Evaluation of the significance of subcarinal lymph node dissection in stage IB non-small cell lung cancer

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Abstract. Lymph node dissection is used to treat early-stage lung cancer. The present study aimed to investigate if resecting the subcarinal lymph nodes affects prognosis of patients with stage IB non-small cell lung cancer (NSCLC). A total of 597 patients with stage IB NSCLC who underwent lung cancer surgery at Sun Yat-Sen University Cancer Center from January 1999 to December 2009 were included in the present study. The potential prognostic factors were evaluated using the Cox proportional hazard regression model. A total of 252 cases were obtained following propensity score matching (PSM). To compare overall survival (OS) and recurrence-free survival (RFS), Kaplan-Meier method and log-rank test were used. Among the 597 cases included, 185 did not undergo subcarinal lymph node resection, whereas 412 did. There were statistically significant differences between the two groups in terms of bronchial invasion, number of resected lymph node stations and resected lymph node numbers (P<0.05). Age, family history of cancer and the number of resected lymph nodes were prognostic factors for OS, whereas age and the number of resected lymph nodes were prognostic factors for RFS (P<0.05). Resection of subcarinal lymph nodes was not associated with OS and RFS. After PSM, survival analysis was recalculated using the Kaplan-Meier method and log-rank test; subcarinal lymph node resection was not statistically associated with OS and RFS. (P>0.05). For stage IB NSCLC, there was no statistically significant association between subcarinal lymph node resection and OS and RFS. Subcarinal lymph node resection in surgery of stage IB NSCLC may be considered optional.

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Introduction

Being the most prevalent type of malignant tumor, lung cancer has the highest cancer-related mortality worldwide with 2093876 new cases and 1761007 cases died of lung cancer in 2018 (1). Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer, accounting for ~85% of lung cancer cases (2). Widespread application of chest CT in physical examination facilitates diagnosis of early-stage NSCLC. Currently, surgery is the first-line treatment option for early-stage NSCLC (3). Lobectomy with systematic lymph node dissection (SLND) has been the standard surgical treatment for lung cancer for several years (4,5). However, there are new options for LND in early-stage NSCLC, among which lobe-specific selective LND (LSLND) is one of the most discussed surgical methods (6-9). Studies have confirmed that LSLND could shorten the operation time and decrease perioperative complications without affecting overall survival (OS) and disease-free survival rate of patients after surgery (8-10). In addition, some studies suggested that for early-stage NSCLC, lymph node sampling (LNS) achieves a prognosis similar to SLND (11,12). The subcarinal lymph node, also known as the #7 lymph node, has been regarded as an essential N2 lymph node in LND of lung cancer in the past and it was required to be removed in SLND. The extent of SLND involves the inclusion of subcarinal lymph nodes, while LSLND and LNS do not require mandatory subcarinal LND (8-10,12). There is still controversy about whether the subcarinal lymph nodes must be dissected in early-stage NSCLC. The present study focused on stage IB NSCLC and investigated if the subcarinal LND is necessary for stage IB NSCLC.

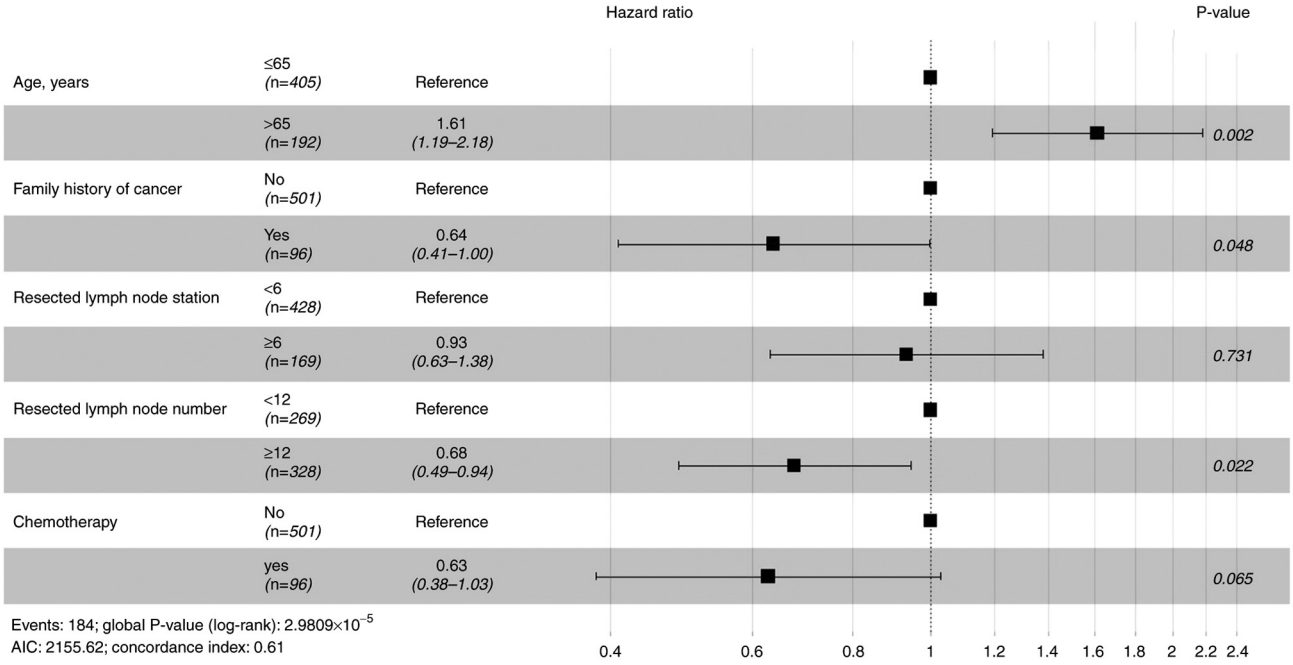

Figure 1. Forest plot showing multivariate analysis for overall survival. AIC, Akaike information criterion.

Materials and methods

Patient selection. Data were collected from patients with lung cancer who had surgery at Sun Yat-Sen University Cancer Center, Guangzhou, China between January 1999 and December 2009. The medical records and the follow-up system were evaluated for patient information, postoperative pathological information, surgical conditions and follow-up outcomes. The inclusion criteria were as follows: i) No neoadjuvant therapy; ii) patients treated with lobectomy and iii) postoperative pathological diagnosis was stage IB NSCLC, which was validated independently by two pathologists. The exclusion criteria were as follows: i) Patients who had preoperative chemotherapy or radiation; ii) patients with other types of tumor and iii) no detailed follow-up information. Finally, 597 patients (age range 19-85; male/female 425/172) were enrolled.

Follow-up. Follow-up began when patients underwent surgery and was performed every 3 months for the first 2 years, every 6 months between 3-5 years and annually after 5 years. The evaluation of the patient condition included routine blood, blood biochemistry, tumor marker, abdominal ultrasound and chest CT. Brain MRI was conducted to determine brain metastasis once per year . The patient survival and recurrence were recorded at each visit. All cases were followed up until January 2013.

Statistical analysis. The variables of the two groups were compared using χ^2 or Fisher's exact (>20% of cells with expected frequency <5) test as appropriate. OS and recurrence-free survival (RFS) were calculated using the Kaplan-Meier method. For univariate and multivariate analysis, the Cox proportional hazard regression model was utilized. Variables with P<0.1 in univariate analysis were used in the multivariate analysis. P<0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed with the R software (version 4.2.0; R-project.org/). The 'matchit' (version 4.4.0; cran.r-project.org/web/packages/MatchIt/vignettes/MatchIt.html) package was used for propensity score matching (PSM). The 'survival' (version 3.3-1 cran.r-project.org/package=survival) and 'survminer' (version 0.4.9 cran.r-project.org/web/packages/survminer/readme/README.html) packages were used to generate survival curves and forest plots. Due to crossover in the survival curves, the two-stage test was used to calculate the P-value using the R package TSHRC (cran.r-project.org/web/packages/TSHRC/index.html) (13). X-tile (version 3.6.1; Yale University, USA; medicine.yale.edu/lab/rimm/research/software/) was used to determine the optimal cutoff values for the number of resected lymph nodes.

Results

Baseline characteristics. The current study included a total of 597 patients with stage IB NSCLC. The baseline characteristics of the study cohort are shown in Table I. The majority of patients were male (71.2%) and 32.2% of the patients were >65 years of age. Among all the included cases, 58.3% had smoking history and 16.1% had family history of malignancy. In terms of postoperative pathology, patients with grades I + II accounted for 60.5%. The most common pathological types were adenocarcinoma (64.2%), followed by squamous cell carcinoma (33.5%), while the remaining 2.3% included large cell carcinoma, sarcomatoid carcinoma and mucoepidermoid carcinoma. The proportion of cases with visceral pleural invasion was 60%, while that of bronchial invasion was 25%. In addition, 54% of the patients had >12 lymph nodes resected, while 28.3% of the patients had ≥6 lymph node stations

Table I. Clinicopathological characteristics of original and matched data.

	Original data set				Matched data set			
		Resection of subcarinal lymph nodes				Resection of subcarinal lymph nodes		
Characteristic	Total	No (n=185)	Yes (n=412)	P-value	Total	No (n=146)	Yes (n=146)	P-value
Sex (%)				0.348				0.524
Male	425 (71.2)	137 (74.1)	288 (69.9)		204 (69.9)	105 (71.9)	99 (67.8)	
Female	172 (28.8)	48 (25.9)	124 (30.1)		88 (30.1)	41 (28.1)	47 (32.2)	
Age, years (%)				0.088				1.000
≤65	405 (67.8)	116 (62.7)	289 (70.1)		203 (69.5)	102 (69.9)	101 (69.2)	
>65	192 (32.2)	69 (37.3)	123 (29.9)		89 (30.5)	44 (30.1)	45 (30.8)	
Smoking status (%)				0.906				0.475
No	249 (41.7)	76 (41.1)	173 (42.0)		119 (40.8)	56 (38.4)	63 (43.2)	
Yes	348 (58.3)	109 (58.9)	239 (58.0)		173 (59.2)	90 (61.6)	83 (56.8)	
Family history of cancer (%)				0.856				1.000
No	501 (83.9)	154 (83.2)	347 (84.2)		250 (85.6)	125 (85.6)	125 (85.6)	
Yes	96 (16.1)	31 (16.8)	65 (15.8)		42 (14.4)	21 (14.4)	21 (14.4)	
Grade (%)				0.402				0.100
I + II	361 (60.5)	117 (63.2)	244 (59.2)		159 (54.5)	87 (59.6)	72 (49.3)	
III + IV	236 (39.5)	68 (36.8)	168 (40.8)		133 (45.5)	59 (40.4)	74 (50.7)	
Histology (%)				0.378				0.658
Adenocarcinoma	383 (64.2)	126 (68.1)	257 (62.4)		188 (64.4)	97 (66.4)	91 (62.3)	
Squamous cell carcinoma	200 (33.5)	56 (30.3)	144 (35.0)		99 (33.9)	46 (31.5)	53 (36.3)	
Other	14 (2.3)	3 (1.6)	11 (2.6)		5 (1.7)	3 (2.1)	2 (1.4)	
Visceral pleura invasion (%)				0.919				0.406
No	239 (40.0)	73 (39.5)	166 (40.3)		122 (41.8)	57 (39.0)	65 (44.5)	
Yes	358 (60.0)	112 (60.5)	246 (59.7)		170 (58.2)	89 (61.0)	81 (55.5)	
Bronchial invasion (%)				0.031				0.668
No	445 (74.5)	149 (80.5)	296 (71.8)		230 (78.8)	117 (80.1)	113 (77.4)	
Yes	152 (25.5)	36 (19.5)	116 (28.2)		62 (21.2)	29 (19.9)	33 (22.6)	
Resected lymph node stations (%)				<0.001				1.000
<6	428 (71.7)	171 (92.4)	257 (62.4)		264 (90.4)	132 (90.4)	132 (90.4)	
≥6	169 (28.3)	14 (7.57)	155 (37.6)		28 (9.59)	14 (9.59)	14 (9.59)	
Resected lymph node number (%)				<0.001				1.000
<12	269 (45.1)	141 (76.2)	128 (31.1)		204 (69.9)	102 (69.9)	102 (69.9)	
≥12	328 (54.9)	44 (23.8)	284 (68.9)		88 (30.1)	44 (30.1)	44 (30.1)	
Chemotherapy (%)				1.000				0.610
No	501 (83.9)	155 (83.8)	346 (84.0)		252 (86.3)	124 (84.9)	128 (87.7)	
Yes	96 (16.1)	30 (16.2)	66 (16.0)		40 (13.7)	22 (15.1)	18 (12.3)	

resected. Following surgery, ~16.1% of patients received adjuvant chemotherapy.

Among all the cases included in the present study, 185 patients did not undergo subcarinal lymph node resection, whereas 412 did. Table I shows statistically significant differences in bronchial invasion, resected lymph node stations and resected lymph node numbers between the two groups.

Prognostic factors for OS and RFS. Before PSM, prognostic factors were evaluated with Cox proportional hazards regression models. Table II shows univariate analysis for OS and RFS. Variables with P<0.1 were included in the multivariate analysis. Age, family history of cancer and the resected lymph nodes number were significant prognostic factors for OS (Fig. 1), whereas only age and resected lymph node number were signifi-

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

		Overall survival		Recurrence-free survival	
Characteristic	Total	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (%)			0.419		0.587
Male	425 (71.2)	Reference		Reference	
Female	172 (28.8)	0.87 (0.63-1.22)		0.93 (0.70-1.22)	
Age, years (%)			0.001		0.032
≤65	405 (67.8)	Reference		Reference	
>65	192 (32.2)	1.68 (1.25-2.26)		1.33 (1.02-1.72)	
Smoking status (%)			0.101		0.594
No	249 (41.7)	Reference		Reference	
Yes	348 (58.3)	1.28 (0.95-1.73)		1.07 (0.83-1.38)	
Family history of cancer (%)			0.035		0.118
No	501 (83.9)	Reference		Reference	
Yes	96 (16.1)	0.62 (0.40-0.97)		0.75 (0.52-1.08)	
Grade (%)			0.324		0.378
I + II	361 (60.5)	Reference		Reference	
III + IV	236 (39.5)	1.16 (0.86-1.55)		1.12 (0.87-1.44)	
Histology (%)			0.514		0.142
Adenocarcinoma	383 (64.2)	Reference		Reference	
Squamous cell carcinoma	200 (33.5)	0.84 (0.61-1.15)		0.77 (0.58-1.01)	
Other	14 (2.3)	0.76 (0.24-2.40)		0.68 (0.25-1.84)	
Visceral pleura invasion (%)			0.882		0.344
No	239 (40.0)	Reference		Reference	
Yes	358 (60.0)	0.98 (0.73-1.31)		1.13 (0.88-1.46)	
Bronchial invasion (%)			0.131		0.169
No	445 (74.5)	Reference		Reference	
Yes	152 (25.5)	0.75 (0.52-1.09)		0.81 (0.60-1.10)	
Resection of subcarinal lymph nodes (%)			0.255		0.237
No	185 (31.0)	Reference		Reference	
Yes	412 (69.0)	0.84 (0.62-1.13)		0.86 (0.66-1.11)	
Resected lymph node station (%)			0.061		0.286
<6	428 (71.7)	Reference		Reference	
≥6	169 (28.3)	0.72 (0.51-1.02)		0.86 (0.65-1.14)	
Resected lymph node number (%)			0.004		0.025
<12	269 (45.1)	Reference		Reference	
≥12	328 (54.9)	0.65 (0.49-0.87)		0.75 (0.59-0.97)	
Chemotherapy (%)			0.014		0.177
No	501 (83.9)	Reference		Reference	
Yes	96 (16.1)	0.55 (0.34-0.89)		0.78 (0.54-1.12)	

cant prognostic factors for RFS (Fig. 2). Cox regression analysis of all included cases suggested that resection of subcarinal lymph nodes was not a prognostic factor for OS and RFS.

Survival analysis. To compare the effect of subcarinal lymph node resection on OS and RFS, 1:1 PSM was performed for all variables. A total of 252 cases, 146 for each group, were selected after PSM (Table I). χ^2 indicated that all variables were not statistically different between the two groups. Fig. 3 shows the distribution of propensity scores before and after matching. A good match was obtained between the two groups. Fig. 4 shows OS and RFS curves stratified with or without subcarinal lymph node resection before and after PSM. All four survival curves were not statistically significant, indicating that resection of subcarinal lymph nodes was not associated with OS and RFS.

Discussion

For LND in NSCLC, SLND (including subcarinal LND) has been the gold standard surgical treatment (14-16). However,

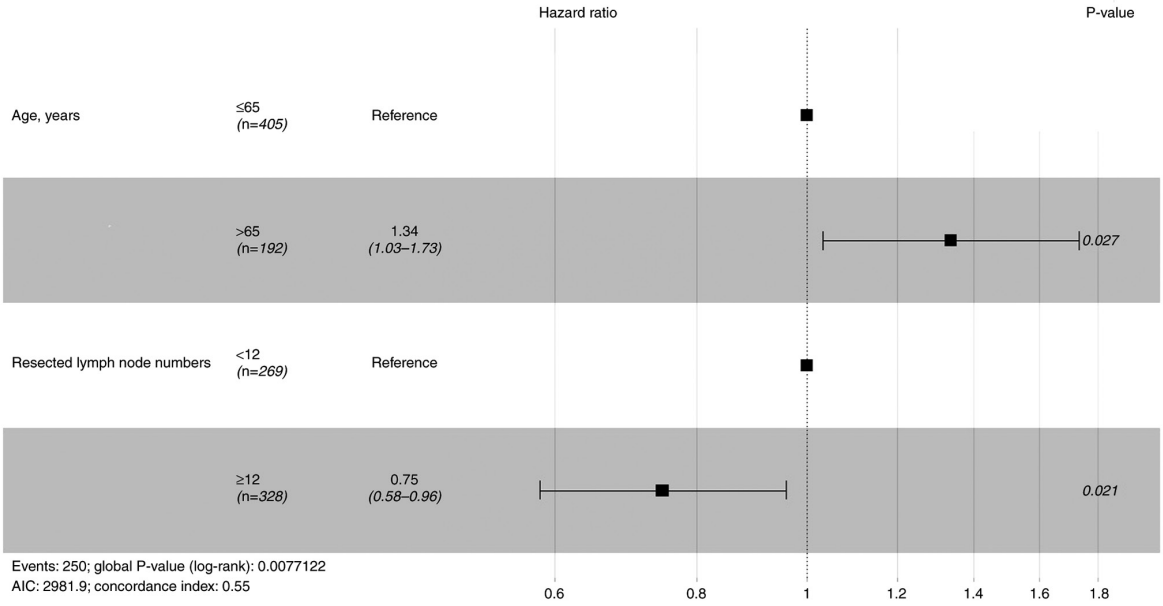

Figure 2. Forest plot showing multivariate analysis for recurrence-free survival. AIC, Akaike information criterion.

with the increase in number of patients undergoing surgery for early-stage NSCLC (10), research has focused on new surgical approaches to LND in early-stage lung cancer. Among them, LSLND and LNS have been proposed by studies for the treatment of early-stage NSCLC (9,10,17,18). However, these LND methods do not emphasize the need to remove subcarinal lymph nodes. To explore the effect of subcarinal lymph node resection on prognosis in early-stage NSCLC, a total of 597 patients with stage IB NSCLC were included in the present study. Cox regression was used to investigate the prognostic factors and resection of the subcarinal lymph node did not affect OS and RFS. To decrease the influence of bias and confounding variables, survival analysis was performed after PSM, which suggested that the resection of subcarinal lymph nodes was not associated with OS and RFS.

International Association for the Study of Lung Cancer proposed the concept of SLND (19,20). In 2006, the European Society of Thoracic Surgeons guidelines defined the extent of resection in SLND as removal of ≥6 stations of lymph nodes, including >3 stations of mediastinal lymph nodes on the same side and the subcarinal lymph nodes (#7 lymph nodes) (14). Studies have found that SLND could improve the survival of patients with advanced NSCLC (12,21-23). SLND may increase surgical complications such as lymphatic fistula, recurrent laryngeal nerve injury, surgical blood loss and prolonged hospitalization (19); however, necessity of SLND remains controversial for early-stage NSCLC (24-26). For early NSCLC, several studies have suggested that LSLND and LNS achieve the same therapeutic effect as SLND (6,8,10-12,27). LSLND is defined as the removal of specific mediastinal and hilar lymph nodes according to the lobe of the tumor (9). LNS is defined as the resection of abnormal lymph nodes found preoperatively and intraoperatively (28). Neither of these two methods of LND for early-stage NSCLC require dissection of subcarinal lymph nodes and, according to the present findings, LNS and LSLND achieve the same therapeutic effect as SLND. The present study found that for stage IB NSCLC,

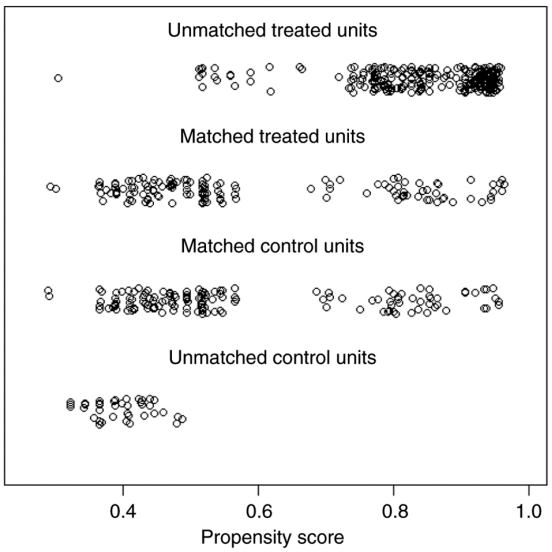

Figure 3. Distribution of propensity score.

there was no association between subcarinal lymph node dissection and OS or RFS. These results were consistent with the aforementioned previous findings on early-stage NSCLC.

Since the subcarinal lymph nodes are adjacent to the carina, esophagus and vagus nerve, these structures are prone to damage during dissection. Therefore, for early-stage NSCLC, surgeons may choose not to remove subcarinal lymph nodes. According to previous studies and the present study, the absence of subcarinal LND for early-stage lung cancer has no significant effect on OS and RFS. In summary, for early-stage NSCLC, not dissecting the subcarinal lymph nodes can decrease potential surgical damage, speed up surgery time and enable patients to recover faster (18,24,28). However, SLND could allow more accurate staging and provide an opportunity for postoperative adjuvant therapy (11,29). Therefore, SLND (including resection of subcarinal lymph nodes) may be

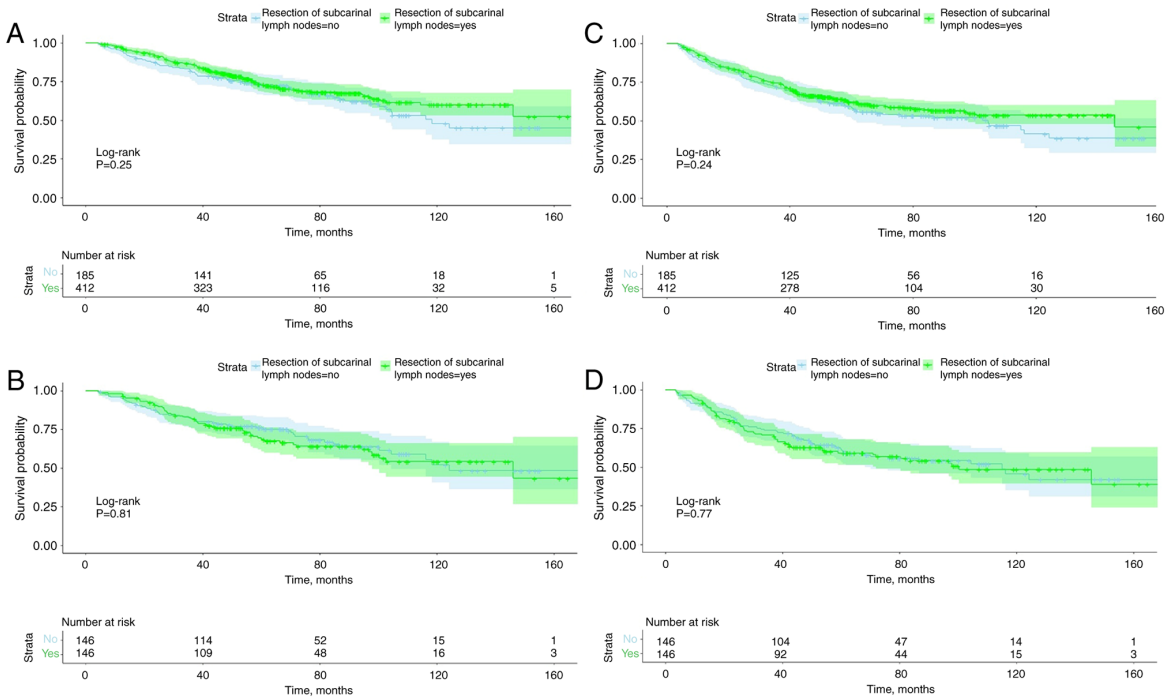

Figure 4. Kaplan-Meier curves. Overall survival before (A) and after (B) propensity score matching and recurrence-free survival (C) before and after (D) propensity score matching.

recommended in patients who are considered at risk of lymph node metastasis in preoperative examination.

The present analysis suggested that subcarinal lymph node resection was not associated with OS or RFS. It could also be concluded that number of resected lymph node stations was not associated with OS or RFS. However, the number of resected lymph nodes in the multivariate analysis was a statistically significant prognostic factor for OS and RFS., while the resection of subcarinal lymph nodes and the resected lymph node stations were not statistically significant. These results indicated that for stage IB NSCLC, the number of dissected lymph nodes may be more meaningful in terms of improving prognosis than resection of the subcarinal lymph nodes and number of lymph node stations. Previous studies on NSCLC have suggested that this view remains controversial and needs to be confirmed by more studies in the future (30-32). If this conclusion is established, it will challenge the current principle of LND in lung cancer.

The current study had limitations. Firstly, this was a single-center retrospective study and multi-center prospective studies are needed to confirm the present conclusions. Secondly, this study enrolled 597 patients; this relatively small sample size could lead to bias. Due to the small sample size, no further subgroup analysis was performed for different pathological subtypes of NSCLC. Finally, the enrolled population of this study included only patients with postoperative pathologically confirmed stage IB; it is difficult to obtain the accurate pathological staging of patients before surgery. Therefore, the conclusions of this study have limitations in their future clinical application.

For stage IB NSCLC, there was no statistically significant association between resection of the subcarinal lymph node and patient survival. Subcarinal lymph node resection in surgery of stage IB NSCLC may be considered optional.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

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

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved (approval no B2018-011) by Ethics Committee of Sun Yat-Sen University Cancer Center (Guangzhou, P.R. China and Beijing Chest Hospital Institutional Review Board (Beijing, P.R. China). The participants provided written informed consent to participate in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, Znaor A and Bray F: Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 144: 1941-1953, 2019.
2. Herbst RS, Heymach JV and Lippman SM: Lung cancer. N Engl J Med 359: 1367-1380, 2008.
3. Masuda M, Kuwano H, Okumura M, Arai H, Endo S, Doki Y, Kobayashi J, Motomura N, Nishida H, Saiki Y, *et al*: Thoracic and cardiovascular surgery in Japan during 2013: Annual report by The Japanese association for thoracic surgery. Gen Thorac Cardiovasc Surg 63: 670-701, 2015.
4. De Leyn P, Lardinois D, Van Schil P, Rami-Porta R, Passlick B, Zielinski M, Waller D, Lerut T and Weder W: European trends in preoperative and intraoperative nodal staging: ESTS guidelines. J Thorac Oncol 2: 357-361, 2007.
5. Howington JA, Blum MG, Chang AC, Balekian AA and Murthy SC: Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143: e278S-e313S, 2013.
6. Ishiguro F, Matsuo K, Fukui T, Mori S, Hatooka S and Mitsudomi T: Effect of selective lymph node dissection based on patterns of lobe-specific lymph node metastases on patient outcome in patients with resectable non-small cell lung cancer: A large-scale retrospective cohort study applying a propensity score. J Thorac Cardiovasc Surg 139: 1001-1006, 2010.
7. Maniwa T, Okumura T, Isaka M, Nakagawa K, Ohde Y and Kondo H: Recurrence of mediastinal node cancer after lobe-specific systematic nodal dissection for non-small-cell lung cancer. Eur J Cardiothorac Surg 44: e59-e64, 2013.
8. Hishida T, Miyaoka E, Yokoi K, Tsuboi M, Asamura H, Kiura K, Takahashi K, Dosaka-Akita H, Kobayashi H, Date H, *et al*: Lobe-specific nodal dissection for clinical stage I and II NSCLC: Japanese multi-institutional retrospective study using a propensity score analysis. J Thorac Oncol 11: 1529-1537, 2016.
9. Adachi H, Sakamaki K, Nishii T, Yamamoto T, Nagashima T, Ishikawa Y, Ando K, Yamanaka K, Watanabe K, Kumakiri Y, *et al*: Lobe-specific lymph node dissection as a standard procedure in surgery for non-small cell lung cancer: A propensity score matching study. J Thorac Oncol 12: 85-93, 2017.
10. Okada M, Sakamoto T, Yuki T, Mimura T, Miyoshi K and Tsubota N: Selective mediastinal lymphadenectomy for clinico-surgical stage I non-small cell lung cancer. Ann Thorac Surg 81: 1028-1032, 2006.
11. Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI, Jones DR, McKenna RJ, Landreneau RJ, Rusch VW and Putnam JB Jr: Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: Results of the American college of surgery oncology group z0030 trial. J Thorac Cardiovasc Surg 141: 662-670, 2011.
12. Hughes MJ, Chowdhry MF, Woolley SM and Walker WS: In patients undergoing lung resection for non-small cell lung cancer, is lymph node dissection or sampling superior? Interact Cardiovasc Thorac Surg 13: 311-315, 2011.
13. Li H, Han D, Hou Y, Chen H and Chen Z: Statistical inference methods for two crossing survival curves: A comparison of methods. PLoS One 10: e0116774, 2015.
14. Lardinois D, De Leyn P, Van Schil P, Porta RR, Waller D, Passlick B, Zielinski M, Lerut T and Weder W: ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 30: 787-792, 2006.
15. Rice D, Chansky K, Nowak A, Pass H, Kindler H, Shemanski L, Opitz I, Call S, Hasegawa S, Kernstine K, *et al*: The IASLC mesothelioma staging project: Proposals for revisions of the N descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma. J Thorac Oncol 11: 2100-2111, 2016.
16. Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P, Kennedy C, Krasnik M, Peake M, Shemanski L, *et al*: The IASLC lung cancer staging project: External validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. J Thorac Oncol 12: 1109-1121, 2017.
17. Jett JR, Schild SE, Kesler KA and Kalemkerian GP: Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143: e400S-e419S, 2013.
18. Adachi H, Maehara T, Nakayama H and Masuda M: Mediastinal lymph node dissection in surgical treatment for early stage non-small-cell lung cancer: Lobe-specific or systematic? J Thorac Dis 9: 2728-2731, 2017.
19. Ma K, Chang D, He B, Gong M, Tian F, Hu X, Ji Z and Wang T: Radical systematic mediastinal lymphadenectomy versus mediastinal lymph node sampling in patients with clinical stage IA and pathological stage T1 non-small cell lung cancer. J Cancer Res Clin Oncol 134: 1289-1295, 2008.
20. Goldstraw P: Report on the international workshop on intrathoracic staging. London, October 1996. Lung Cancer 18: 107-111, 1997.
21. Wu Y, Huang ZF, Wang SY, Yang XN and Ou W: A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. Lung Cancer 36: 1-6, 2002.
22. Keller SM, Adak S, Wagner H and Johnson DH: Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern cooperative oncology group. Ann Thorac Surg 70: 358-365; discussion 365-356, 2000.
23. Misthos P, Sepsas E, Kokotsakis J, Skottis I and Lioulias A: Prognosis of stage pIIIA non small cell lung cancer after mediastinal lymph node dissection or sampling. J BUON 14: 45-49, 2009.
24. Doddoli C, Aragon A, Barlesi F, Chetaille B, Robitail S, Giudicelli R, Fuentes P and Thomas P: Does the extent of lymph node dissection influence outcome in patients with stage I non-small-cell lung cancer? Eur J Cardiothorac Surg 27: 680-685, 2005.
25. Allen MS, Darling GE, Pechet TT, Mitchell JD, Herndon JE II, Landreneau RJ, Inculet RI, Jones DR, Meyers BF, Harpole DH, *et al*: Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: Initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg 81: 1013-1019; discussion 1019-1020, 2006.
26. Bille A, Woo KM, Ahmad U, Rizk NP and Jones DR: Incidence of occult pN2 disease following resection and mediastinal lymph node dissection in clinical stage I lung cancer patients. Eur J Cardiothorac Surg 51: 674-679, 2017.
27. Huang X, Wang J, Chen Q and Jiang J: Mediastinal lymph node dissection versus mediastinal lymph node sampling for early stage non-small cell lung cancer: A systematic review and meta-analysis. PLoS ONE 9: e109979, 2014.
28. Watanabe S: Lymph node dissection for lung cancer: Past, present, and future. Gen Thorac Cardiovasc Surg 62: 407-414, 2014.
29. Meng D, Zhou Z, Wang Y, Wang L, Lv W and Hu J: Lymphadenectomy for clinical early-stage non-small-cell lung cancer: A systematic review and meta-analysis. Eur J Cardiothorac Surg 50: 597-604, 2016.
30. Samayoa AX, Pezzi TA, Pezzi CM, Gay EG, Asai M, Kulkarni N, Carp N, Chun SG and Putnam JB Jr: Rationale for a minimum number of lymph nodes removed with non-small cell lung cancer resection: Correlating the number of nodes removed with survival in 98,970 patients. Ann Surg Oncol 23: 1005-1011, 2016.
31. Liang W, He J, Shen Y, Shen J, He Q, Zhang J, Jiang G, Wang Q, Liu L, Gao S, *et al*: Impact of examined lymph node count on precise staging and long-term survival of resected non-small-cell lung cancer: A population study of the US SEER database and a Chinese multi-institutional registry. J Clin Oncol 35: 1162-1170, 2017.
32. Riquet M, Arame A and Pricopi C: Subcarinal lymph node importance revisited. Ann Thorac Surg 105: 666-667, 2018.