant differences in the distribution of the other baseline characteristics between the two groups. After propensity score matching, 196 pairs of patients were 1:1 matched in the two groups and all baseline characteristics were well-balanced. Details of each confounding variable before and after matching are summarized in Table 1. Standardized difference plots for variables and mirror histograms for propensity scores are provided in the Supplementary material.

3.2. Survival analyses

Results of univariable and multivariable Cox proportional hazards regression and competing risks regression for the entire cohort are summarized in Table 2. In multivariable analyses, age, tumor size, and tumor differentiation were independent prognostic factors for cancer-specific survival, including both CS-OS and CS-DFS. Patients who were older, had larger tumors, or had poorly differentiated tumors had worse cancer specific prognosis. Lymph node resection status (sampling vs dissection) was an independent favorable predictor for DFS, and both lymph node resection status and female gender were independent favorable predictors for OS. Adjuvant chemotherapy was not a predictor for prognosis either in univariable or in multivariable analysis.

Before propensity score matching, no significant survival difference was observed between patients treated with ACT and those who only underwent surgical resection (OS: HR 0.765, 95%CI 0.949–1.183, $p = 0.228$; DFS: HR 0.764, 95%CI 0.550–1.062, $p = 0.109$; CS-OS: SHR 0.801, 95%CI 0.505–1.272, $p = 0.347$; CS-DFS: SHR 0.783, 95%CI 0.558–1.100, $p = 0.158$; Fig. 1). The survival outcome of patients was assessed according to tumor size using a 4 cm diameter threshold. Patients with larger tumors (≥ 4 cm) had significantly worse OS and DFS than those with smaller tumors (< 4 cm) (OS: HR 2.048, 95%CI 1.413–2.966, $p < 0.001$; DFS: HR 1.364, 95%CI 1.011–1.841, $p = 0.042$; Fig. 2).

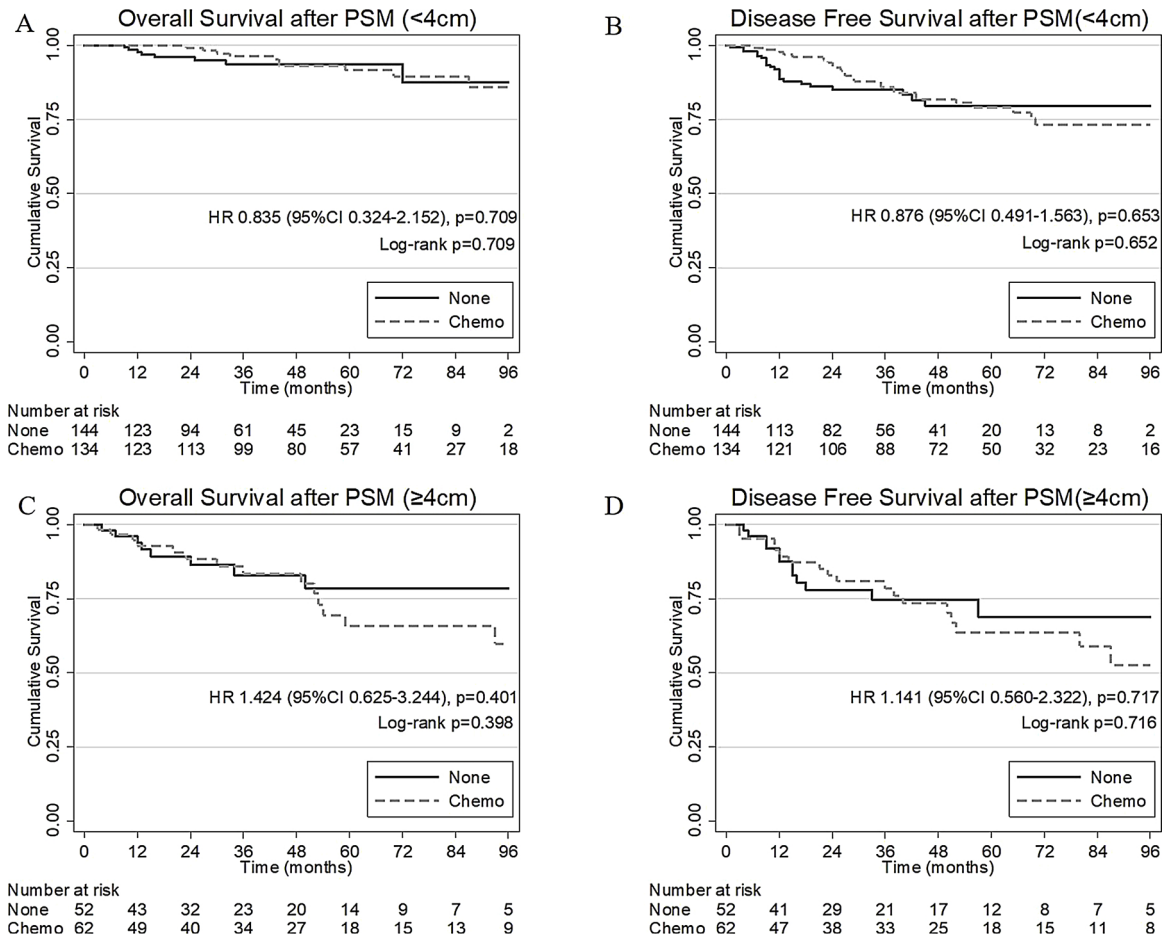

Fig. 4. Kaplan-Meier survival curves of OS (A) and DFS (B) for adjuvant chemotherapy(Chemo) group or none group of patients with tumor < 4 cm after PSM; Kaplan-Meier survival curves of OS (C) and DFS (D) for adjuvant chemotherapy(Chemo) group or none group of patients with tumor ≥ 4 cm after PSM.

Propensity score matching was performed to balance confounding covariates across treatment groups. After matching, ACT was not associated with improved survival outcomes either (OS: HR 1.058, 95%CI 0.569-1.968, p = 0.858; DFS: HR 0.956, 95%CI 0.611–1.497, p = 0.845; CS-OS: SHR 1.000, 95%CI 0.520–1.924, p = 1.000; CS-DFS: SHR 0.920, 95%CI 0.584–1.450, p = 0.720; Fig. 3). Subgroup analysis stratified by tumor size was also performed in the matched population (Fig. 4). ACT did not contribute to a survival benefit for patients with small tumors (< 4 cm) unsurprisingly (OS: HR 0.835, 95%CI 0.324–2.152, p = 0.709; DFS: HR 0.876, 95%CI 0.491–1.563, p = 0.653). For patients with large tumors (≥ 4 cm), there was no significant survival difference between the ACT and observation groups (OS: HR 1.424, 95%CI 0.625–3.244, p = 0.401; DFS: HR 1.141, 95%CI 0.560–2.322, p = 0.717).

4. Discussion

Five-year survival improvement of 5%–10% has been reported for cisplatin-based ACT in multiple large randomized clinical trials [6–10] and meta-analyses [17,25]. Most of the positive results were reported in randomized clinical trials involving completely resected stage II and IIIA NSCLC [6–9]. However, these trials were not powered to specifically assess the potential benefits of chemotherapy for stage IB patients. Only one large randomized trial, CALGB9633, focused on completely resected T2N0 tumors, and there were no differences in overall survival and disease-free survival associated with adjuvant therapy [10]. As a result, whether ACT benefits patients with resected stage IB NSCLC remains controversial.

Although several retrospective studies reported potential benefits of ACT in this group of patients, uncertainty remains. Park et al. [18] found that platinum-based ACT might offer better survival than observation alone for stage IB patients. Tsutani and colleagues [19] reported that DFS and OS were considerably better in patients who received ACT. In a study by Hung et al. [20], only freedom from recurrence was found to be associated with adjuvant chemotherapy, with no difference in OS between the two groups. In a large retrospective analysis from the National Cancer Data Base (NCDB) that included 25,267 patients with completely resected T2N0M0 NSCLC [26], ACT was associated with improved survival even in patients with tumors smaller than 4 cm. Although the authors used propensity-matched analysis to help mitigate selection bias, the lack of relevant clinical variables in the dataset that may have influenced survival outcomes is of concern. In the current study, detailed clinical information was collected including comorbidities, smoking history, resection condition, lymph node resection condition and postoperative complications, any of which may influence survival results.

The lack of prognostic influence demonstrated for ACT in this study contrasts with many previous reports. Before PSM, we identified a mild survival advantage in the ACT group, particularly for DFS, which was not statistically significant. The two groups were different with regards to tumor size and rates of lymphovascular invasion, and patients with ACT were much younger and experienced fewer post-operative complications which may have led to better survival. Therefore, we used PSM to minimize imbalances between the groups and the resultant analyses demonstrated no survival advantage associated with ACT. Based on the detailed clinical information available in our study, which helps provide more accurate survival analyses, our study helps focus attention on whether adjuvant chemotherapy has utility in patients

with R0 resected stage IB NSCLC.

The survival time after cancer recurrence may be quite long and varies among patients with differing performance status, treatment regimens, and economic status [4,27–29]. Patients in this study were of pure Asian ethnicity, which has a higher incidence of adenocarcinoma than in Western populations. Asian patients have a higher possibility of having EGFR mutations that are sensitive to targeted therapy. Such patients have more treatment options when they relapse, and have longer OS after recurrence than EGFR wild type patients [27]. Therefore, OS may not be the optimal metric for assessing the prognostic value of ACT in this group of patients. DFS may be more accurate for addressing this question. However, neither OS results nor DFS results demonstrated any survival benefits from ACT in current study.

Many stage I patients, especially those older than 60 years, have a high rate of comorbidities [30,31], which is associated with a high risk of competing non-cancer events. Therefore, it is important to consider competing risks when evaluating their prognosis. CS-OS and CS-DFS use cancer death as the endpoint and censors people dying of other causes of death. This assessment may be more accurate than OS when evaluating whether ACT provides a survival advantage for patients with stage IB NSCLC. Regardless none of our analyses demonstrated any survival benefit from ACT for completely resected stage IB NSCLC patients.

An inclusion criterion of this study was pathological stage IB non-small cell lung cancer according to AJCC/UICC 7 [21]. Therefore, we only included tumors ≤ 5 cm in diameter. When the eighth edition of AJCC/UICC stage classification for lung cancer took effect in January 2018, some previous stage IB tumors were assigned to stage IIA (tumor diameter > 4 cm but ≤ 5 cm) [3]. Considering that the current NCCN guidelines include the same post-operative treatment recommendations for stages IB and IIA NSCLC, this change in staging had no influence on our study design. Nevertheless, a key question arises regarding AJCC/UICC 7 stage IIA (T2bN0) patients whose tumors are > 5 cm but ≤ 7 cm. These patients are grouped into stage IIB because of tumor size in the eighth edition AJCC/UICC stage classification, and are recommended for adjuvant chemotherapy by NCCN guidelines. However, this recommendation lacks supporting evidence.

Our study should be interpreted with caution because of several limitations. There was patient selection bias, as the choice of ACT was not randomized but instead reflected physician and patient preferences. In addition, we lacked detailed chemotherapy information for about 15% patients in the ACT group. Importantly, the chemotherapy regimens were not consistent in the adjuvant group, and we could not definitely conclude that no platinum-based ACT had benefit for stage IB lung cancer. Finally, we did not include subtypes of adenocarcinoma in our analyses. The subclassification of adenocarcinoma is an important factor in considering ACT for stage IB tumors. Several population-based studies have found a poorer prognosis in patients with solid or micropapillary patterns [32–35], and one of them demonstrated that ACT was associated with survival benefit in patients with these subtypes. However, ACT did not contribute to a survival benefit for propensity score-matched patients overall [35]. Subtyping adenocarcinoma may aid in the selection of patients who will benefit from ACT and contribute to the management of patients with stage IB lung adenocarcinoma.

5. Conclusion

We found that adding ACT after complete resection in patients with stage IB NSCLC was not associated with improved survival. Caution should be exercised when recommending ACT for this group of patients. Additional large multicenter studies are needed to help settle this controversy.

Conflict of interest

The authors have no relevant interests to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.04.024.

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