ORIGINAL ARTICLE

Assessment of non-lobe-specific lymph node metastasis in clinical stage IA non-small cell lung cancer

Zhirong Zhang [ORCID], Jinbai Miao, Qirui Chen, Yili Fu, Hui Li & Bin Hu

Department of Thoracic Surgery, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

Abstract

Background: The rationality of selective mediastinal lymph node dissection based on lobe-specific metastasis is still controversial. The correlation of lymph node metastasis in lobe-specific lymphatic drainage regions (LSDRs) and non-LSDRs has not been widely reported. The purpose of this study was to investigate the variables affecting nodal metastasis in non-LSDRs and to further evaluate the rationality of selective lymphadenectomy in clinical stage IA non-small cell lung cancer (NSCLC) patients.

Methods: The clinicopathological information of 316 patients with clinical stage IA NSCLC who underwent lobectomy with systematic lymph node dissection between June 2014 and June 2018 was retrospectively collected for analysis.

Results: The overall lymph node metastasis rate was 19.3%. For 35 patients with positive LSDR lymph nodes, the non-LSDR lymph node metastasis rate was 31.4%. Only one patient (0.4%) among 281 patients with negative LSDR lymph nodes had nodal spread in non-LSDRs. Univariate analysis identified that solid consistency, worse differentiation, and positive status in LSDRs were unfavorable predictive variables of lymph node metastasis in non-LSDRs. Multivariate analysis showed that nodal metastasis in LSDRs was the only independent predictor of nodal involvement in non-LSDRs ($P < 0.001$).

Conclusion: For patients with clinical stage IA NSCLC, non-LSDR lymph node metastasis mainly depends on the involvement of the LSDR lymph node. Our observations may indicate the potential implications for the reasonable management of lymphadenectomy in stage IA NSCLC patients.

Introduction

Lobectomy, along with systematic lymph node dissection (SLND), including mediastinal and hilar lymphadenectomy, remains the primary and preferred approach for the treatment of early stage non-small cell lung cancer (NSCLC).[1] However, not all NSCLC patients have mediastinal lymph node metastasis and whether SLND is necessary for all early-stage NSCLC patients is controversial. With advances in early-stage lung cancer detection and more comprehensive study of lymphatic drainage and the metastasis pathway, the lymph node spread pattern in NSCLC has been investigated in detail and it has been determined that nodal metastasis follows a predictable lobe-specific manner.[2–5] Based on this, several scholars have advocated that nodal dissection in the lobe-

specific lymphatic drainage region (LSDR), so called "selective lymphadenectomy," may be sufficient, especially for early-stage NSCLC.[6–8] Ishiguro et al. suggested that it is more reasonable to perform selective LND, especially in patients with no apparent lymph node metastasis, poor pulmonary reserve, or elderly patients.[9]

Nevertheless, selective lymphadenectomy has not been broadly accepted, partly because it is unknown whether lymph node involvement could occur in non-LSDRs in a lobe-specific pattern, and the correlation of nodal spread in LSDRs and non-LSDRs and the predictors for nodal metastasis in non-LSDRs are not very clear.

Therefore, the purpose of this study was to investigate the relation of nodal spread between LSDRs and non-LSDRs and variables affecting lymph node metastasis in

non-LSDRs to provide reliable evidence to evaluate the rationality of lobe-specific nodal dissection for clinical stage IA NSCLC patients.

Methods

Study design and patient selection

We selected 760 patients with primary clinical stage IA NSCLC who underwent lobectomy with systematic hilar and mediastinal LND between June 2014 and June 2018. One hundred eighty-three patients without positron emission tomography-computed tomography (PET-CT) results with tumor diameters > 1 cm, 34 patients with multiple lung lesions, 211 patients who did not meet the established study criteria for SLND, and 16 patients with a history of other non-pulmonary malignances were excluded. A total of 316 patients were enrolled in the study (Fig 1). Clinicopathological information was retrospectively collected. Clinical and pathological staging was determined based on the 8th edition American Joint Council on Cancer Tumor Node Metastasis Staging system. This study was approved by the Institutional Review Board and conducted according to the guidelines approved by the ethics committee.

Preoperative evaluation

Whole body PET-CT or contrast-enhanced chest CT scans were performed preoperatively. Other routine preoperative examinations of lung cancer patients included chest radiography, abdominal ultrasonography, magnetic resonance imaging of the brain, bone scan, bronchoscopy, and cardiopulmonary function tests. All enrolled patients underwent curative lobectomy and lymphadenectomy via thoracotomy or video-assisted thoracic surgery (VATS).

Lobe-specific lymphatic drainage region (LSDR)

The lobe-specific pattern of nodal metastasis is widely recognized. We classified the sites of hilar and mediastinal lymph nodes into LSDR and non-LSDR according to each lobe based on previous studies and International Association for the Study of Lung Cancer staging.[2,9–11] The LSDR and non-LSDR of different tumor locations are shown in Table 1. LSDRs were defined as: stations 2R, 4R, and 10 for right upper lobe tumors; stations 7 and 10 for the right middle lobe; stations 2L, 4L, 5, 6, and 10 for left upper lobe tumors; and stations 7, 8, 9, and 10 for lower lobe tumors on both sides. Non-LSDRs were defined as: stations 7, 8, and 9 for both side upper lobes; stations 2R and 4R for the right middle and lower lobes; and stations 2L, 4L, 5, and 6 for the left lower lobe.

Systematic lymph node dissection

SLND combined with lobectomy was performed for all patients as the standard surgical procedure and curative
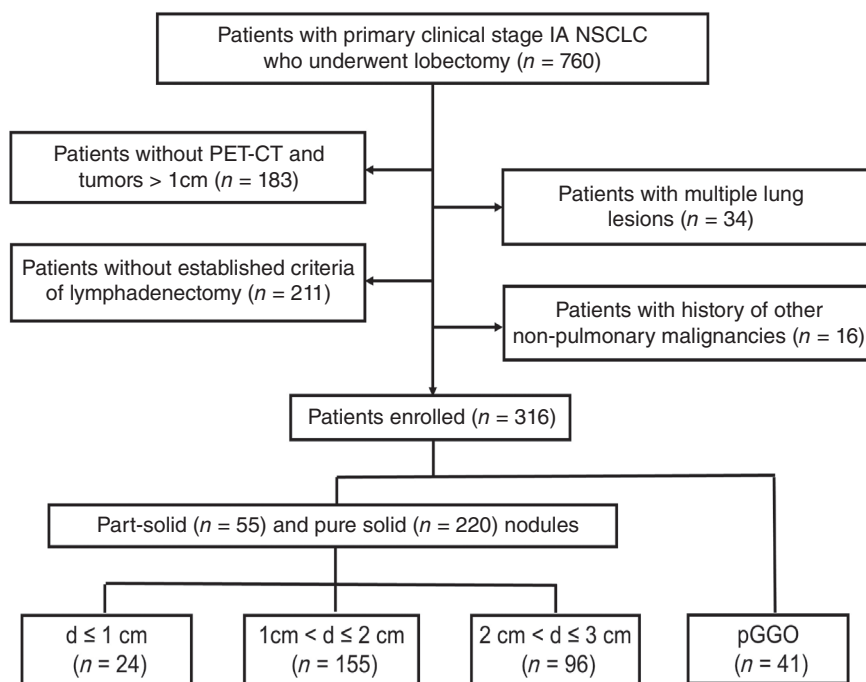
Figure 1 Flowchart of eligible patients enrolled in this study. NSCLC, non-small cell lung cancer; PET-CT, positron emission tomography-computed tomography; pGGO, pure ground-glass opacity.

surgery via thoracotomy or VATS. The en block removal of all tissue including the lymph nodes and surrounding fatty tissue within anatomic landmarks was performed in SLND. Patients who underwent nodal sampling were excluded. In this study, the inclusion criteria for SLND were defined as a pathological examination of a minimum of six lymph nodes, from the hilar and at least three mediastinal stations, in which a subcarinal station must be included. For right-side tumors, the en block fatty tissues, including stations 2R, 3, 4R, 7, 8, 9, and 10R (hilar), were removed, as well as stations 2L, 4L, 5, 6, 7, 8, 9, and 10L (hilar) on the left side. Moreover, all of the patients in this study had at least one lymph node or one mediastinal station from the non-LSDR.

Statistical analysis

Continuous variables were summarized using mean ± standard deviation. Student's t, chi-square, or Fisher's exact tests were used to analyze differences in clinical characteristics and frequencies of lymph node metastasis among the different groups. The Fisher's exact test was used to test univariate associations between pN status in non-LSDRs and clinicopathological factors, and multivariable analysis was performed using logistic regression analysis. All data analyses were performed using SPSS version 20.0, and a P value of < 0.05 was considered statistically significant.

Results

Patient characteristics

The patient's demographic characteristics and clinicopathological information are presented in Table 2. The median age was 59 years (range: 31–79), and 55.1% of the patients were male. Most patients were non-smokers ($n = 208$, 65.8%) and asymptomatic ($n = 224$, 70.9%). The median tumor size was 2.0 cm (range: 0.6–3.0). In terms of consistency on appearance, 220 patients (69.6%) had solid tumors, 55 patients (17.4%) had part-solid tumors, and 41 patients (13.0%) had pure ground-glass opacity (pGGO)

Table 1 LSDRs and non-LSDRs of different tumor locations

Location	LSDRs	Non-LSDRs
Right upper	2R, 4R, 10	7, 8, 9
Right middle	7, 10	2R, 4R
Right lower	7, 8, 9, 10	2R, 4R
Left upper	2L, 4L, 5, 6, 10	7, 8, 9
Left lower	7, 8, 9, 10	2L, 4L, 5, 6

LSDRs, lobe-specific lymphatic drainage regions.

tumors. A GGO ratio of $> 25\%$ was found in 72 patients (22.8%). One hundred and seventy-seven patients (56.0%) underwent VATS, while thoracotomy was performed on 139 patients (44.0%). Most tumors were located at the right upper (36.4%) and left upper (23.4%) lobes. Peripherally located tumors were found in 284 (89.9%) patients by means of pathology, and pathologic examination of the

Table 2 Baseline characteristics of 316 patients

Variables	Total
Age, years, median (range)	59 (31–79)
Gender, n (%)	
Male	174 (55.1)
Female	142 (44.9)
Smoking status, n (%)	
Never	208 (65.8)
Former and current	108 (34.2)
Symptom status, n (%)	
Asymptomatic	224 (70.9)
Symptomatic	92 (29.1)
Preoperative CEA level, n (%)†	
≤ 5 ng/mL	230 (5.5)
> 5 ng/mL	39 (14.5)
Tumor SUVmax‡	
≤ 2.5	83 (33.1)
> 2.5	168 (66.9)
Tumor size, cm, median (range)	2.0 (0.6–3.0)
Consistency, n (%)	
Solid	220 (69.6)
Part solid	55 (17.4)
Pure GGO	41(13.0)
GGO ratio, n (%)	
≤ 25%	244 (77.2)
> 25%	72 (22.8)
Approach, n (%)	
VATS	177 (56.0)
Thoracotomy	139 (44.0)
Lobe of tumor, n (%)	
Right upper	115 (36.4)
Right middle	22 (7.0)
Right lower	62 (19.6)
Left upper	74 (23.4)
Left lower	43 (13.6)
Location, n (%)	
Central	32 (10.1)
Peripheral	284 (89.9)
Cell type, n (%)	
ADC	285 (90.2)
Non-ADC	31 (9.8)
Differentiation, n (%)§	
Well Moderately	73 (23.6)173 (56.0)
Poorly	63 (20.4)
pN status, n (%)	
pN0	255 (80.7)
pN1	31 (9.8)
pN2	30 (9.5)

Table 2 Continued

Variables	Total
pTNM stage, *n* (%)	
0	1 (0.3)
IA	113 (35.8)
IB	137 (43.4)
IIA	29 (9.2)
IIB	3 (0.9)
IIIA	31 (9.8)
IIIB	2 (0.6)

†Forty-seven patients without preoperative CEA value. ‡Sixty-five patients without maximum standardized uptake value (SUVmax). §Seven patients could not be evaluated. ADC, adenocarcinoma; GGO, ground-glass opacity; pTNM, pathological tumor node metastasis; VATS, video-assisted thoracic surgery.

resected specimen confirmed adenocarcinoma in 285 patients (90.2%); squamous cell carcinoma in 21 patients (6.6%); and other types in 10 patients, including 4 carcinoid, 2 large cell carcinoma, 3 adenosquamous carcinoma, and 1 sarcomatoid carcinoma. Of the 309 patients whose tumor differentiation was evaluated, well-differentiated tumors were observed in 73 patients (23.6%), while moderately and poorly differentiated tumors were observed in 173 (56.0%) and 63 (20.4%) patients, respectively. There were 255 node-negative patients (80.7%) and lymph node metastases were found in 61 patients (19.3%): 31 had pN1 disease and 30 had pN2 disease. One hundred thirteen (35.8%) patients were at stage IA, 137 (43.4%) patients with invasion of the visceral pleura were at stage IB, 32 (10.1%) patients were at stage II, and 33 patients (10.4%) were at stages IIIA and IIIB.

Incidence and factors of nodal involvement in non-LSDRs

Twelve patients (3.8%) had lymph node metastasis in non-LSDRs. In 35 patients with positive LSDR lymph nodes, the non-LSDR lymph node metastasis rate was 31.4% (11/35). Only one (0.4%) out of 281 patients with negative LSDR lymph nodes had non-LSDR lymph node involvement. Table 3 shows the results of univariate analysis of clinicopathological factors associated with nodal spread in non-LSDRs. Solid consistency (*P* = 0.021), worse differentiation (*P* = 0.034), and positive status in LSDRs (*P* < 0.001) showed significant associations with lymph node metastasis in non-LSDRs. There was no significant difference among patients by age, gender, smoking or symptom status, preoperative CEA level, total tumor size, approach, location, pT stage (T1 vs. T2), or cell type. In multivariate analysis, the variable identified as the independent predictor for lymph node metastasis in non-LSDRs was pN status in

LSDRs (hazard ratio [HR] 137.5; 95% confidence interval [CI] 17.0-1114.6; *P* < 0.001) (Table 4). The positive nodal stations in non-LSDRs for each lobe in 12 patients are summarized in Table 5. All of the positive lymph nodes in non-LSDRs for lung cancers in upper lobes were from subcarinal stations.

Discussion

It has been widely recognized that adequate lymph node assessment plays a vital role in the accurate staging and prognostic evaluation of NSCLC patients,[12] for which SLND has been universally recommended and accepted.[13] However, because of an increase in the detection of early-stage lung cancer, some scholars have advocated that this classic approach might not be necessary for all early-stage lung cancer patients. In our study, univariate analysis identified solid consistency, worse differentiation, and lymph node metastasis in LSDRs as unfavorable predictive variables for pN status in non-LSDRs. Moreover, multivariate analysis revealed that pN status in LSDRs was an independent predictor for lymph node metastasis in non-LSDRs (*P* < 0.001). In other words, non-LSDR lymph node metastasis mainly depends on LSDR lymph node involvement. Thus, it could be a useful index for planning limited surgical resection and benefit surgeons in the management of lymphadenectomy for stage IA NSCLC patients, especially when selective lymphadenectomy is suggested as an acceptable mode of dissection, at least for selected populations.

We classified the sites of hilar and mediastinal lymph nodes into LSDRs and non-LSDRs. Detailed descriptions of the drainage regions of the different lobes are presented in Table 1. At present, the lobe-specific pattern of nodal metastasis is widely recognized and there is growing evidence that the extent of LND could be tailored for patients with early-stage NSCLC. Upper lobe cancers tend to metastasize to the superior mediastinal lymph node. If the hilar or superior mediastinal lymph node is not involved, positive subcarinal lymph node metastasis is rarely found. In addition, the probability of skipping metastasis from lower lobe lesions to the upper mediastinum is very low.[2–5,14] Based on these results, researchers have argued that selective mediastinal dissection is as effective as SLND, and does not negatively impact the survival of patients.[9,15] However, many previous studies did not report the incidence of nodal involvement in non-LSDRs when lymph nodes are positive in LSDRs. We found that for 35 patients with positive lymph nodes in LSDRs, the nodal metastasis rate in non-LSDRs was 31.4%, while only one (0.4%) among 281 patients with negative LSDR lymph nodes had non-LSDR lymph node involvement. The rarity of non-LSDR lymph node involvement in patients with negative LSDRs may highlight the feasibility and necessity of

Table 3 Clinicopathological factors associated with pN status in non-LSDRs

Variables	n	pN(+) in non-LSDRs n (%)	pN(−) in non-LSDRs n (%)	P
Age (years)		60.67 ± 7.83	58.58 ± 8.93	0.926
Gender				0.665
Male	151	5 (3.3)	146 (96.7)	
Female	165	7 (4.2)	158 (95.8)	
Smoking status				1.000
Never	208	8 (3.8)	200 (96.2)	
Former and current	108	4 (3.7)	104 (96.3)	
Symptom status				0.196
Asymptomatic	224	11 (4.9)	213 (95.1)	
Symptomatic	92	1 (1.1)	91 (98.9)	
Preoperative CEA level†				0.140
> 5 ng/mL	39	4 (10.3)	35 (89.7)	
≤ 5 ng/mL	230	8 (3.5)	222 (96.5)	
Tumor SUVmax‡				1.000
> 2.5	168	8 (4.8)	160 (95.2)	
≤ 2.5	83	4 (4.8)	79 (95.2)	
Total size				0.365
> 2 cm	96	7 (7.2)	89 (92.7)	
≤ 2 cm	179	5 (2.8)	174 (97.2)	
Consistency				0.021
Solid	220	12 (5.5)	208 (94.5)	
Part solid + Pure GGO	96	0 (0.0)	96 (100.0)	
GGO ratio				0.041
≤ 25%	244	12 (4.9)	221 (95.1)	
> 25%	72	0 (0.0)	83 (100.0)	
Approach				0.869
VATS	177	7 (4.0)	170 (96.0)	
Thoracotomy	139	5 (3.6)	134 (96.4)	
Location				0.619
Central	32	0 (0.0)	32 (100.0)	
Peripheral	284	12 (4.2)	272 (95.8)	
pT stage§				0.308
T1	135	2 (1.5)	133 (98.5)	
T2	172	7 (4.1)	165 (95.9)	
Cell type				1.000
ADC	285	11 (3.9)	274 (96.1)	
Non-ADC	31	1 (3.2)	30 (96.8)	
Differentiation¶				0.034
Well	73	0 (0.0)	73 (100.0)	
Moderately	173	7 (4.0)	166 (96.0)	
Poorly	63	5 (7.9)	58 (92.1)	
Station 11–13				0.070
N(+)	44	4 (9.1)	40 (90.9)	
N(−)	272	8 (2.9)	264 (97.1)	
pN in LSDRs				< 0.001
N(+)	35	11 (31.4)	24 (68.6)	
N(−)	281	1 (0.4)	280 (99.6)	

†Forty-seven patients without preoperative CEA value. ‡Sixty five patients without maximum standardized uptake value (SUVmax). §Nine patients with stage Tis. ¶Seven patients could not be evaluated. ADC, adenocarcinoma; GGO, ground glass opacity; LSDRs, lobe-specific lymphatic drainage regions; VATS, video-assisted thoracic surgery.

selective lymphadenectomy for early-stage NSCLC patients. But for those with positive LSDR nodes, SLND might well be preferable to a selective mode. Thus, it would provide thoracic surgeons with more reliable information on lymph node metastasis and allow them to be more cautious in performing complete or selective LND.

Intraoperative lymph node assessment for the rapid examination of frozen sections to select the appropriate

Table 4 Multivariate analysis of lymph node metastasis in non-LSDRs

Variables	Hazard ratio	95% confidence interval	*P*
Consistency	0.96	0.62–1.53	0.787
GGO ratio	1.19	0.75–1.87	0.569
Differentiation	1.06	0.67–1.83	0.858
pN in LSDRs	137.5	17.0–1114.6	< 0.001

GGO, ground glass opacity; LSDRs, lobe-specific lymphatic drainage regions.

type of dissection has been described or recommended by researchers in European Society of Thoracic Surgeons (ESTS) guidelines and previous literature.[15–18] Therefore fully examining all dissected lymph nodes in LSDRs would be feasible, although it may be difficult or complicated. We do not recommend that nodal examination in the time of an operation should be taken into account as a routine practice, but we do believe it will contribute to the adequate assessment of non-LSDR lymph node metastasis.

Univariate analysis indicated that patients with solid tumors (*P* = 0.021) and a GGO ratio < 25% (*P* = 0.041) were more prone to lymph node involvement in non-LSDRs, although the power was lost in multivariate analysis. The solid component represents the portion of invasive growth, and lung adenocarcinoma with a wider GGO area always has a better prognosis.[19,20] Therefore, preoperative

Table 5 Positive nodal stations in non-LSDRs for each lobe in 12 patients

Location	*n*	Non-LSDRs	Prognosis (postoperative)
Right upper	Patient 1	7	No recurrence (16 months)
	Patient 2	7	No recurrence (33 months)
	Patient 3	7	Local relapse (20 months)
Right middle	Patient 1	2R, 4R	Lung metastasis (24 months)
Right lower	Patient 1	2R	Died (13 months)
Left upper	Patient 1	7	No recurrence (46 months)
	Patient 2	7	Bone metastasis (5 months)
	Patient 3	7	Lung metastasis (30 months)
	Patient 4	7	Left supraclavicular lymph node metastasis (27 months)
Left lower	Patient 1	4L	No recurrence (36 months)
	Patient 2	4L	Brain metastasis (10 months)
	Patient 3	5	Pleural metastasis (15 months)

LSDRs, lobe-specific lymphatic drainage regions.

examination of radiological appearance would be significant to determine an appropriate LND method and solid consistency, or the GGO ratio could be a useful index of prediction for pN status in non-LSDRs.

Of the 309 patients with available tumor differentiation information, positive lymph node involvement in non-LSDRs was present in patients with moderately and poorly differentiated tumors, significantly higher than the patients with well-differentiated tumors. Information on the histological degree of differentiation information can be obtained not only from postoperative surgical specimens, but also from preoperative biopsy specimens or intraoperative frozen sections. Therefore, identification of the degree of differentiation in preoperative biopsy specimens or intraoperative frozen sections might alert thoracic surgeons to the possibility of lymph node metastasis in non-LSDRs, and would be helpful to narrow down eligible candidates for minimally invasive LND.

Previous studies reported that the lymphatic route of sentinel node migration to mediastinal stations was also lobe-specific and the station of the sentinel node at the mediastinum mainly located in LSDR for each lobe.[21,22] The sentinel node is defined as the first lymph node that the lymphatic flux flows into from the primary tumor and should be the first site metastasis occurs in. The utility and feasibility of sentinel node mapping for NSCLC has been demonstrated and improved using different techniques.[23,24] Thus, the status of the sentinel node for each lobe may be important to indicate the likelihood of nodal involvement in LSDRs for NSCLC patients, which may provide more information for determining LND approach. However, further investigation is necessary.

There were some limitations to our study. First, it was inevitable that an inherent selection bias was present, because of the design nature of a retrospective study. Second, the mode of mediastinal lymph node metastasis based on a lobe-specific manner is a very complicated issue; therefore the study of lobe-specific nodal metastasis requires further investigation, although it has a certain rationality. The clinical JCOG1413 trial commenced in January 2017 and will be the first phase III trial to confirm the benefit of lobe-specific nodal dissection for clinical stage I–II NSCLC.[25] We hope that the conclusions of this ongoing randomized trial will contribute to a clarification of whether selective lymphadenectomy is equal to SLND as a potential nodal dissection approach for stage IA NSCLC.

In conclusion, in this study, 19.3% of clinical stage IA NSCLC patients showed unexpected lymph node metastasis. Solid consistency, degree of differentiation, and pN status in LSDRs were predictive factors for lymph node metastasis in non-LSDRs, while multivariate analysis showed that lymph node metastasis in LSDRs was the only independent predictor. Our results provide thoracic

surgeons with more reliable information to assess non-lobe-specific lymph node metastasis in clinical stage IA NSCLC patients and will contribute to clinical decision-making for a reasonable approach to LND.

Disclosure

No authors report any conflict of interest.

References

1 Howington JA, Blum MG, Chang AC, Balekian AA, 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* 2013; **143**: e278S–313S.

2 Okada M, Tsubota N, Yoshimura M, Miyamoto Y. Proposal for reasonable mediastinal lymphadenectomy in bronchogenic carcinomas: Role of subcarinal nodes in selective dissection. *J Thorac Cardiovasc Surg* 1998; **116**: 949–53.

3 Asamura H, Nakayama H, Kondo H, Tsuchiya R, Naruke T. Lobe-specific extent of systematic lymph node dissection for non-small cell lung carcinomas according to a retrospective study of metastasis and prognosis. *J Thorac Cardiovasc Surg* 1999; **117**: 1102–11.

4 Watanabe S, Asamura H, Suzuki K, Tsuchiya R. The new strategy of selective nodal dissection for lung cancer based on segment-specific patterns of nodal spread. *Interact Cardiovasc Thorac Surg* 2005; **4**: 106–9.

5 Aokage K, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Subcarinal lymph node in upper lobe non-small cell lung cancer patients: Is selective lymph node dissection valid? *Lung Cancer* 2010; **70**: 163–7.

6 Turna A, Solak O, Kilicgun A, Metin M, Sayar A, Gurses A. Is lobe-specific lymph node dissection appropriate in lung cancer patients undergoing routine mediastinoscopy? *Thorac Cardiovasc Surg* 2007; **55**: 112–9.

7 Shapiro M, Kadakia S, Lim J *et al*. Lobe-specific mediastinal nodal dissection is sufficient during lobectomy by video-assisted thoracic surgery or thoracotomy for early-stage lung cancer. *Chest* 2013; **144**: 1615–21.

8 Hishida T, Miyaoka E, Yokoi K *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* 2016; **11**: 1529–37.

9 Ishiguro F, Matsuo K, Fukui T, Mori S, Hatooka S, 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* 2010; **139**: 1001–6.

10 Haruki T, Aokage K, Miyoshi T *et al*. Mediastinal nodal involvement in patients with clinical stage I non-small-cell lung cancer: Possibility of rational lymph node dissection. *J Thorac Oncol* 2015; **10**: 930–6.

11 Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC Lung Cancer Staging Project: A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2009; **4**: 568–77.

12 Macia I, Ramos R, Moya J *et al*. Survival of patients with non-small cell lung cancer according to lymph node disease: Single pN1 vs multiple pN1 vs single unsuspected pN2. *Ann Surg Oncol* 2013; **20**: 2413–8.

13 Bille A, Woo KM, Ahmad U, Rizk NP, 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* 2017; **51**: 674–9.

14 Watanabe Y, Shimizu J, Tsubota M, Iwa T. Mediastinal spread of metastatic lymph nodes in bronchogenic carcinoma. Mediastinal nodal metastases in lung cancer. *Chest* 1990; **97**: 1059–65.

15 Okada M, Sakamoto T, Yuki T, Mimura T, Miyoshi K, Tsubota N. Selective mediastinal lymphadenectomy for clinico-surgical stage I non-small cell lung cancer. *Ann Thorac Surg* 2006; **81**: 1028–32.

16 Lardinois D, De Leyn P, Van Schil P *et al*. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg* 2006; **30**: 787–92.

17 De Leyn P, Lardinois D, Van Schil P *et al*. European trends in preoperative and intraoperative nodal staging: ESTS guidelines. *J Thorac Oncol* 2007; **2**: 357–61.

18 Watanabe S, Suzuki K, Asamura H. Superior and basal segment lung cancers in the lower lobe have different lymph node metastatic pathways and prognosis. *Ann Thorac Surg* 2008; **85**: 1026–31.

19 Iwata H, Shirahashi K, Mizuno Y, Yamamoto H, Takemura H. Feasibility of segmental resection in non-small-cell lung cancer with ground-glass opacity. *Eur J Cardiothorac Surg* 2014; **46**: 375–9.

20 Asamura H, Hishida T, Suzuki K *et al*. Radiographically determined noninvasive adenocarcinoma of the lung: Survival outcomes of Japan Clinical Oncology Group 0201. *J Thorac Cardiovasc Surg* 2013; **146**: 24–30.

21 Khullar OV, Gilmore DM, Matsui A, Ashitate Y, Colson YL. Preclinical study of near-infrared-guided sentinel lymph node mapping of the porcine lung. *Ann Thorac Surg* 2013; **95**: 312–8.

22 Gilmore DM, Khullar OV, Jaklitsch MT, Chirieac LR, Frangioni JV, Colson YL. Identification of metastatic nodal disease in a phase 1 dose-escalation trial of intraoperative sentinel lymph node mapping in non-small cell lung cancer using near-infrared imaging. *J Thorac Cardiovasc Surg* 2013; **146**: 562–70.

23 Taghizadeh Kermani A, Bagheri R, Tehranian S, Shojaee P, Sadeghi R, N Krag D. Accuracy of sentinel node biopsy in

the staging of non-small cell lung carcinomas: Systematic review and meta-analysis of the literature. *Lung Cancer* 2013; **80**: 5–14.

24 Eo JS, Kim HK, Kim S, Lee YS, Jeong JM, Choi YH. Gallium-68 neomannosylated human serum albumin-based PET/CT lymphoscintigraphy for sentinel lymph node

mapping in non-small cell lung cancer. *Ann Surg Oncol* 2015; **22**: 636–41.

25 Hishida T, Saji H, Watanabe SI *et al.* A randomized phase III trial of lobe-specific vs. systematic nodal dissection for clinical stage I-II non-small cell lung cancer (JCOG1413). *Jpn J Clin Oncol* 2018; **48**: 190–4.