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Clinical significance of intrapulmonary lymph node dissection in pathological stage IA non-small cell lung cancer: A propensity score matching analysis

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Abstract

Background: This study aimed to investigate the prognostic impact of intrapulmonary lymph node (ILN, stations 13–14) dissection on disease-free survival (DFS) in stage IA non-small cell lung cancer (NSCLC) patients in order to facilitate a more suitable determination of surgical strategies for early-stage cases.

Methods: We retrospectively analyzed 416 patients with pathological stage IA NSCLC from February 2016 to November 2019. The patients were divided into a group with ILN dissection (ILN^{D+} group) and a group without ILN dissection (ILN^{D-} group). DFS was compared using the Kaplan–Meier method and compared statistically using the log-rank test before and after propensity score matching (PSM). Subgroup analysis of DFS stratified based on tumor size was also calculated.

Results: Both before and after PSM, the four-year DFS of the ILN^{D+} group was greatly increased compared to that of ILN^{D-} group (90.1% vs. 79.7%, p = 0.003; 95.5% vs. 80.6%, p = 0.003, respectively) and multivariable cox regression analysis revealed ILN dissection was an independent factor favoring DFS in stage IA NSCLC (p = 0.016 and p = 0.015, respectively). Subgroup analysis revealed the four-year DFS was comparable between the ILN^{D+} and ILN^{D-} groups with regard to tumor size ≤1.5 cm (90.6% vs. 92.7%, p = 0.715). However, the ILN^{D+} group was found to have a better oncological outcome compared with the ILN^{D-} group with regard to tumor size >1.5 cm (90.0% vs. 73.8%, p = 0.003).

Conclusions: The prognostic impact of ILN dissection on patients with stage IA NSCLC appears to be significantly influenced by tumor size, and this should be taken into account when choosing the most appropriate therapeutic modality.

KEYWORDS
early-stage, intrapulmonary lymph node, non-small cell lung cancer, prognosis, surgical strategy

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer and a leading cause of cancer-related deaths.[1] With the rapid improvement and widespread deployment of medical screening methods, such as low-dose helical computed tomography (CT), more and more early-stage lung cancers are detected,[2] and surgical radical resection still remains the standard of care with an overwhelming majority of excellent survival outcomes. More and more studies indicate that segmentectomy may have the advantage of preserving more lung function and providing a safe window for future resection for secondary lung malignancy, which has been oncologically equivalent and potentially less risky compared with lobectomy, and intensively investigated as a safe option to treat early-stage NSCLC.[3–7] It is widely accepted that adequate resection of NSCLC requires a surgical margin ≥2 cm or maximum diameter of the tumor.[8] Therefore, if an adequate surgical margin and necessary hilar and mediastinal lymph node dissection is warranted, the only significant

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difference between lobectomy and intentional segmentectomy is the extent of intrapulmonary lymph node dissection. Hence, intentional segmentectomy should be conducted with sufficient lymph node dissection to enable confirmation of pathological N0 status, otherwise a complementary lobectomy is required when positive lymph nodes are found in NSCLC.[9] Nevertheless, lymphatic drainage is always from near to distant, from intrapulmonary through the hilum to the mediastinum.[10] As intrapulmonary lymph nodes (ILNs) (stations 13–14) surround primary lung cancer, these may be affected in the very early stages and become the initial stations for metastasis. Therefore, the prerequisite for segmentectomy should at least ensure that the likelihood of positive ILNs being detected in the remaining lung segments within the same lobe is minimal. However, the dissection of ILNs remaining within the preserved segments is impossible, thus segmentectomy with uncertain ILNs metastatic status remains a potential risk for local recurrence. This may be one of the reasonable explanations for the only prospective randomized controlled trial (RCT) reported by the Lung Cancer Study Group in 1995, which found that segmentectomy yielded a significant tripling of local recurrence and poorer survival compared with lobectomy, and as a matter of course, the RCT basically established lobectomy as the gold standard for treating stage IA NSCLC.[11]

In clinical practice, the hilar (stations 10–12) and mediastinal (stations 2–9) LNs are mainly regularly sought and removed for pathological examination. However, the ILNs are not routinely dissected and labeled because they are generally resected within the lobectomy (or greater) specimen.[12] Nevertheless, ILNs play an important role in the pathological staging of NSCLC.[13] A previous report discovered that missed ILN dissection may have caused six patients with pN1 to be downstaged to N0 and two patients with multiple station pN1 to be misdiagnosed with single stations.[13] Similar results were concluded by Huang et al. who reported that 16 patients with pN1 were downgraded to N0, and five multiple stations pN1 were misdiagnosed as single station N1.[14] In addition, in a previous study, a precise protocol via thin gross dissection for pathological examination of inadvertently discarded intrapulmonary lymph nodes in remnant lung resection specimens after routine examination demonstrated that approximately 60% of intrapulmonary lymph nodes are left unexamined, having partly identifiable metastasis, which may lead to upgrading in 11% of NSCLC patients at the final pathological stage.[12] We are all very familiar with the fact that pN stage is the main determinant of postsurgical treatment. For pathological stage IA NSCLC, no postoperative adjuvant therapy is required. However, if positive ILNs are confirmed on pathological examination, adjuvant chemotherapy is indicated as many patients may benefit from such treatment.[15] Theoretically, if ILNs are neglected, patients with early stage NSCLC with pathological N0 status harboring ILN metastasis (actually N1) are likely to be misdiagnosed and the administration of adjuvant therapy omitted, and they may subsequently experience an adverse prognosis, even after lobectomy or greater. Therefore, this study was designed in order to evaluate the possibility of this hypothesis. To the best of our knowledge, this is the first study which analyzes the prognostic impact of ILN dissection on patients with early stage NSCLC.

In this study we aimed to assess the clinical significance of ILN dissection by comparing the prognostic outcomes of patients with pathological stage IA NSCLC stratified based on tumor size who underwent either ILN dissection or omitted before and after propensity score matching (PSM), in order to facilitate more accurate determination of surgical mode and adjuvant interventions.

METHODS

Patients

Between February 2016 and November 2019, a total of 416 consecutive patients diagnosed with pathological stage IA NSCLC who were treated with standard radical lung resection (lobectomy or greater) with systematic lymphadenectomy and postoperative pathology confirmed complete resection (R0) within our department were enrolled. The patients were divided into two groups: 265 patients underwent ILN dissection (ILN^{D+} group), in whom N1 nodes included stations 10 to 14; the other 151 patients with N1 nodes only included stations 10 to 12 and did not undergo dissection (ILN^{D-} group). The following patients were excluded: patients who were treated with preoperative neoadjuvant chemotherapy, and patients who who did not have primary lung cancer. LN station nomenclature was assessed based on the International Association for the Study of Lung Cancer (IASLC) classification system.[16] This study was approved by the ethics committees of Nanjing Chest Hospital and all patients participating in this study provided informed consent after completely discussing with their surgeons about the benefits and risks of radical lung resection.

Operative procedure and lymph node evaluation

All patients received preoperative staging procedures including chest contrast-enhanced high-resolution computed tomography (CT) with a slice thickness of 1 mm, brain magnetic resonance imaging, CT scan or ultrasonography of the abdomen, bone scintigraphy and positron emission tomography-computed tomography (PET-CT). In addition, preoperative cardiopulmonary function tests were also performed to assess tolerance to the planned pulmonary resection. The lobectomy or greater (i.e., sleeve lobectomy, bilobectomy, or pneumonectomy) was conducted according to the tumor position and lymphadenectomy was based on the National Comprehensive Cancer Network (NCCN) guidelines.[17]

After lobectomy or greater was completed, for N1 stations, station 10 (hilar), station 11 (interlobar) and station 12 (lobar) LNs were intraoperatively dissected in vitro by

the second surgical assistant and labeled separately. However, station 13 (segmental) and station 14 (subsegmental) LNs were collected and sent for pathological examination at the surgeon's discretion. In our center, ILN dissection was encouraged but was not mandatory.

Postoperative follow-up

All patients were followed up every three months after surgery for the first two years and subsequently every six months and all clinical data were obtained from hospital and outpatient medical records. The primary endpoint was disease-free survival (DFS), which was defined as the time interval between the date of surgical resection and the date of first locoregional recurrence, or death because of lung cancer or the last follow-up. The follow-up period was conducted in February 2020. The median follow-up was 18 months (range: 3–48 months) for the ILN^{D+} group and 24 months (range: 3–48 months) for the ILN^{D-} group.

Statistical analysis

Propensity score matching analysis was applied to balance observed confounders between the ILN^{D+} and the ILN^{D-} groups, and was calculated by multiple logistic regression which considered the following variables: age, gender, smoking history, imaging feature, tumor size, tumor location, serum CEA level (ng/ml), pathological subtype, pathological T (pT) stage, tumor differentiation and mediastinal lymphadenectomy. The two groups were matched 1:1 with 0.01-caliper width using the nearest neighbor method. For further analysis, we subgrouped these patients into three groups based on tumor size (≤1; 1–2; 2–3 cm), and the 1–2 cm group was further divided into 1–1.5 and 1.5–2 cm. The continuous variables were presented as mean and standard deviation and compared with a *t* test. Chi-squared or Fisher's exact test was used for categorical variables. Survival curves were generated by the Kaplan–Meier method to calculate four-year DFS in different groups using confirmed recurrences, and survival rates were evaluated by log-rank test. Univariate and multivariate cox regression analysis were performed to estimate the significant impact of ILN dissection and other factors on the prognosis, and the hazard ratio (HR) was calculated for 95% confidence intervals (95% CI). Statistical analysis was two-sided, and a *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS version 24.0 software (IBM Corp).

RESULTS

Baseline characteristics before and after PSM

A total of 416 patients were included in the final analysis. Table 1 summarizes the characteristics of all early-stage NSCLC patients. There were 212 (51%) male patients with a median age of 61 years (range: 28–84 years). A total of 265 (63.7%) patients underwent ILN dissection (ILN^{D+} group) and 151 (36.3%) patients in the group did not undergo dissection (ILN^{D-} group). After 1:1 PSM, 140 matched pairs (n = 280) were selected with balanced clinicopathological characteristics.

Survival analysis of ILN dissection before PSM based on tumor size

Before PSM, Kaplan–Meier and log-rank method showed that the prognostic outcome was better for patients who underwent ILN dissection compared with those in whom ILN dissection was omitted (90.1% vs. 79.7%, p = 0.003) (Figure 1). Several variables, such as imaging feature (p = 0.026), tumor size (p = 0.032), and pathological T stage (p = 0.026), were all significant factors for DFS on univariate analysis. The remaining variables had no impact on DFS. Multivariate analysis showed that the ILN dissection was an independent risk factor for DFS (HR: 0.389, 95% CI: 0.180–0.841, p = 0.016). Detailed information is shown in Table 2.

We further evaluated the impact of ILN dissection on the prognosis stratified by tumor size. Kaplan–Meier survival analysis and log-rank comparison revealed no statistical difference between the ILN^{D+} and ILN^{D-} groups with a tumor size ≤1.0 cm (93.3% vs. 100%, p = 0.371). In patients with a tumor size between 2 and 3 cm, however, the log-rank test showed that the ILN^{D+} group had a significantly superior DFS compared with the ILN^{D-} group (88.4% vs. 71.8%, p = 0.038). In addition, DFS was improved in the ILN^{D+} group compared with the ILN^{D-} group in patients with a tumor size between 1–2 cm (90.6% vs. 80.6%, p = 0.022). However, patients with 1–2 cm tumor size were further subgrouped into two groups (1–1.5 cm and 1.5–2 cm). Interestingly, similar results in tumor size ≤1.5 but >1 cm were found in patients with a tumor size ≤1.0 cm (p = 0.346); however, tumor size ≤2 but >1.5 cm had similar results in patients with a 2–3 cm tumor size (p = 0.044).

In total, the Kaplan–Meier method and log-rank comparison revealed no statistical difference between the ILN^{D+} and ILN^{D-} groups with a tumor size ≤1.5 cm (90.6% vs. 92.7%, p = 0.715) (Figure 2(a)). However, the log-rank test showed that the ILN^{D+} group had a significantly superior survival compared with the ILN^{D-} group when the tumor size was >1.5 cm (90.0% vs. 73.8%, p = 0.003) (Figure 2(b)).

Survival analysis of ILN dissection after PSM based on tumor size

After PSM, Kaplan–Meier and log-rank method showed that the prognostic outcome was still better for patients who underwent ILN dissection compared with those that did not

TABLE 1 Clinicopathological characteristics of patients with and without ILN dissection before and after propensity score matching

Characteristics	Before 1:1 PSM (%)			After 1:1 PSM (%)		
	ILN^{D+} group (n = 265)	ILN^{D-} group (n = 151)	p-value	ILN^{D+} group (n = 140)	ILN^{D-} group (n = 140)	p-value
Gender, n (%)			0.685			0.401
Male	133 (50.2)	79 (52.3)		80 (57.1)	73 (52.1)	
Female	132 (49.8)	72 (47.7)		60 (42.9)	67 (47.9)	
Age (years)			0.184			0.230
<61, n (%)	132 (49.8)	65 (43.0)		69 (49.3)	59 (42.1)	
≥61, n (%)	133 (50.2)	86 (57.0)		71 (50.7)	81 (57.9)	
Mean ± SD	60.4 ± 9.5	60.7 ± 10.3	0.761	60.1 ± 9.4	60.7 ± 10.3	0.655
Median (minimum, maximum)	61 (33, 83)	62 (28, 84)		61 (33, 80)	62 (28, 84)	
Smoking history, n (%)			0.875			0.783
Never	200 (75.5)	115 (76.2)		104 (74.3)	106 (75.7)	
Current/former	65 (24.5)	36 (23.8)		26 (25.7)	34 (24.3)	
Imaging feature, n (%)			0.996			0.964
Pure ground glass	17 (6.4)	10 (6.6)		10 (7.1)	10 (7.1)	
Part-solid	77 (29.1)	44 (29.1)		38 (27.1)	40 (28.6)	
Pure solid	171 (64.5)	97 (64.2)		92 (75.7)	90 (64.3)	
Tumor size (cm)			0.674			0.719
≤1.5, n (%)	125 (47.2)	68 (45.0)		62 (44.3)	65 (46.4)	
>1.5, n (%)	140 (52.8)	83 (55.0)		78 (55.7)	75 (53.6)	
Mean ± SD	1.8 ± 0.7	1.8 ± 0.7	0.724	1.8 ± 0.7	1.7 ± 0.7	0.845
Median (minimum, maximum)	1.7 (0.5, 3)	1.8 (0.5, 3)		1.8 (0.6, 3)	1.8 (0.5, 3)	
Tumor location, n (%)			0.745			0.849
RUL	92 (34.7)	44 (29.1)		45 (32.1)	40 (28.6)	
RML	18 (6.8)	10 (6.6)		12 (8.6)	9 (6.4)	
RLL	39 (14.7)	24 (15.9)		19 (13.6)	24 (17.1)	
LUL	77 (29.1)	52 (34.4)		45 (32.1)	47 (33.6)	
LLL	39 (14.7)	21 (13.9)		19 (13.6)	20 (14.3)	
Serum CEA level (ng/mL)			0.746			0.472
<2.3, n (%)	122 (46.0)	72 (47.7)		62 (44.3)	68 (48.6)	
≥2.3, n (%)	143 (54.0)	79 (52.3)		78 (55.7)	72 (51.4)	
Mean ± SD	2.8 ± 2.1	3.2 ± 3.1	0.166	2.9 ± 2.2	2.9 ± 2.0	0.744
Median (minimum, maximum)	2.3 (0.2, 17)	2.4 (0.3, 23.1)		2.4 (0.2, 12.4)	2.3 (0.3, 13.3)	
Pathological subtype n (%)			0.838			0.426
Adenocarcinoma	242 (91.3)	137 (90.7)		124 (88.6)	128 (91.4)	
Squamous cell carcinoma	23 (8.7)	14 (9.3)		16 (11.4)	12 (8.6)	
Tumor differentiation, n (%)			0.509			0.860
Well	110 (41.5)	54 (35.8)		50 (35.7)	51 (36.4)	
Moderate	143 (54.0)	89 (58.9)		82 (58.9)	83 (59.3)	
Poor	12 (4.5)	8 (5.3)		8 (5.7)	6 (4.3)	
Pathological T stage, n (%)			0.595			0.980
T1a	54 (20.4)	35 (23.2)		33 (23.6)	35 (25.0)	
T1b	147 (55.5)	76 (50.3)		72 (51.4)	70 (50.0)	
T1c	64 (24.2)	40 (26.5)		35 (25.0)	35 (25.0)	
Number of resected TLNs						
Mean ± SD	15.4 ± 4.8	11.3 ± 3.1	<0.001	15.0 ± 4.2	11.2 ± 3.0	<0.001
Median (minimum, maximum)	15 (7, 36)	11 (6, 21)		15 (7, 29)	11 (6, 21)	

(Continues)

TABLE 1 (Continued)

Characteristics	Before 1:1 PSM (%)			After 1:1 PSM (%)		
	ILN^{D+} group (n = 265)	ILN^{D-} group (n = 151)	p-value	ILN^{D+} group (n = 140)	ILN^{D-} group (n = 140)	p-value
Number of resected N1 nodes						
Mean ± SD	8.3 ± 3.5	4.3 ± 1.2	<0.001	8.1 ± 3.2	4.2 ± 1.2	<0.001
Median (minimum, maximum)	8 (3, 24)	4 (3, 8)		8 (3, 18)	4 (3, 8)	
Number of resected N2 nodes						
Mean ± SD	7.1 ± 2.2	7.1 ± 2.3	0.755	7.0 ± 2.2	7.0 ± 2.2	0.826
Median (minimum, maximum)	7 (3, 14)	7 (3, 14)		7 (3, 14)	7 (3, 14)	

Abbreviations: LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SD, standard deviation; TLNs, total lymph nodes.

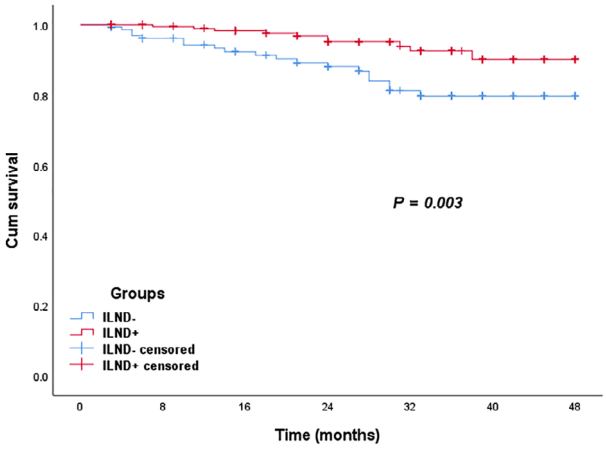

FIGURE 1 Survival curves for patients with or without ILN dissection in stage IA NSCLC before propensity score matching. ILND, intrapulmonary lymph node dissection; NSCLC, non-small cell lung cancer

undergo ILN dissection (95.5% vs. 80.6%, p = 0.003) (Figure 3). The prognostic factors affecting DFS were imaging feature (p = 0.046), tumor size (p = 0.040) and pathological T stage (p = 0.049) by univariate analysis. Additional multivariate analysis showed that the ILN dissection was an independent risk factor for DFS (HR: 0.216, 95% CI: 0.063–0.743, p = 0.015). Detailed information is presented in Table 3.

Subgroup analysis stratified by tumor size was also carried out after PSM. Kaplan–Meier survival analysis and log-rank comparison revealed that DFS was comparable between the ILN^{D+} and ILN^{D-} groups with a tumor size ≤1.5 cm (100% vs. 91.6%, p = 0.132) (Figure 4(a)). However, the four-year DFS of the ILN^{D+} group was much improved compared to that of the ILN^{D-} group when the tumor size was >1.5 cm (93.2% vs. 75.6%, p = 0.013) (Figure 4(b)).

DISCUSSION

Lymph node dissection is one of the most crucial components for accurately staging NSCLC, providing important prognostic factors and subsequently deciding the most appropriate therapeutic modality. The standard treatment mode for patients with early-stage NSCLC involves lobectomy with systemic mediastinal and hilar LN dissection without requirements for ILN dissection.[11] As such, the clinical application of ILN dissection for pathological examination varies in patients with early-stage NSCLC. Therefore, to date, no study involving the prognostic impact of ILN dissection in pathological stage IA NSCLC patients has been reported. One possible explanation is the extent of ILN excision and its benefits remain under debate and controversy.[18]

In our study, the results revealed that the four-year DFS was significantly higher in the ILN^{D+} group than in the ILN^{D-} group and multivariate analysis confirmed that ILN dissection was the independent predictor of better DFS in patients with stage IA NSCLC before and after PSM. The reason for this may be that ILN dissection assists by removing nodes harboring ILN metastasis and undetected micrometastases, thereby achieving a minimum incidence of local recurrence, which could subsequently facilitate better control of local tumors. Moreover, after subgrouping the stage IA NSCLC patients by tumor size, we found that there was no difference in prognostic outcome of patients in the ILN^{D+} group and the ILN^{D-} group with tumor size ≤1 cm, both by multivariate analysis before PSM. This indicated that ILN metastasis seldom occurred in patients with tumor size ≤1 cm and that ILN dissection may not be required. As a result, intentional segmentectomy should be utilized for patients with tumor size ≤1 cm, provided that a sufficient surgical margin and lymph node dissection are achievable. However, we found a significant difference in the prognostic outcome of patients with tumor size >2 but ≤3 cm in both groups both by multivariate regression analysis before and after PSM, which suggested that ILN metastasis may be more frequently detected, and extensive ILN dissection should be conducted in these patients. As a result, in order to achieve accurate pathological staging, the necessary adjuvant therapy should be administered in order to minimize local recurrence and systematic spread, and lobectomy with a complete ILN examination is preferable for patients with tumor size >2 but ≤3 cm, especially those diagnosed as pN0. Moreover, we further subgrouped patients with tumor size >1 but ≤2 cm into

TABLE 2 Univariate and multivariate cox regression analysis of prognostic factors in stage IA NSCLC before PSM

	Univariate analysis		Multivariate analysis	
Predictor	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**
Gender	0.416	0.736 (0.351–1.541)		
Age	0.135	1.758 (0.839–3.681)		
Smoking history	0.823	1.108 (0.451–2.722)		
Imaging feature	**0.026**	2.757 (1.127–6.745)	0.072	2.323 (0.929–5.808)
Tumor size	**0.032**	2.864 (1.092–7.513)	0.365	1.748 (0.523–5.844)
Tumor location	0.891	1.017 (0.796–1.299)		
Serum CEA level (ng/ml)	0.460	0.754 (0.356–1.596)		
Pathological subtype	0.304	1.740 (0.605–5.003)		
Tumor differentiation	0.066	1.795 (0.963–3.347)		
Pathological T stage	**0.026**	2.000 (1.085–3.688)	0.381	1.400 (0.660–2.969)
Number of resected TLNs	0.683	0.981 (0.897–1.074)		
Number of resected N1 nodes	0.719	0.978 (0.865–1.105)		
Number of resected N2 nodes	0.791	0.978 (0.828–1.154)		
ILN dissection	**0.005**	0.332 (0.154–0.715)	**0.016**	0.389 (0.180–0.841)

Abbreviations: CI, confidence interval; HR, hazard ratio; ILN, intrapulmonary lymph node; NSCLC, non-small cell lung cancer; PSM, propensity score matching; TLNs, total lymph nodes.

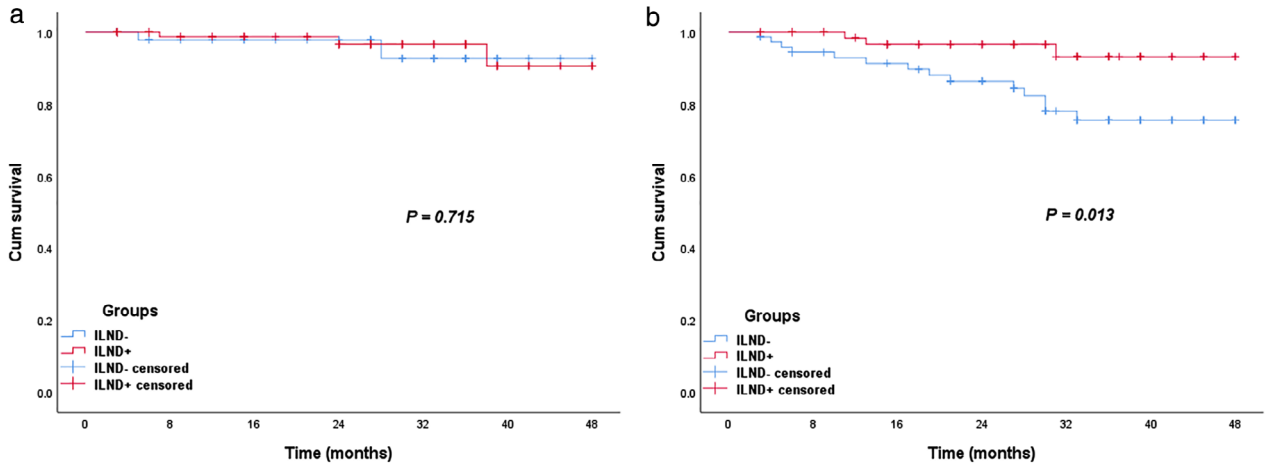

FIGURE 2 (a) and (b) Impact of ILN dissection on disease-free survival (DFS) in patients with stage IA NSCLC stratified by tumor size (≤1.5 and > 1.5 cm) before propensity score matching. ILND, intrapulmonary lymph node dissection; NSCLC, non-small cell lung cancer

two groups (1–1.5 and 1.5–2 cm) before PSM. We also found that the prognostic outcome was similar for patients in the ILN^{D+} and ILN^{D-} groups with tumor size >1 but ≤1.5 cm, and similar results for patients with tumor size ≤1 cm, which suggested that intentional segmentectomy not only permitted ILN sampling but also saved lung function, and should be applied in patients with tumor size >1 but ≤1.5 cm. However, there was a significant difference in prognostic outcome between patients who underwent ILN dissection, or in whom it was omitted, with tumor size >1.5 but ≤2 cm, which was consistent with tumor size >2 but ≤3 cm. Therefore, the same surgical mode of lobectomy, with assessment of all relevant ILNs, is still preferable for patients with tumor size >1.5 but ≤2 cm. Therefore, we further divided the patients with stage IA NSCLC into two groups stratified by tumor size (≤1.5 and > 1.5 cm), and we found no difference in the prognostic outcome of patients with tumor size ≤1.5 cm that underwent either ILN dissection, or in whom ILN dissection was omitted, by multivariate regression analysis before and after PSM. However, the prognostic outcome was significantly different between patients with tumor size >1.5 cm who underwent either ILN dissection or in whom ILN dissection was omitted, by multivariate regression analysis before and after PSM. These results indicate that for patients with tumor size ≤1.5 cm, intentional segmentectomy with systemic mediastinal and hilar LN dissection, with or without ILN sampling, could be utilized; for patients with tumor size >1.5 cm, lobectomy with systemic mediastinal and thorough N1 including ILN dissection is preferable in order to identify high-risk early-stage cases, particularly those with a pure-solid component.

Theoretically, ILNs are closest to the tumor-bearing and may be affected in the very early-stages, becoming the initial station for metastasis because the lymphatic drainage is always from the near to the distant, from intrapulmonary through the hilum to the mediastinum.[10] Therefore, ILNs are dissected after resection for two main reasons: accurate staging and confirmation of "pN0" as pN1 or true pN0 for postoperative management decision-making. In addition, the accuracy of staging can be optimized by this procedure because of the exclusion of confounding data in patients with ILN involvement. In recognition of these, the Association of Directors of Anatomic and Surgical Pathology recommended retrieving each node for pathological examination including a thorough ILN dissection.[19] However, in current clinical practice, ILNs are rarely collected in early-stage NSCLC for three main reasons. First, some surgeons and pathologists are not aware of the importance of ILNs in improving the accuracy of routine nodal staging evaluation of NSCLC and accurate staging information for use in postoperative treatment. Second, some surgeons and pathologists consider that detection of ILNs is time-consuming and challenging. Third, to date, there is no data related to prognosis regarding the impact on patients with early-stage NSCLC implementation of ILN dissection. This raises the question as to whether the cost in not only money but time and resources is necessary with no clearly stated benefits. As a result, ILN dissection in the resection specimen for pathological examination is variable in patients with early-stage NSCLC. Therefore, it is meaningful to only select patients in which pathological examination of ILNs is essential, thereby reducing an unnecessary use of resources on patients with early-stage NSCLC in which pathology of ILNs is nonessential. In the present study, our results indicated that ILN dissection should be routinely conducted only in high-risk early-stage patients with tumor size >1.5 but ≤3 cm for accurate affirmation of true pN0 in pathological stage IA NSCLC because of the significant difference in prognostic outcome of patients in the ILN^{D+} and ILN^{D-} groups, which might be because of the higher ILN metastatic rate and this further indicates the importance of ILN dissection to provide a basis for improvement in patient prognosis. In contrast, according to there being no difference in prognostic outcome of patients with tumor size ≤1.5 cm, ILN dissection could be ignored.

As a type of radical resection, intentional segmentectomy is now generally accepted as the safer option when treating selected early-stage patients with tumor size ≤2 cm without hilar or mediastinal lymph node metastasis.[20] However, considering the line of lymphatic drainage, intentional segmentectomy should at least ensure the least possibility of ILN metastasis in the surrounding segments within the same lobe and ILN metastasis is another contraindication for this

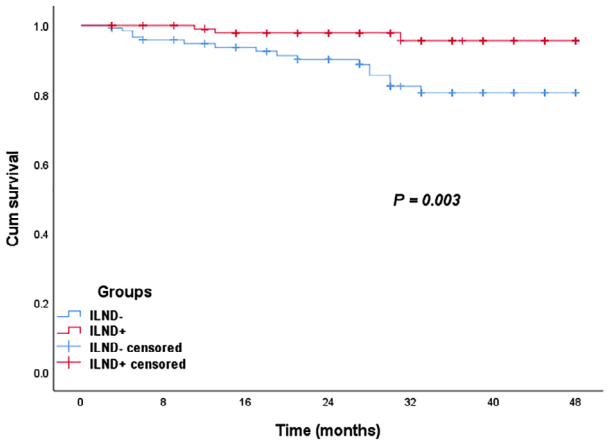

FIGURE 3 Survival curves for patients with or without ILN dissection in stage IA NSCLC after propensity score matching. ILND, intrapulmonary lymph node dissection; NSCLC, non-small cell lung cancer

TABLE 3 Univariate and multivariate cox regression analysis of prognostic factors in stage IA NSCLC after PSM

	Univariate analysis		Multivariate analysis	
Predictor	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**
Gender	0.540	0.747 (0.294–1.899)		
Age	0.698	0.837 (0.340–2.060)		
Smoking history	0.833	1.116 (0.402–3.100)		
Imaging feature	**0.046**	4.168 (1.028–16.891)	0.096	3.393 (0.805–14.302)
Tumor size	**0.040**	4.661 (1.075–20.215)	0.222	2.992 (0.526–17.352)
Tumor location	0.785	1.043 (0.771–1.410)		
Serum CEA level (ng/ml)	0.604	1.128 (0.504–3.252)		
Pathological subtype	0.384	1.729 (0.503–5.938)		
Tumor differentiation	0.128	1.887 (0.833–4.274)		
Pathological T stage	**0.049**	2.114 (1.003–4.458)	0.649	1.236 (0.495–3.087)
Number of resected TLNs	0.144	0.900 (0.781–1.037)		
Number of resected N1 nodes	0.186	0.866 (0.700–1.072)		
Number of resected N2 nodes	0.422	0.914 (0.733–1.139)		
ILN dissection	**0.009**	0.192 (0.056–0.661)	**0.015**	0.216 (0.063–0.743)

Abbreviations: CI, confidence interval; HR, hazard ratio; ILN, intrapulmonary lymph node; NSCLC, non-small cell lung cancer; PSM, propensity score matching; TLNs, total lymph nodes.

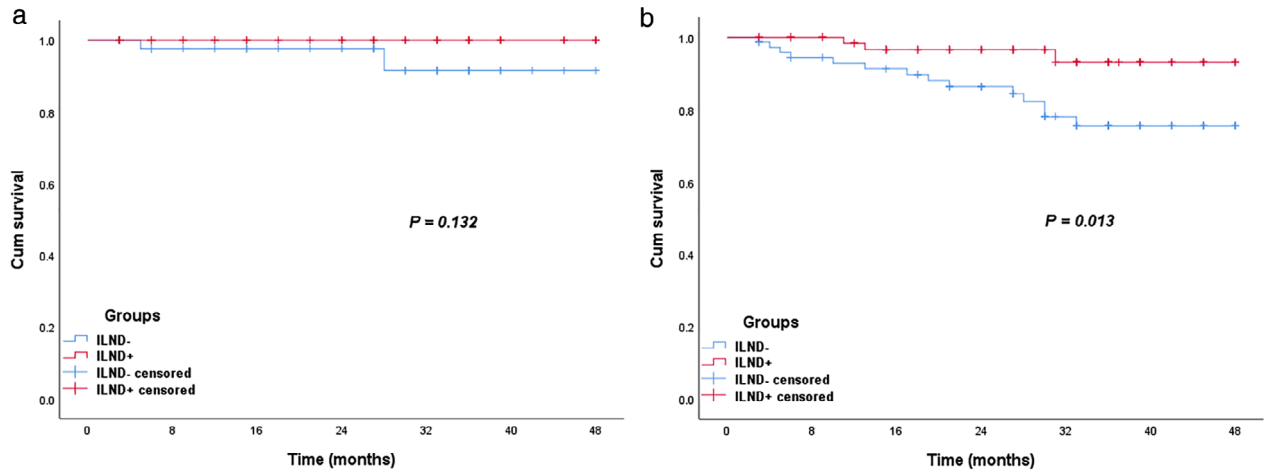

FIGURE 4 (a) and (b) Impact of ILN dissection on disease-free survival (DFS) in patients with stage IA NSCLC stratified by tumor size (≤1.5 and > 1.5 cm) before propensity score matching. ILND, intrapulmonary lymph node dissection; NSCLC, non-small cell lung cancer

operative mode. In addition, complete ILN dissection is limited by anatomic location and may cause accessory injury to the preserved segmental bronchi, arterial branches, venous branches or pulmonary parenchyma. These cases are extremely dependent on a surgeon's skills and thus almost impossible to implement. Intentional segmentectomy with unclear ILN metastasis holds a potential oncological risk, which might illustrate the high incidence of local recurrence observed after this procedure, even in those patients where the tumor size is ≤2 cm.[21] Several studies have previously compared the oncological results to intentional segmentectomy and lobectomy in patients with early-stage NSCLC. However, controversial conclusions were proposed, even though they were estimated from the same large database of the Surveillance, Epidemiology, and End Results (SEER).[22–25] Some of the studies discovered that intentional segmentectomy yielded a significantly higher incidence rate of recurrence and adverse survival than lobectomy in patients with early-stage NSCLC with a tumor size ≤2 cm.[22,23] On the contrary, others discovered that prognostic outcomes in early-stage NSCLC, particularly in those patients with tumor size ≤2 cm, were comparable between intentional segmentectomy and lobectomy.[24,25] In addition, similar disagreement also exists in some previous meta-analyses and the potential explanations have not yet been clarified.[26–28]

According to the eighth edition of the Tumor Node Metastasis (TNM) staging system, tumor size ≤2 cm (T1a in the seventh edition) could be further divided into ≤1 cm (T1a) and 1–2 cm (T1b),[29] hinting that tumor size still remains a significant factor in predicting the prognosis of patients with early-stage NSCLC. It therefore seems extremely important for a suitable surgical mode to be selected for patients with early-stage NSCLC stratified by tumor size. In our study, we further divided patients with tumor size >1 but ≤2 cm into two subgroups (1–1.5 and 1.5–2), and significant different survival outcomes were found in the ILN $^{D+}$ and ILN^{D-} groups between the two subgroups, indicating that multiple heterogeneities existed, even in patients with tumor size >1 but ≤2 cm. Therefore, this finding may present a preliminary response to previous studies that have drawn different conclusions regarding the comparison between intentional segmentectomy and lobectomy in patients with early-stage NSCLC with a tumor size ≤2 cm.[22,30]

There were several limitations in our study. First, similar to other retrospective series, the potential selection bias was inevitable. Therefore, PSM was used to balance the intergroup differences to reduce the influence in outcomes between the groups. Second, we performed a multivariate Cox regression analysis to filter potential prognostic factors; however, other variables such as lymphovascular invasion and adenocarcinoma subtype were not provided, which may have affected the prognosis. Third, the ILN location was not divided into tumor-bearing and nontumor bearing depending on the segmental bronchus involved. Fourth, it was difficult to retrieve the ILNs in the lobectomy specimens in the ILN^{D-} group, so the metastasis rate of ILN in ILN^{D-} group was unclear. Finally, the conclusions were drawn from only a small-size population of patients with early-stage NSCLC undergoing lobectomy without outcome evaluation from a direct comparison between intentional segmentectomy and lobectomy. Hence, the impact of our surgical strategies on oncological outcomes remains unclear, and recommending intentional segmentectomy based on this study is inherently risky. Consequently, long-term oncological outcomes remain to be thoroughly confirmed and need to be assessed further with a large-scale sample size and multicenter randomized clinical trials, which may affect the choice of patients with early-stage NSCLC for lobectomy or intentional segmentectomy.

In conclusion, the prognostic impact of ILN dissection appears to be significantly influenced by tumor size in patients with pathological stage IA NSCLC. Based on these findings, surgical strategies for early-stage cases stratified by tumor size are as follows: for tumor size ≤1.5 cm, intentional segmentectomy with systemic mediastinal and hilar LN dissection could be utilized, regardless of ILN sampling; for tumor size >1.5 cm, lobectomy with systemic lymph node dissection including ILN dissection is preferable to identify high-risk early-stage cases, particularly in patients with pure-solid

component lesions who might be potential candidates for post surgical treatment.

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CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest.

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