

# Selective lymph node dissection in early-stage non-small cell lung cancer

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**Abstract:** Lymph node dissection is a vital part of surgical treatment in early-stage non-small cell lung cancer (NSCLC). Removal of metastatic lymph nodes while preservation of intact lymph nodes are equally important. For hospitalized early-stage patients with limited lymph node metastasis, the operation treatment should be made according to some rules such as lobe-specific lymph node drainage pattern. In order to prevent unnecessary surgical trauma in early-stage patients, a minimally invasive approach with selective lymph node excision is preferred for more clinical benefits. This review summarizes the existing findings on lobe-specific lymph node drainage pattern and we hope to provide guidance for selective lymph node dissection (SLND). Furthermore, we include information on histologic views, a tumor marker and protocols of SLND, with hope to inspire creative research and clinical trials in this field.

**Keywords:** Non-small cell lung cancer (NSCLC); lymph node dissection; minimally invasive surgery

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## Introduction

Morbidity and mortality of lung cancer are the highest among all neoplastic diseases in China (1) and worldwide (2). Among all the lung cancer-therapeutic methods, surgery plays a pivotal role, especially in the early-stage non-small cell lung cancer (NSCLC). Nowadays, the standard surgical treatment of early-stage NSCLC is lobectomy with systematic lymph node dissection (LND) as recommended by the guidelines (3,4), which capable of providing accurate staging (5,6), detecting occult metastasis (7) and improving survival (5,8,9). However, randomized trials have not demonstrated that LND has more survival benefit than sampling (7,10). Since advanced radiographic techniques become available and regular medical examination grows popular, early-stage NSCLC patients have occupied a larger proportion. Accordingly, minimally invasive approaches

may be more favorable for those patients. In general, there are three approaches: video-assisted thoracic surgery, parenchyma-preserving resection and selective lymph node dissection (SLND) (11). The research and practice of the first two are comprehensive and deeply (12-14) while SLND remains controversial. Based on the metastatic rules derived from lobe-specific lymphatic drainage pattern (15,16), histologic component, a tumor marker and so on, SLND may be valid and applicable for selected patients to minimize surgical trauma so that patients can benefit from shorter operation time, less blood loss and shorter length of hospital stay (17,18). Still, some questioned remain unsolved.

## Lobe-specific lymphatic drainage pattern

The mediastinal lymph node map is based on the International Association for the Study of Lung Cancer

**Table 1** Different designs of regional lymph nodes

Author	Location of tumor				
	RUL	RLL	LUD	LLD	LLL
Yoshimasu (27)	#2 #3 #4	#3 #7 #8	#4 #5 #7	–	#4 #7 #8
Miyoshi (28)	#2 #3 #4 #10	#7 #8 #11	#4 #5 #6	#5 #7 #11	#7 #8 #11
Kawano (29)	#3 #4R	#3 #4R #7	#4L #5 #6	–	#7 #8 #9
Shien (30)	–	–	–	#5 #11 #12	–

LUD, left upper division; LLD, left lingular division; LLL, left lower lobe; RUL, right upper lobe; RLL, right lower lobe.

(IASLC) node map in the Seventh Edition of the TNM Classification (19).

### Upper lobes

Lymphatic drainage pattern has been found in the upper lobe. Okada (20) investigated the lymphatic drainage pattern in 406 upper lobe NSCLC patients (64.3% pN0, 16.5% pN1 and 19.2% pN2) and showed that none of them had subcarinal node (SCN) metastasis. Similarly, Aokage and colleagues (21) reviewed 1,099 consecutive upper lobe NSCLC patients (72.6% pN1, 12.7% pN2 and 14.7% pN3) and revealed that upper lobe NSCLC rarely metastasized to subcarinal node (1.8%, 20/1,099), especially among squamous cell patients (0.5%, 1/182). In addition, for patients with upper lobe NSCLC without superior mediastinal lymph nodes (SMN) involved, even rare skip SCN metastasis (0.2%, 2/941) was found and no patients with squamous cancer had SCN metastasis (21). Notably, SCN metastasis contributes to cancer staging, highly correlated with poor survival and recurrence, while SCN dissection did not improve the outcome of upper lobe NSCLC patients (17,21-23). In conclusion, it is valid to exclude SCN dissection for early-stage upper lobe NSCLC patients, especially for clinical-N0 patients with squamous cell (21).

Other findings have confirmed such rules in the right upper lobe (RUL). Shimada (15) showed that most SCN metastasis in pathological N2 RUL NSCLC patients was accompanied by simultaneous SMN or hilar lymph node involvement (92%, 11/12) and skip metastasis merely occurred (8%, 1/12). Based on this study, it might be unnecessary for upper lobe NSCLC patients without SMN or hilar metastasis on frozen sections to undergo SCN dissection.

As for the left upper lobe, the most common sites of lymph node metastasis were the SMN and aortic nodes. No skip metastasis, i.e., SCN metastasis without SMN or

AN involvement, occurred in 41 pathological-N2 NSCLC patients (15). This study indicates that SCN can be spared during surgery when SMN and aortic nodes are tumor-free.

### Lower lobes

Lower lobe has its unique lymphatic drainage pattern. A retrospective analysis indicated that SMN skip metastasis without hilar lymph node or SCN involved only occurred in 8% (3/40) pathological-N2 right lower lobe NSCLC patients (15). Similar results have been reported by Okada (20), only 2 of 47 pathological-N2 patients had skip metastasis to SMN without SCN involvement. Both SCN (24) and SMN metastasis (25) in the lower lobe indicated poor prognosis. Based on such findings, SMN dissection may be unnecessary for right lower lobe NSCLC patients when hilar lymph node and SCN are both intraoperatively intact (17,20,26).

### Regional mediastinal lymph nodes

Yoshimasu and colleagues (27) chose three mediastinal lymph nodes (MLN) for each lobe (*Table 1*) as regional mediastinal lymph nodes (RMLN), which are similar to sentinel lymph nodes of breast cancer. They propose that if the RMLN are tumor-free, the rest MLN should be preserved. After investigation of 58 patients, they suggested that limited MLN dissection is applicable to NSCLC patients whose RMLN are intact. Likewise, another Japanese team have defined regional lymph node stations: #2, #3, #4 and #10 for RUL, #7, #8 and #11 for RLL, #4, #5 and #6 for LUD, #5, #7 and #11 for LLD and #7, #8 and #11 for LLL (28). They believed that the intraoperative pathological examination on regional lymph node stations might lead to an appropriate choice between LND and SLND. Kawano (29) also selected several MLN for each lobe (*Table 1*) as target nodes. If metastasis found

in these target nodes, LND was recommended. Shien and colleagues (30) assigned three stations (#5, #11, #12) as the regional lymph node stations for left lingular division (LLD). Based on their findings, the existence of pathological-N2 metastasis can be accurately predicted by intraoperative pathological examination and SLND or LND would be properly adopted in LLD-NSCLC patients with clinical-T2N1M0 or earlier stage (30). It is worth mentioning that only a few teams investigate in this area, and the reliability of RMLN should be further confirmed.

### Predominant histological component

Despite the fact that upper lobe squamous cell patients rarely having SCN metastasis as mentioned above, adenocarcinoma patients showed dramatic difference. Above all, patients with adenocarcinoma were more likely to have N1 and N2 diseases compared with squamous cell patients (16). In regard of predominant histologic component of adenocarcinoma, lepidic predominant component was associated with node-negative while micropapillary and solid predominant components were correlated with node-positive (31). Hence, the specific relationship between predominant histological component and lymph node metastasis needs to be comprehensively revealed.

### Tumor marker

Interestingly, Hattori (32) revealed that carcinoembryonic antigen (CEA) level was a significant predictor of lymph node metastasis. In addition, Haruki (26) elucidated that CEA elevation was highly associated with SMN metastasis in lower lobe clinical-stage I adenocarcinoma. Based on these studies, it is reasonable to preserve SMN for lower lobe clinical-stage I NSCLC patients with a normal level of CEA (26). However, we need more evidence to confirm the significance of CEA and elucidate the role of other tumor markers.

### Strategies of lymph node dissection

#### *Systematic lymph node dissection*

When LND is operated in the right lobes, mediastinal lymph node stations #2R, #4R, #7, #8 and #9 should be dissected, while for the left lobes, mediastinal lymph node stations #4L, #5, #6, #7, #8 and #9 dissection is required.

On both sides, N1 nodes are dissected as part of lung resection.

#### *Protocols of SLND*

Several retrospective studies have been carried out to determine whether SLND is an applicable option as a standard procedure and can provide clinical benefits. However, different groups selected various protocols of lobe-specific SLND. Hishida (33) chose the protocol as follows. For RUL, SMN (stations #2R and #4R) were dissected, while SMN and aortic nodes (stations #4L, #5 and #6) were dissected for left upper lobe. Inferior mediastinal nodes (station #7, #8 and #9) were preserved for both upper sides. For lower lobe on both sides, inferior mediastinal nodes (stations #7, #8 and #9) were dissected, while SMN and/or aortic nodes kept preserved. Adachi (34) shared the same protocol (*Table 2*). Intraoperative frozen section analysis was introduced in Futoshi Ishiguro's protocol (17), where SMN for RUL, SMN and aortic nodes for LUL and inferior mediastinal nodes for lower lobe were removed. Intraoperative frozen section analyses were performed when dissected lymph node metastasis was suspected, and if positive, such patients would undergo LND. Protocols from other teams are similar to those above (*Table 2*).

### Discussion

Some retrospective studies have demonstrated SLND is an alternative to LND for selected clinical-stage I–II patients and has the potential to become a standard procedure in surgical treatment for NSCLC (11,33,34,36,37). Meanwhile, Izbicki (10) and Graham (38) argued that LND should be routinely operated for resectable NSCLC. On one hand, whether LND would increase postoperative morbidity associated with complications is not clear (10,36) and the influence on outcome such as overall survival and disease-free survival remains controversial (5,8,17,33,34). On the other hand, the reported benefit that SLND can shorten the entire medical period along with its validity, reliability and applicability are still not very clear. Moreover, SLND was reported increasing the possibility of recurrence (35). In order to provide unambiguous answer, multi-institutional randomized clinical trials are expected to carry out in the future.

Although some doubt exists (39), lobe-specific lymphatic drainage pattern becomes increasingly credible and practical with more literature published (11,15,16,33,34).

**Table 2** Different protocols of selective lymph node dissection<sup>a</sup>

Author	Location of tumor				
	RUL	RML	RLL	LUL	LLL
Hishida (33)	#2R #4R	Excluded	#7 #8 #9	#4L #5 #6	#7 #8 #9
Adachi (34)	#2R #4R	Excluded	#7 #8 #9	#4L #5 #6	#7 #8 #9
Ishiguro (17) <sup>b</sup>	#1R #2R #3 #4R	Unknown	#7 #8 #9	#4L #5 #6	#7 #8 #9
Jiang (18)	#2R #4R	Unknown	#7 #8 #9	#5 #6	#7 #8 #9
Shapiro (11) <sup>c</sup>	#4R (#2R or #3)	#7	#7 (#8 or #9)	#5 #6	#7 (#8 or #9)
Maniwa (35) <sup>b</sup>	#2R #4R	Unknown	#7 #8 #9	#4L #5 #6	#7 #8 #9

LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe. <sup>a</sup>, N1 nodes were dissected as a part of lung resection; <sup>b</sup>, intraoperative frozen section analysis was performed; <sup>c</sup>, lymph node before the bracket was constantly dissected while those enclosed in the bracket were removed only if suspicious of metastases.

Still, several important questions remain to be answered. The complicated impacts of tumor location, size, mutation, differentiation and significant tumor markers have on lymph node metastasis are not well understood. As we all know, pathological classification is closely related to oncological characteristics and behaviors. It is really crucial to clarify the association between pathological classification and SLND. Importantly, only with a comprehensive understanding of lymphatic drainage pattern can we design an optimal protocol for SLND, which is the key to a well-designed clinical trial. Meanwhile, the positron emission computed tomography-computed tomography (PET-CT) and intraoperative frozen section analysis (12) should be considered for accurate clinical stage and precise intraoperative diagnosis.

A minimally invasive approach is the trend of surgical treatment for early-stage NSCLC and SLND is a vital component of it. Also, it is another solid step towards precision medicine.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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