Prognostic value of upper paratracheal lymph node resection in stage IB right-sided lung cancer: A retrospective cohort study

FENG WANG[1*], XIANGYANG YU[2*], YI HAN[1], LANJUN ZHANG[3] and SHUKU LIU[1]

[1]Department of Minimally Invasive Surgery, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing 101149, P.R. China; [2]Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer, Cancer Hospital and Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, Guangdong 518116, P.R. China; [3]State Key Laboratory of Oncology in South China, Department of Thoracic Surgery, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P.R. China

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Abstract. The aim of the present study was to investigate the impact of upper paratracheal lymph node resection on the prognosis of patients with stage IB non-small cell lung cancer (NSCLC). A retrospective analysis of 339 patients with upper lobe stage IB NSCLC who underwent surgery at Sun Yat-Sen University Cancer Center (Guangzhou, China) between 1999 and 2009 was conducted. The Cox regression model was used to investigate prognostic factors. Variables with P<0.1 in univariate analysis were incorporated into multivariate analysis. A 1-to-1 propensity score matching (PSM) was conducted to decrease potential bias when comparing the impact of upper paratracheal lymph node resection on survival outcomes. Following PSM, 202 cases were identified. Kaplan-Meier analysis and log-rank test were used to assess recurrence-free survival (RFS) and overall survival (OS). Of the 339 patients identified, 152 did not undergo resection of upper paratracheal lymph node, while 187 did undergo the surgery. Cases were separated into two groups based on the resection of the upper paratracheal lymph node. Cox regression analysis demonstrated that a family history of malignant tumors and smoking were considered significant prognostic variables for OS. Age and family history of malignant tumors were significant independent prognostic variables for RFS. Resection of the upper paratracheal lymph node was not significantly associated with OS and RFS. Additionally, resection of the upper paratracheal lymph node was not significantly associated with OS and RFS. In conclusion, there was no statistical association between upper paratracheal lymph node resection and OS or RFS for patients with stage IB NSCLC. Therefore, upper paratracheal lymph node resection may not be necessary for patients with early stage NSCLC, and application of this knowledge could reduce unnecessary surgical trauma and decrease lymph node-related complications.

Correspondence to: Professor Shuku Liu, Department of Minimally Invasive Surgery, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, 9 Beiguan Street, Beijing 101149, P.R. China
E-mail: liushuku@sina.com

Professor Lanjun Zhang, State Key Laboratory of Oncology in South China, Department of Thoracic Surgery, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, 651 Dong Feng East Road, Guangzhou, Guangdong 510060, P.R. China
E-mail: zhanglj@sysucc.org.cn

*Contributed equally

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Introduction

Worldwide, lung cancer has the highest mortality rate of all types of cancer; ~1.8 million people die from lung cancer every year (1). Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, accounts for approximately 85% of all lung cancers (2). Surgery is an essential treatment for patients with early stage NSCLC, and a lobectomy with systematic lymph node dissection (SLND) is regarded as the standard surgical procedure for patients with NSCLC (3,4).

Nonetheless, the use of lymph node dissection in early stage NSCLC remains contentious (5-11). Some studies have suggested that lobe-SLND (LSLND) or lymph node sampling (LNS) yields survival outcomes comparable to those of SLND in patients with early stage NSCLC (12-16). In addition, excessive lymph node dissection and sampling can increase potential postoperative complications such as bleeding, chylothorax and nerve damage (17,18). Furthermore, it has been reported that normal lymph nodes serve an important role in antitumor immunity, and that lymph node dissection may alter endogenous antitumor mechanisms, accelerating tumor growth (17). Therefore, excessive lymph node dissection may not only be unhelpful, but also potentially harmful to patients. The right upper paratracheal lymph nodes (2R lymph nodes) are significant in the development of right-sided lung cancer. However, in LSLND of lower lobe cancer and LNS, the dissection of 2R lymph nodes may be unnecessary. Dissection of the 2R lymph node for right-sided NSCLC is challenging due

to the anatomical constraints imposed by the left innominate vein. Therefore, some surgeons may choose not to dissect the 2R lymph nodes during surgical procedures to treat right lung cancer. Consequently, the present study aimed to investigate the significance of 2R lymph node resection in patients with early stage right lung cancer.

Materials and methods

Patient details. Between January 1999 and October 2009, data was gathered for patients with NSCLC who underwent surgery at the Sun Yat-Sen University Cancer Center (Guangzhou, China). The inclusion criteria used were as follows: i) Patients with stage IB NSCLC located in the right lung; ii) patients treated with a lobectomy; and iii) no prior history of other malignancies. The exclusion criteria used were as follows: i) Patients treated with neoadjuvant chemotherapy; ii) patients who died during the first month after surgery; and iii) patient records with no detailed follow-up data. All pathological specimens were confirmed for pathological results through H&E and immunohistochemical staining. For H&E staining, the specimen was fixed in 10% neutral buffered formalin at 37˚C for 12-18 h. The section thickness was 4 μm. This was followed by staining with hematoxylin-eosin for 3-8 min at 37˚C. Finally, the slides were examined under a light microscope and images (magnification, x200) were acquired. The immunohistochemical staining process was as follows. Initial fixation was performed with 10% neutral buffered formalin solution at 37˚C for 12-18 h, followed by paraffin embedding with a section thickness of 4 μm. The blocking reagent was 3% hydrogen peroxide for 10 min at 37˚C. The primary antibody was working solution (TTF-1, MAB-0677; NapsinA, MAB-0704; p40, RMA-0815; CK5/6, MAB-0744, Fuzhou Maixin Biotechnology Development), undiluted, at 37˚C for 30 min, and the secondary antibody was the working solution (DAKO K8002, Agilent Technologies), undiluted, at 37˚C for 30 min. The conjugate is biotin/streptavidin, which is labeled with horseradish peroxidase (HRP). The final slides were examined under a light microscope (magnification, x200). To clarify the pathological type, immunohistochemical staining indicators are usually thyroid transcription factor-1 (TTF-1), NapsinA, p40 and cytokeratin (CK)5/6. Patients who were positive for TTF-1 and NapsinA were diagnosed with adenocarcinoma, and those who were positive for p40 and CK5/6 were diagnosed with squamous cell carcinoma. If the cytological morphology suggested the possibility of SCLC, synaptophysin and CD56 staining were added. If these stains were positive, the case was diagnosed as SCLC and was not included in this study. All tumors and lymph node samples were evaluated by two experienced senior pathologists who were blinded to the clinical outcomes of the patients. T and N stages were adjusted according to tumor size and lymph node information in the database, and the Tumor-Node-Metastasis stage was determined according to the 8th edition of the International Association for the Study of Lung Cancer staging system (19). A total of 339 patients were included in the study cohort.

Patient follow-up. The follow-up information was obtained by contact with patient's relatives by telephone or collected from the hospital records. Routine examinations, such as blood tests, chest computed tomography scan images and ultrasound images of the abdomen and neck were conducted every 3 months for 2 years, every 6 months for the subsequent 3-5 years and annually thereafter. Brain MRI scans were performed annually and a bone scan was performed based on the patient's symptoms. Overall survival (OS) was determined from the surgery date to the date of death and recurrence-free survival (RFS) was determined from the surgery date to the recurrence date. All patients were monitored until January 2013.

Statistical analysis. The χ^2 test was applied for evaluating categorical variables between two groups. The Kaplan-Meier method and log-rank test were used to estimate OS and RFS. Cox regression analysis was performed both for univariate and multivariate analyses. Variables with a P-value <0.1 in the univariate analysis were included in the multivariate analysis. P<0.05 was considered to indicate a statistically significant difference. Hazard ratios and 95% confidence intervals were calculated to quantify the association between covariates and survival outcomes. Statistical analyses were conducted using R software (version 4.2.0; R Foundation). The 'matchit' package was used to perform propensity score matching (PSM). In PSM analysis, all variables included in the study were included for calculating propensity score, with a caliper width set to 0.3. The survival curves and forest plots were produced utilizing the 'survival' and 'survminer' packages. The X-tile software (version 3.6.1; Yale University) was utilized to ascertain the appropriate cut-off values for resected lymph node counts, which were identified as <12 and ≥12.

Results

Patient characteristics. The baseline characteristics of all 339 patients in the present study are summarized in Table I. The patients were separated into two groups according to whether their upper paratracheal lymph nodes were resected (Yes, n=187 cases/No, n=152 cases). Male patients accounted for most patients in the present study (70.2%). The mean age is 59.5, with a range of 18 to 85 and a total of 34.2% of patients were aged >65 years. Patients with a smoking history and a family history of malignant tumors accounted for 57.5 and 15.9% of all cases, respectively. The pathological grade of most of the cases was I + II (61.7%) and the pathological type was mainly adenocarcinoma (64.6%). The proportion of cases with tumors located in the upper, middle and lower lobes were 53.7, 13.0 and 33.3%, respectively. Patients with visceral pleural invasion and bronchial invasion constituted 61.7 and 25.4% of the total patients, respectively. A total of 31.0% of cases involved the dissection of ≥6 lymph nodes, whereas 61.7% of cases involved the dissection of ≥12 lymph nodes. Chemotherapy was used to treat 15.0% of the patients.

Prognostic factors. Prior to PSM, Cox proportional hazards regression models were applied to explore prognostic factors for OS and RFS. The results of univariate analysis (Table II) and the results of multivariate analysis were summarized (Figs. 1 and 2). Patient age, smoking status, family history of malignant tumor, resected lymph node stations, resected lymph node numbers, upper paratracheal lymph node resection

Table I. Clinicopathological characteristics between original and matched data set.

	Original data set				Matched data set			
		Upper paratracheal lymph node resection				Upper paratracheal lymph node resection		
Variables	Total (n=339)	No (n=152)	Yes (n=187)	P-value	Total (n=202)	No (n=101)	Yes (n=101)	P-value
Sex, n (%)	0.506				0.446			
Female	101 (29.8)	42 (27.6)	59 (31.6)		62 (30.7)	28 (27.7)	34 (33.7)	
Male	238 (70.2)	110 (72.4)	128 (68.4)		140 (69.3)	73 (72.3)	67 (66.3)	
Age, n (%)	0.567				0.659			
>65 years	116 (34.2)	55 (36.2)	61 (32.6)		72 (35.6)	34 (33.7)	38 (37.6)	
≤65 years	223 (65.8)	97 (63.8)	126 (67.4)		130 (64.4)	67 (66.3)	63 (62.4)	
Smoking, n (%)	0.498				0.203			
No	144 (42.5)	61 (40.1)	83 (44.4)		90 (44.6)	40 (39.6)	50 (49.5)	
Yes	195 (57.5)	91 (59.9)	104 (55.6)		112 (55.4)	61 (60.4)	51 (50.5)	
Family history of malignant tumor, n (%)	0.932				>0.999			
No	285 (84.1)	127 (83.6)	158 (84.5)		173 (85.6)	86 (85.1)	87 (86.1)	
Yes	54 (15.9)	25 (16.4)	29 (15.5)		29 (14.4)	15 (14.9)	14 (13.9)	
Grade, n (%)	0.127				>0.999			
I + II	209 (61.7)	101 (66.4)	108 (57.8)		124 (61.4)	62 (61.4)	62 (61.4)	
III + IV	130 (38.3)	51 (33.6)	79 (42.2)		78 (38.6)	39 (38.6)	39 (38.6)	
Histology, n (%)	0.735				0.592			
Adenocarcinoma	219 (64.6)	102 (67.1)	117 (62.6)		140 (69.3)	67 (66.3)	73 (72.3)	
Squamous cell carcinoma	110 (32.4)	46 (30.3)	64 (34.2)		55 (27.2)	31 (30.7)	24 (23.8)	
Others	10 (2.9)	4 (2.6)	6 (3.2)		7 (3.5)	3 (3.0)	4 (4.0)	
Site, n (%)	0.002				0.753			
Right lower lobe	113 (33.3)	52 (34.2)	61 (32.6)		65 (32.2)	35 (34.7)	30 (29.7)	
Right middle lobe	44 (13.0)	30 (19.7)	14 (7.5)		23 (11.4)	11 (10.9)	12 (11.9)	
Right upper lobe	182 (53.7)	70 (46.1)	112 (59.9)		114 (56.4)	55 (54.5)	59 (58.4)	
Visceral pleura invasion, n (%)	>0.999				>0.999			
No	130 (38.3)	58 (38.2)	72 (38.5)		71 (35.1)	35 (34.7)	36 (35.6)	
Yes	209 (61.7)	94 (61.8)	115 (61.5)		131 (64.9)	66 (65.3)	65 (64.4)	
Bronchial invasion, n (%)	0.605				>0.999			
No	253 (74.6)	116 (76.3)	137 (73.3)		159 (78.7)	80 (79.2)	79 (78.2)	
Yes	86 (25.4)	36 (23.7)	50 (26.7)		43 (21.3)	21 (20.8)	22 (21.8)	
Resected lymph node stations, n (%)	<0.001				0.148			
<6	234 (69.0)	129 (84.9)	105 (56.1)		150 (74.3)	80 (79.2)	70 (69.3)	
≥6	105 (31.0)	23 (15.1)	82 (43.9)		52 (25.7)	21 (20.8)	31 (30.7)	
Resected lymph node numbers, n (%)	<0.001				0.472			
<12	130 (38.3)	93 (61.2)	37 (19.8)		80 (39.6)	43 (42.6)	37 (36.6)	
≥12	209 (61.7)	59 (38.8)	150 (80.2)		122 (60.4)	58 (57.4)	64 (63.4)	
Chemotherapy, n (%)	0.847				0.847			
No	288 (85.0)	128 (84.2)	160 (85.6)		170 (84.2)	84 (83.2)	86 (85.1)	
Yes	51 (15.0)	24 (15.8)	27 (14.4)		32 (15.8)	17 (16.8)	15 (14.9)	

Table II. Univariate analysis of overall survival and recurrence free survival before propensity score matching.

		Overall survival		Recurrence-free survival	
Variables	Total, n (%)	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex			0.226		0.379
Female	101 (29.8)	Reference		Reference	
Male	238 (70.2)	1.33 (0.84-2.13)		1.18 (0.81-1.72)	
Age, years			0.001		0.018
65	116 (34.2)	Reference		Reference	
≤65	223 (65.8)	0.52 (0.34-0.77)		0.67 (0.48-0.94)	
Smoking			0.024		0.476
No	144 (42.5)	Reference		Reference	
Yes	195 (57.5)	1.62 (1.06-2.46)		1.13 (0.81-1.58)	
Family history of malignant tumor			0.014		0.006
No	285 (84.1)	Reference		Reference	
Yes	54 (15.9)	0.43 (0.22-0.86)		0.47 (0.27-0.82)	
Grade			0.750		0.866
I + II	209 (61.7)	Reference		Reference	
III + IV	130 (38.3)	1.07 (0.71-1.61)		1.03 (0.73-1.45)	
Histology			0.455		0.306
Adenocarcinoma	219 (64.6)	Reference		Reference	
Others	10 (2.9)	0.36 (0.05-2.60)		0.46 (0.11-1.88)	
Squamous cell carcinoma	110 (32.4)	0.85 (0.55-1.30)		0.81 (0.56-1.16)	
Site			0.850		0.395
Right lower lobe	113 (33.3)	Reference		Reference	
Right middle lobe	44 (13.0)	1.19 (0.63-2.22)		1.17 (0.67-2.05)	
Right upper lobe	182 (53.7)	1.01 (0.65-1.57)		1.29 (0.89-1.87)	
Visceral pleura invasion			0.401		0.807
No	130 (38.3)	Reference		Reference	
Yes	209 (61.7)	0.84 (0.56-1.26)		1.04 (0.74-1.47)	
Bronchial invasion			0.355		0.480
No	253 (74.6)	Reference		Reference	
Yes	86 (25.4)	0.79 (0.48-1.30)		0.87 (0.58-1.29)	
Resected lymph node stations			0.034		0.401
<6	234 (69.0)	Reference		Reference	
≥6	105 (31.0)	0.60 (0.37-0.97)		0.85 (0.59-1.23)	
Resected lymph node numbers			0.007		0.152
>12	130 (38.3)	Reference		Reference	
≥12	209 (61.7)	0.58 (0.39-0.87)		0.78 (0.56-1.09)	
Upper paratracheal lymph node resection			0.007		0.271
No	152 (44.8)	Reference		Reference	
Yes	187 (55.2)	0.58 (0.39-0.87)		0.83 (0.60-1.16)	
Chemotherapy			0.018		0.197
No	288 (85.0)	Reference		Reference	
Yes	51 (15.0)	0.41 (0.19-0.88)		0.72 (0.43-1.19)	

and chemotherapy treatment were all significant prognostic indicators for OS (Table II). These variables were included in the multivariate analysis; age, smoking and family history of malignant tumor were statistically significant factors (Fig. 1). Univariate analysis demonstrated that patient age and family history of malignant tumors were statistically significant prognostic factors for RFS (Table II). Multivariate analysis also demonstrated that these factors were statistically significant. Therefore, patient age and family history of malignant tumors were both significant independent prognostic factors for RFS.

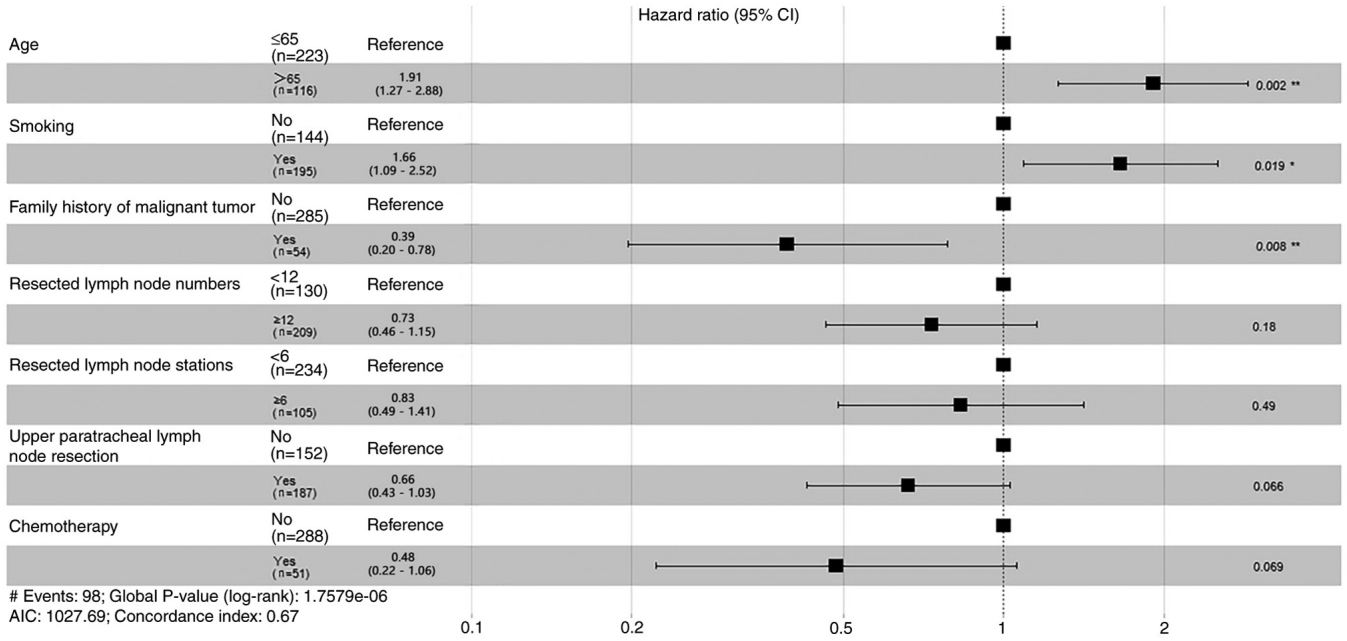

Figure 1. Forest plot showing multivariate analysis of Cox proportional hazard regression model for OS. *P<0.05, **P<0.01. OS, overall survival; CI, confidence interval; AIC, Akaike information criterion.

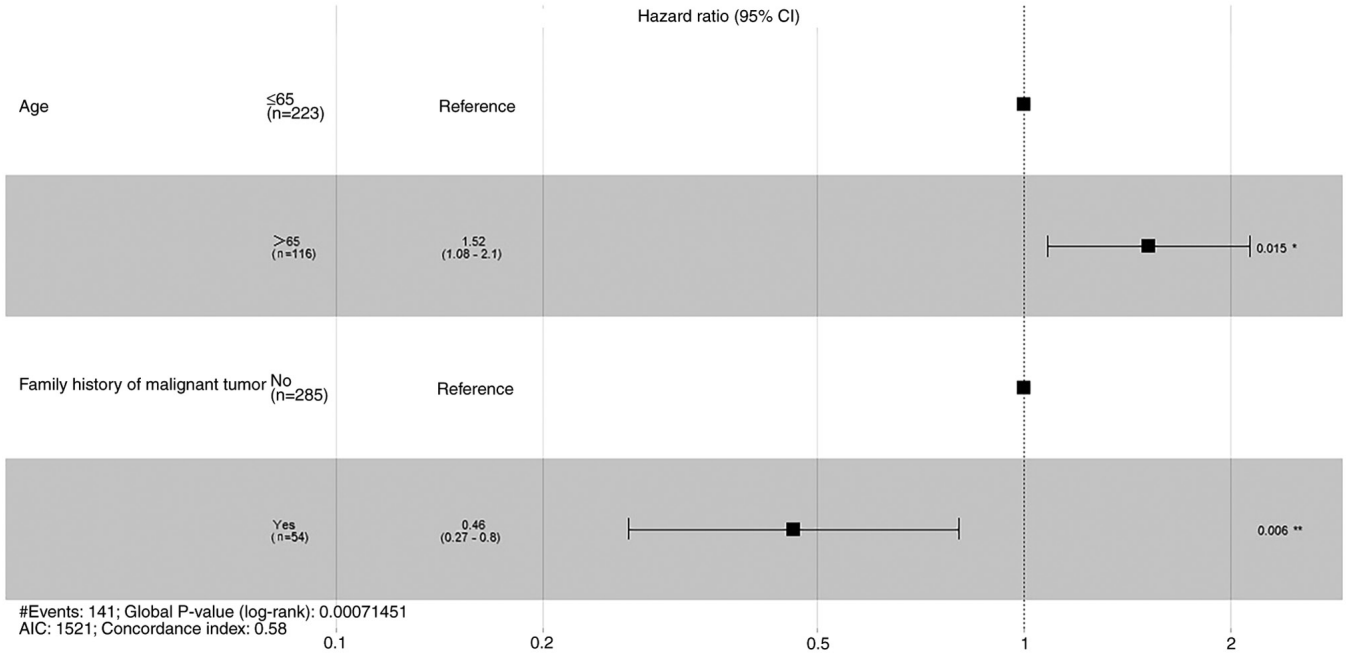

Figure 2. Forest plot showing multivariate analysis Cox proportional hazard regression model for RFS. *P<0.05 and **P<0.01. RFS, recurrence-free survival; CI, confidence interval; AIC, Akaike information criterion.

Survival analysis. Comparisons of the two groups of patients showed statistically significant differences between tumor site, resected lymph node stations and the number of resected lymph nodes (Table I). A 1-to-1 PSM was performed to minimize potential bias when comparing the impact of upper paratracheal lymph node resection on survival. The distribution of propensity scores were assessed and a perfect match was obtained (Fig. 3). Additionally, there were no statistically significant differences between the two groups of patients in each variable tested following PSM (Table I). Kaplan-Meier curves of OS (Fig. 4A and C) and RFS (Fig. 4B and D) before and after PSM were constructed. Before PSM, upper paratracheal lymph node resection had a statistically significant association with OS but not RFS. However, after PSM, the log-rank test demonstrated that upper paratracheal lymph node resection was not significantly associated with either OS or RFS.

As the upper paratracheal lymph nodes were significantly associated with OS in univariate analysis and before PSM, to further clarify the impact of upper paratracheal lymph

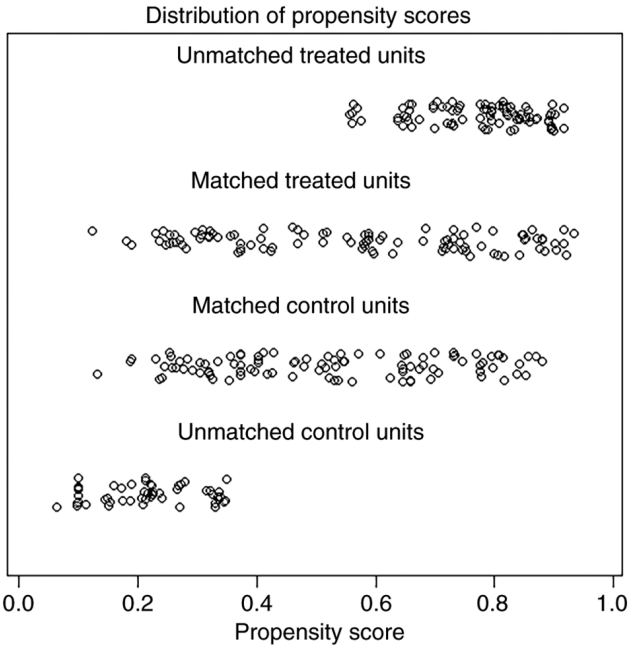

Figure 3. Distribution of propensity score before and after propensity score matching

node resection on OS in different lobes, patients were further divided into three groups (upper, middle and lower lobes). Next, Kaplan-Meier curves were generated and log-rank tests were conducted before and after PSM. The impact of upper paratracheal lymph node resection in different lobes on OS before and after PSM was assessed (Fig. 5). Before PSM, for right lower lobe tumors, upper paratracheal lymph node resection was significantly associated with OS, while after PSM, there was no significant association between upper paratracheal lymph node resection and OS, regardless of the tumor lobe location.

Discussion

The metastasis of tumor cells is an important factor affecting patient prognosis, and lymph nodes serve a key role in lung cancer metastasis; therefore, lymph node dissection is important for the success of lung cancer surgery (20). However, lymph node dissection may cause potential surgery-related complications, such as lymphatic fistula, recurrent laryngeal nerve injury and increased blood loss (21,22). Therefore, the extent of lymph node dissection for lung cancer treatment, particularly in early stage NSCLC, has previously been a contentious issue. Although SLND is currently considered the standard lymph node dissection in lung cancer treatment, studies have reported differing results. A prospective clinical trial that included 1,023 patients with early stage NSCLC showed no significant difference in RFS and OS between patients who underwent SLND and LNS (13,23). In patients with early stage NSCLC, several studies reported no significant difference in survival and recurrence rate between patients who underwent LSLND and SLND (16,24,25).

The 2R lymph nodes are located above the left innominate vein, adjacent to the manubrium and the brachiocephalic artery. Due to its complex anatomical position, it can be difficult and risky to dissect. Some surgeons may choose not to resect upper paratracheal lymph nodes when performing right-sided lung cancer surgery. A number of studies on the lymph node metastasis of NSCLC suggest that right upper lobe cancer typically metastasizes to lymph nodes 4R, 10 and 11, that right middle lobe cancer typically metastasizes to lymph nodes 4R, 7, 10 and 11, and that right lower lobe cancer typically metastasizes to lymph nodes 7, 10 and 11 (26-28). Therefore, the 2R lymph node is not a common metastasis zone for right-sided lung cancer. It is recommended that the upper paratracheal lymph nodes should be dissected for all right-sided lung cancers in SLND (3,4). The National Comprehensive Cancer Network guidelines recommend that station 2, 4, 7, 8 and 9 lymph nodes should be dissected for all right-sided lung cancers (29). However, the upper paratracheal lymph nodes should only be dissected for tumors in the upper and middle lobes in LSLND (5,7,12,14). The LNS has no particular requirements for 2R lymph node dissection (30-32). Due to the proximity of 2R lymph nodes to the superior vena cava, innominate vein and brachiocephalic artery, dissecting 2R lymph nodes increases the risk of large vessel bleeding and increases surgical time due to the complexity of the operation. It could be suggested that the necessity of upper paratracheal lymph node dissection for early stage right lung cancer is currently still controversial; to the best of our knowledge, there are no reports on the effect of 2R lymph node dissection on survival outcomes for patients with right-sided lung cancer, highlighting the importance of the present study.

The present study included 339 patients with stage IB right-sided lung cancer. A Cox proportional hazards model was used to investigate prognostic factors before PSM. In univariate analysis, upper paratracheal lymph node resection was associated with OS. However, following multivariate analysis, upper paratracheal lymph node resection was not an independent prognostic factor for OS and RFS. To reduce bias, the original data were divided into two groups according to whether the upper paratracheal lymph nodes were resected and matched with a 1:1 propensity score. The Kaplan-Meier method was used for survival analysis. Following PSM, there was no significant difference in OS and RFS between the two groups of patients. However, before PSM, the survival curve of OS demonstrated a significant difference between the two groups of patients. To clarify the effect of upper paratracheal lymph node resection on OS in different lobes, survival curves analyzing OS in different lobes before and after PSM were constructed. There was a significant difference between the two groups for OS in the right lower lobe cancer before PSM, but not after PSM. For the upper and middle lobes of the right lung, no significant difference was demonstrated between groups before and after PSM. The results of the present study contradict a number of previous studies that showed that 2R lymph node dissection was required for right upper lobe cancer in both SLND and LSLND (5,7,10,12). A number of previous studies reported that 2R lymph nodes are more likely to metastasize in right upper lobe cancer (26,28). The contradictory results obtained in the present study may be related to the small sample size. In the future, larger sample size studies on lymph node metastasis in lung cancer are required to validate the results of the present study.

The present study had a number of limitations. First, the present study was a single-center retrospective study and the sample size was relatively small, although PSM was used to

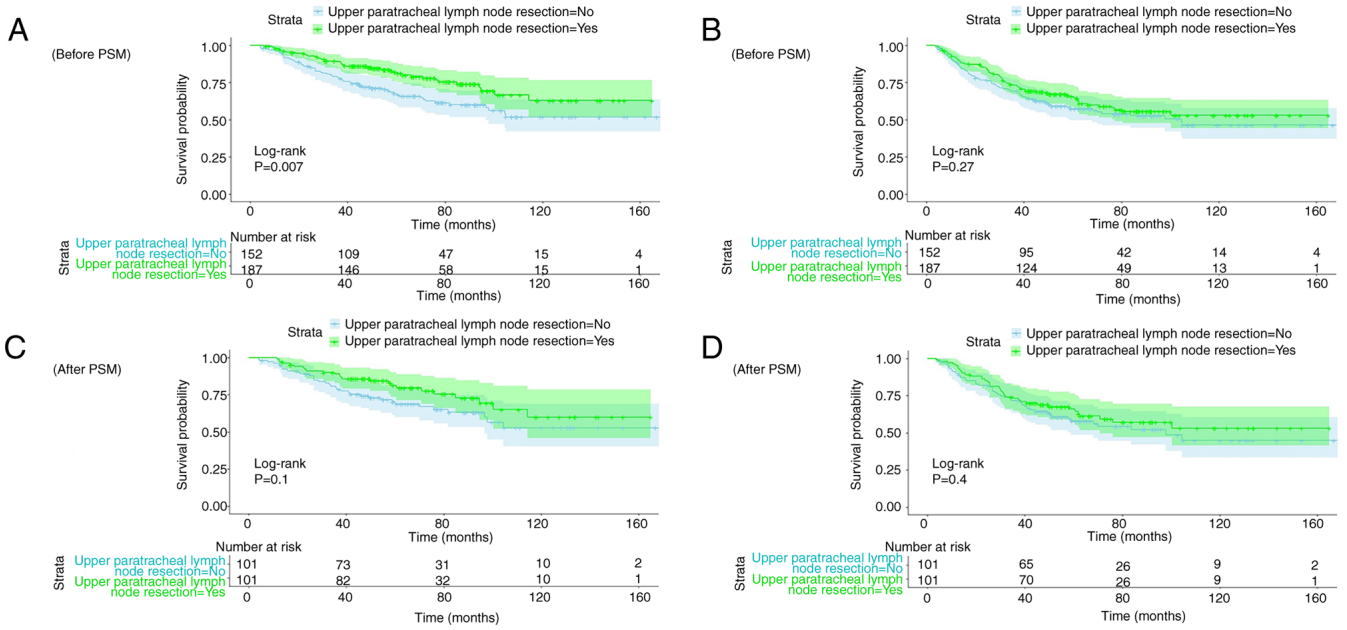

Figure 4. Kaplan-Meier curves of OS and RFS before and after PSM. [(A) OS before PSM; (B), RFS before PSM; (C), OS after PSM; (D), RFS after RFS]. OS, overall survival; RFS, recurrence-free survival; PSM, propensity score matching.

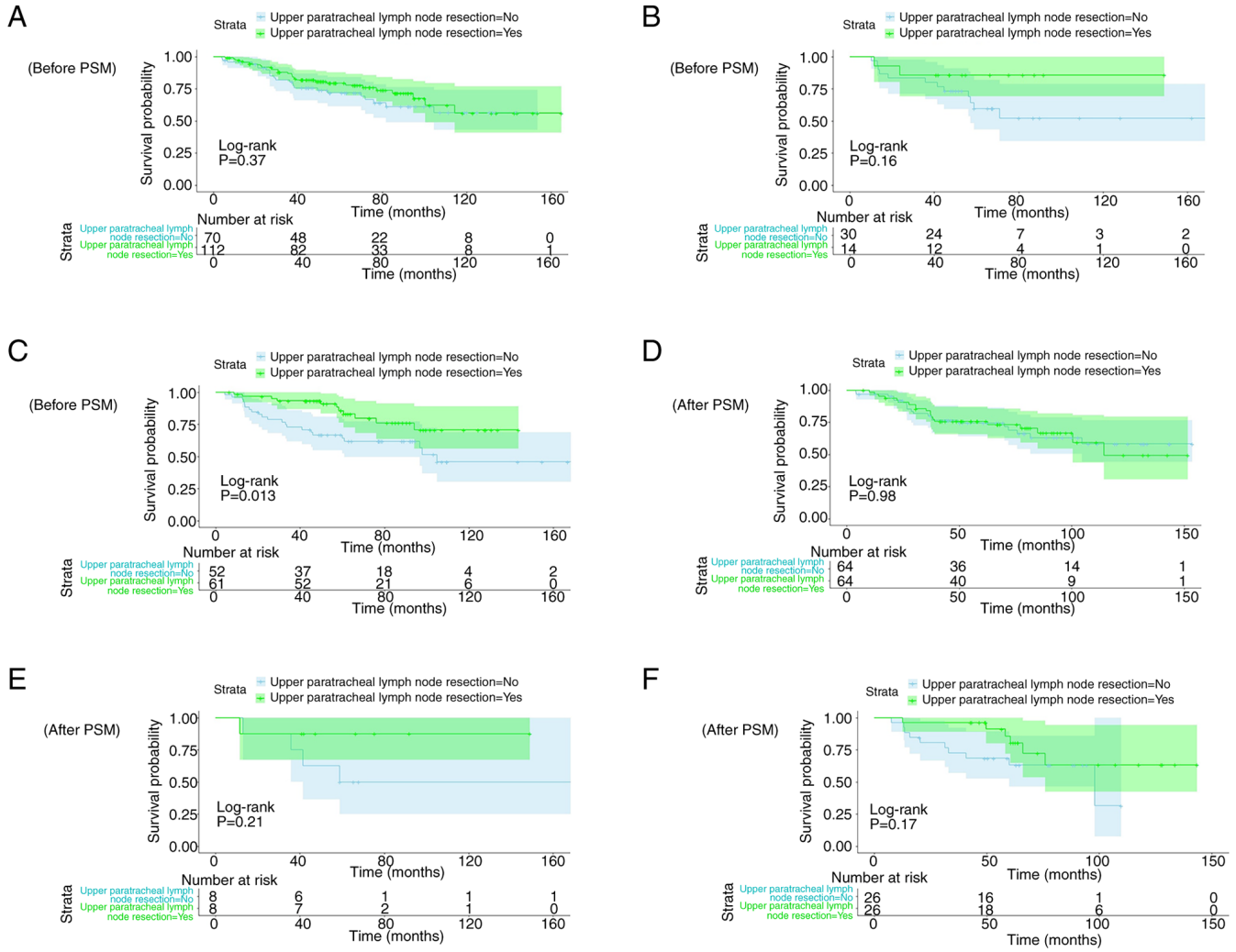

Figure 5. Kaplan-Meier curves before PSM and after PSM. OS for upper lobe, middle lobe and lower lobe [(A), OS for upper lobe before PSM; (B), OS for middle lobe before PSM; (C), OS for lower lobe before PSM; (D), OS for upper lobe after PSM; (E), OS for middle lobe after PSM; (F), OS for lower lobe after PSM]. OS, overall survival; PSM, propensity score matching.

balance variables that may have influenced the results. In addition, although no sensitivity analysis of PSM was performed in this study, consistent conclusions were drawn through two different statistical methods, PSM and Cox regression, which also proves the robustness of the findings. Sensitivity analyses will be performed in future research to further validate the outcomes. Second, due to the inclusion of early lung cancer cases in the present study, a longer follow-up time is required to obtain OS data, as the present study cohort was followed from 1999-2009. However, using earlier data may affect research conclusions due to certain factors, such as new treatment methods, not being included. Third, since the present study did not collect information on the surgeon, it could not be included in the present study. In addition, information on perioperative management was not included in the study variables due to the difficulty in quantification. In conclusion, a multicenter prospective clinical trial with a larger sample size may validate the findings of the present study in the future. As research progresses, there could be more accurate lymph node dissection guidelines for patients with early stage lung cancer in the future, so that these patients could experience less surgical trauma and achieve increased survival rates.

Overall, for patients with stage IB NSCLC, upper paratracheal lymph node resection did not demonstrate a statistically significant association with OS or RFS. Upper paratracheal lymph node resection may therefore be unnecessary for early stage NSCLC, which could potentially reduce unnecessary surgical trauma and decrease lymph node-related complications.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FW and XY wrote the manuscript. FW, YH and XY participated in the design of the study and were involved in data collection. LZ and SL participated in the design and oversight of the study. YH and XY participated in the design of the study and were involved in data collection. FW and XY were involved in statistical analysis. FW, XY and LZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was reviewed and approved by the Ethics Committee of Sun Yat-Sen University Cancer Center and Beijing Chest Hospital Institutional Review Board (Beijing, China; approval no. B2018-011). The patients provided written informed consent to participate in this study.

Patient consent for publication

The patients/participants provided written informed consent for the publication of any data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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