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Intrapulmonary lymph node (stations 13 and 14) metastasis in peripheral non-small cell lung cancer

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Abstract

It remains unknown whether dissecting the intrapulmonary lymph nodes (stations 13 and 14) when resecting peripheral non-small cell lung cancer (NSCLC) is necessary for accurate tumor node metastasis (TNM) staging. This study investigated intrapulmonary lymph node dissection (stations 13 and 14) on the pathological staging of peripheral NSCLC and the metastatic pattern of the lymph nodes.

This retrospective study included patients with primary peripheral NSCLC who underwent radical dissection between January 2013 and December 2015. The clinical data of patients and examination results of intrapulmonary stations 12, 13, and 14 lymph nodes were analyzed.

Of 3019 resected lymph nodes in a total of 234 patients (12.9/patient), 263 (8.7%) had metastasis. Ninety-nine patients had lymph node metastasis (42.3%): 40 (17.1%) were N1, 11 (4.7%) were N2, 48 (20.5%) were both N1 and N2, and 135 (57.7%) had no N1 or N2 metastasis. Sixteen (6.8%) patients had metastasis of stations 13 and/or 14. Metastasis in N1 positive patients of stations 10, 11, 12, 13, and 14 were 2.7%, 10.5%, 9.8%, 10.4%, and 8.5%, respectively. Missed detection without station 13 and 14 dissection was up to 6.8% (16/234).

Dissection of stations 13 and 14 could be helpful for the identification of lymph node metastasis and for the accurate TNM staging of primary NSCLC.

Abbreviations: NSCLC = Non-small Cell Lung Cancer, TNM = tumor node metastasis.

Keywords: carcinoma, lymph node excision, lymph nodes, lymphatic metastasis, neoplasm staging, non-small-cell lung

1. Introduction

Lung cancer is a leading cause of morbidity and mortality both worldwide and in China.[1] The most common type of lung cancer is non-small cell lung cancer (NSCLC), which accounts for up to 85% of the cases.[2] While not recommended for late-stage patients, surgical treatment brings benefit to the patients with early-stage NSCLC who can survive for a long time after radical surgery.[3] Nevertheless, the extent of lymph node metastasis affects the patients' survival rates.[4,5]

The most common staging system for NSCLC is the tumor node metastasis (TNM) staging system.[6] Prior to surgery, the clinical N stage is based on imaging, usually through computed tomography (CT) or magnetic resonance imaging.[7] After surgery, the N staging is often corrected to provide the more accurate pathological TNM staging. The resulting post-surgical TNM stage is of great significance for the prognosis of patients and for planning the adjuvant treatments.[8]

The number of mediastinal lymph nodes with metastasis and the size of the tumor are significantly related to the survival of patients with NSCLC.[9,10] Dissecting the mediastinal lymph nodes during surgical resection of the primary tumor for cancer staging and increasing survival of the patients is widely accepted by many authoritative organizations.[3,11–13] In the ACOSOG Z0030 study, stations 13 and 14 were sampled in some patients, but they do not recommend their resection since they specifically recommend 2R, 4R, 7, 8, 9, and 10R for the right lung, and 4L, 5, 6, 7, 8, 9, and 10L for the left lung.[14] Therefore, in clinical practice, thoracic surgeons often systematically dissect the lymph

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nodes in the mediastinum but usually neglect sampling lymph nodes in the lung because they are not aware of their clinical significance. This could result in false-negative results for the lymph nodes. Therefore, studying the intrapulmonary lymph nodes and the metastasis pattern in peripheral NSCLC is of great significance to improve the accuracy of clinical staging for patients with NSCLC.

Therefore, the aim of this study was to undertake a retrospective analysis of patients with primary peripheral NSCLC who underwent systemic dissection of the intrathoracic and intrapulmonary lymph nodes to investigate the metastasis pattern of the lymph nodes and determine whether the dissection of stations 13 and 14 is necessary for the accurate TNM staging and treatment of peripheral NSCLC.

2. Methods

2.1. Patients

This retrospective study included patients with primary peripheral NSCLC who underwent radical dissection at the Department of Thoracic and Cardiovascular Surgery of a single institution between January 2013 and December 2015. The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Patients were eligible if they fulfilled the following inclusion criteria: diagnosed with peripheral NSCLC, and the tumor was located inferior to segment according to chest CT and fiberoptic bronchoscopy results to exclude peripheral NSCLC; underwent open or thoracoscopic lobectomy and lymph node dissection; had relevant staging examinations such as cranial magnetic resonance imaging, CT of the upper abdomen, whole-body bone scan using radionuclides or positron emission tomography (PET)/CT; and had samples from the intrapulmonary stations 12, 13, and 14 lymph nodes, and had resected nodes of stations 10 and 11 during hilar separation. Patients were excluded if they had neoadjuvant radiotherapy or chemotherapy before surgery.

2.2. Treatment approach

All patients underwent radical dissection, including lobectomy and systematic mediastinal lymph node dissection. All surgeries were performed by the same chief surgeon (Dr. Ge Mingjian, Director, a professor with 25 years of experience in thoracic surgery).

Systematic dissection of the lymph nodes in the mediastinum was performed according to the Naruke mapping of pulmonary lymph node distribution.[15] The lymph node stations were defined according to the International Association for the Study of Lung Cancer.[16] In particular, lymph nodes of stations 2R, 3a, 3p, 4R, 7, 8, and 9 on the right were resected while stations 4L, 5, 6, 7, 8, and 9 on the left were resected. The pulmonary lobes were dissected from lobe bronchus lymph nodes (station 12), segmental bronchi lymph nodes (station 13), and sub-segmental bronchi lymph nodes (station 14) were resected according to the development of the bronchial tree (Fig. 1A). The lymph nodes of stations 10 and 11 were resected during the lobectomy hilar separation, and the resected lymph nodes were stored in separate bags (Fig. 1B) and fixed in formaldehyde for pathological examination. The N1 lymph node hilar (station 10), interlobar (station 11), lobar (station 12), and segmental (stations 13 and 14) sites were analyzed after surgery.

2.3. Clinical data collection and examination method

Baseline clinical data were collected from the patients' medical records. Histologic examinations of the lymph node samples were undertaken by standard hematoxylin and eosin staining with light microscopy and were completed by 6 pathologists (3 attending doctors, 2 associate chief physicians, and 1 chief physician) who were all highly qualified to diagnose independently and with 5 to >30 years of experience in pathological diagnosis. The histological types were classified according to World Health Organization histological typing of lung tumors,[17] and the TNM staging was classified according to UICC2007.[18]

2.4. Statistical analysis

The data were processed using SPSS 19.0 (IBM, Armonk, NY). The continuous data that conformed to the normal distribution (Kolmogorov-Smirnov test) were presented as means ± standard deviations. The categorical data were presented as numbers and percentages and were tested using the Pearson chi-square test.

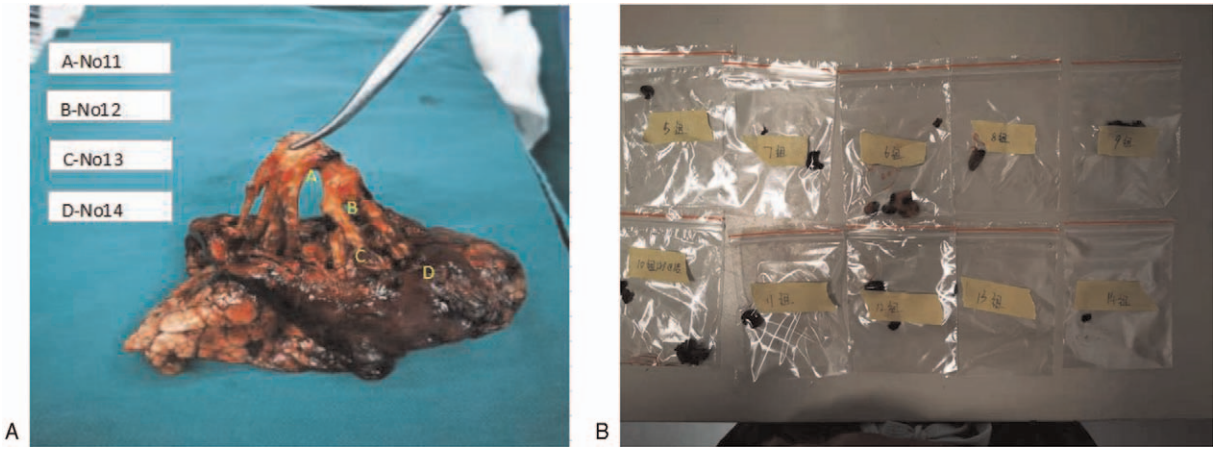

Figure 1. During surgery, intrapulmonary lymph nodes in stations 12, 13, and 14 were anatomically resected along the bronchial tree. (A) Gross intraoperative specimen. (B) After surgery, the resected lymph nodes are separately packed and marked for pathological examination.

Table 1

The clinicopathological characteristics of patients in the study.

Parameter	N0 (n=135)	N1 (n=40)	N2 (n=11)	N1 + N2 (n=48)
Sex				
Male	88	32	6	33
Female	47	8	5	15
Pathological type				
Squamous cell carcinoma	40	16	3	9
Adenocarcinoma	90	19	7	34
Neuroendocrine carcinoma	1	2	0	2
Sarcomatoid carcinoma	3	1	1	0
Adenosquamous carcinoma	1	1	0	2
Cystadenocarcinoma	0	0	0	1
Large cell carcinoma	0	1	0	0
Tumor stage				
T1	27	4	2	3
T2	91	31	7	26
T3	17	5	2	19
pTNM stage				
I	114	0	0	0
II	19	35	0	0
III	2	5	11	48
Smoking status*				
Yes	75	28	6	29
No	60	12	5	19

pTNM = pathological tumor node metastasis.
* Smoking status was defined as a smoking index ≥400 calculated based on number of cigarettes smoked per day × years of smoking.

The data were statistically significant when $P < .05$. Pearson linear regression was used to analyze the correlation between the diameter of the tumor and the lymph node metastasis rate.

3. Results

3.1. Metastasis of the lymph node stations

A total of 234 patients were included, with 159 men and 75 women. The mean age was 61.4 ± 8.6 years old. The NSCLC subtypes included 68 cases of squamous cell carcinoma, 150 of adenocarcinoma, and 16 of others (5 with sarcomatoid carcinoma, 5 with neuroendocrine carcinoma, 4 with adenosquamous carcinoma, 1 with large cell carcinoma, and 1 with cystadenocarcinoma) (Table 1). Ninety-nine patients were confirmed as having lymph node metastasis out of 234 patients (metastatic rate of 42.3%), of which 40 patients had N1 lymph node metastasis only, accounting for 17.1% of the total cases, 11 patients had N2 lymph node metastasis only, accounting for 4.7%, and 48 patients had both N1 and N2 metastasis, accounting for 20.5% of the total cases. A total of 3019 N1 lymph nodes were dissected, of which 263 were metastatic; therefore, this represents a mean of 12.9 lymph nodes dissected per patient and a metastatic rate of 8.7%. In addition, 599 lymph nodes were resected from 40 patients with N1 lymph node metastasis.

3.2. N1 metastasis rate

The 40 patients with N1 metastasis included 5 patients with lymph node metastasis at station 14, 9 patients with lymph node metastasis at station 13, and 2 patients with lymph node metastasis at stations 13 and 14. The number of patients with lymph node metastasis at stations 13 or/and 14 was 16 (6.8%). Seven patients had lymph node metastasis at station 12, 5 patients at stations 12, 13, and 14, and 28 patients at stations 12 and/or 13 and/or 14 (12.0%). Therefore, if lymph node dissection had not been performed for stations 13 and 14, 16 patients would have had a biased staging (6.8%), which manifested as advanced TNM staging, and among which 9 (3.9%) patients were classified stage I.

3.3. Metastatic rate of N1 lymph nodes

In the 88 patients who developed N1 lymph node metastasis (37.6%) with or without N2 metastasis, the rate of positive lymph nodes was similar at stations 11, 12, 13, and 14 but lower at station 10 (Table 2). The metastatic rate of lymph nodes at stations 13 and 14 was 9.7% (86/886), compared with 8.3% at stations 10, 11, and 12 (177/2133), but the difference was not statistically significant ($X^2 = 1.561$, $P = .212$).

3.4. Relationship between tumor size and N1 lymph node metastasis

The metastatic rate of the N1 lymph nodes increased correspondingly with the increase in tumor diameter when the diameter was <5 cm (Table 3). The metastatic rate of lymph nodes was 0 (0/121) when the tumor diameter was between 0 and

Table 2

The metastatic rate of N1 lymph node.

Station number	Metastatic LN/resected LN	Positive rate (%)
10	15/557	2.7
11	110/1047	10.5
12	52/529	9.8
13	58/556	10.4
14	28/330	8.5

Table 3

The relationship between N1 lymph node metastasis and tumor diameter.

Tumor size, cm	Metastatic lymph node	Non-metastatic lymph node	Rate %
0–1	0	121	0
1–2	32	707	4.3
2–3	64	784	7.6
3–4	58	495	10.5
4–5	64	306	17.3

1 cm, 4.3% (32/739) when the tumor diameter was between 1 and 2 cm, and 7.6% (64/848) when the tumor diameter was between 2 and 3 cm, and the relationship was statistically significant ($P = .0004$). Pearson regression analysis showed that the tumor diameter was positively correlated with the lymph node metastasis rate ($R = 0.9868$, $P = .0018$), and the regression equation was ($y = 4.222 + 4.314x$).

4. Discussion

The aim of this retrospective study was to investigate the metastatic pattern of the lymph nodes in patients with primary peripheral NSCLC, in particular, to discover whether dissection of the intrapulmonary lymph nodes stations 13 and/or 14 is important for accurate TNM staging. The results showed that 8.7% of the 3019 resected lymph nodes had metastasis. One-hundred and thirty-five patients (57.5%) had no N1 or N2 metastasis, and 99 patients had lymph node metastasis (42.3%). Of these, 40 patients (17.1%) had N1 metastasis, 11 patients (4.7%) had N2 metastasis, and 48 patients (20.5%) had both N1 and N2 metastasis. Sixteen (6.8%) patients had metastasis at stations 13 and/or 14. Metastasis in N1 positive patients of stations 10, 11, 12, 13, and 14 were 2.7%, 10.5%, 9.8%, 10.4%, and 8.5%, respectively. Missed detection without stations 13 and 14 dissection would have been up to 6.8% (16/234). Therefore, this study suggests that dissection of intrapulmonary lymph node stations 13 and 14 is helpful for the identification of lymph node metastasis and for accurate staging of primary NSCLC. This information may assist in selecting the most appropriate treatment post-surgery.

At present, surgery is the main treatment for lung cancer of early stage, which includes pulmonary resection and regional dissection of lymph nodes. Mediastinal lymph node dissection includes systematic node dissection, selected lymph node biopsy, systematic sampling, sampling, lobe-specific systematic node dissection, and extended lymph node dissection.[19] Nevertheless, there are few reports on the degree, approach, and range of intrapulmonary lymph node dissection, and no general consensus has been achieved in this regard. One study suggested that in patients with pN0 NSCLC, neglecting intrapulmonary lymph nodes could lead to inadequate staging and may lead to poor patient outcomes.[20] Another study also found that intrapulmonary lymph node metastasis is common in patients initially diagnosed with N0 stage 1A adenocarcinoma.[21] These studies support the results of this study that suggests that the dissection of stations 13 and 14 is useful for staging early-stage NSCLC.

Whether there is metastasis in intrapulmonary, hilar, and mediastinal lymph nodes are independent factors that affect patients' survival rate.[4,5] There are certain patterns for lymph node metastasis in lung cancer: intrapulmonary lymph nodes (stations 12, 13, and 14) → interlobar lymph nodes (station 11) → hilar lymph nodes (station 10) → mediastinal lymph nodes (stations 2–9), which are observed as spreading to distant metastasis from the local metastasis and from the bottom up.[22] Primary peripheral lung cancer occurs in segments and reflects the entire pattern of lymph node metastasis. In contrast, central lung cancer often invades the adjacent intrapulmonary lymph nodes and causes difficulty in analyzing metastasis patterns. Therefore, in this study, we investigated patients with peripheral lung cancer to reduce the impact of different tumor locations on the pattern of lymph node metastasis. According to the backflow pattern of lymph fluid in the intrathoracic lymphatic system, the intrapulmonary lymph node is the first target of primary peripheral NSCLC metastasis. In this study, the metastatic rates of primary N1 NSCLC were 2.7% (station 10), 10.5% (station 11), 9.8% (station 12), 10.4% (station 13), and 8.5% (station 14), respectively. Except for the lower rate at station 10, no significant differences were found in the numbers of lymph node metastasis and the metastatic rates among those stations.

If the lymph nodes of stations 13 and 14 are not dissected, there will be a decrease in N staging (from N1 to N0) and in some pathological stages (from stage II to I), which would lead to patients who are supposed to receive postoperative chemotherapy not receiving their adjuvant treatment, affecting their prognosis. Therefore, the accurate diagnosis of NSCLC, according to intrapulmonary lymph nodes, will have an important impact on patient survival. Currently, dissection of N1 lymph nodes is mostly only at station 12, and this may result in neglected and undetected intrapulmonary lymph nodes, thus affecting the accuracy of postoperative TNM staging for patients with lung cancer or even depriving them of their opportunity to receive adjuvant treatment after surgery. In this study, there were 40 patients (out of 234) whose N1 lymph nodes were positive, among which 16 with positive lymph nodes at stations 13 and/or 14. If lymph nodes at stations 13 and 14 had not been submitted for examination, the 16 patients would have been staged as N0, and 9 patients (3.86%) would have been classified as stage IA, resulting in these patients not receiving adjuvant chemotherapy. Smeltzer et al[23] studied cases in which the lymph node metastasis in the residual lung tissue was neglected after lung cancer resection. Of the 110 patients enrolled, 25% were found to have positive lymph nodes in discarded tissue by pathological examination, and the survival rate of these patients with missed lymph nodes metastases was lower than that of patients without metastasis. Wang et al[20] showed that patients with pN0 NSCLC but in whom the intrapulmonary lymph nodes were not sampled had poor oncologic outcomes than the other pN0 patients, highlighting the importance of stations 13 and 14 sampling and supporting the present study. Zhang et al[21] and Suzuki et al[24] also proved that intrapulmonary lymph node metastasis was frequent in stage IA NSCLC. This indicated that false-negative lymph nodes in the diseased lung after radical resection, which is overlooked by thoracic surgeons and pathologists, could lead to reduced survival in NSCLC. In clinical practice, most thoracic surgeons do not dissect or examine the intrapulmonary lymph nodes, leaving the lymph nodes of stations 13 and 14 unexamined.

An important factor related to lymph node metastasis found in this study is that the lymph node metastasis in peripheral NSCLC is closely related to tumor diameter. This study showed that the metastatic rate of lymph nodes was 0% (0/121) when the tumor

diameter was between 0 and 1 cm, 4.3% (32/739) when the tumor diameter was between 1 and 2 cm, and 7.6% (64/848) when the tumor diameter was between 2 and 3 cm. This indicated that when tumor diameter was <3 cm, the metastatic rate of N1 lymph nodes increased correspondingly with increased tumor diameter. This is consistent with Watanabe et al,[25] who also concluded that hilar and mediastinal lymph node metastasis did not occur in different types of lung cancer in patients with a tumor diameter ≤1 cm. Tumor size has also been shown to be important in studies published in Chinese. Chen et al[26] found that in patients with peripheral lung cancer at station T1, no mediastinal and intrapulmonary lymph node metastasis was observed when the tumor diameter was <1 cm. When the tumor diameter was between 1 and 3 cm, the metastatic rate increased correspondingly with the increase of tumor diameter. Jiang et al[27] and Xie et al[28] also found that the metastatic rate of lymph nodes increased with the increase of tumor diameter when the tumor diameter was ≤3 cm. The results of this study also indicated that the systematic dissection of lymph nodes might not be necessary when the tumor diameter of the peripheral NSCLC was <1 cm. Minimally invasive methods such as lymph node sampling would be sufficient. But when the tumor diameter is >1 cm, systematic dissection of mediastinal lymph nodes should be performed to ensure that the lymph nodes are completely resected and the chance of recurrence after surgery is reduced.

The results of this study suggest that thoracic surgeons should dissect the intrapulmonary lymph nodes according to their anatomic observation and send them for an examination so as to avoid the impact of undetected lymph nodes on the staging, treatment, and prognosis of the disease. Although all patients with intrapulmonary and/or mediastinal lymph node metastases will have different prognoses, because the numbers of involved lymph nodes are different, the 8th edition of TNM staging divides the N1 lymph nodes into N1a and N1b in details according to whether they are single-station metastases.[29,30] Failure to perform N1 lymph node dissection may result in inaccurate pathological staging and deprive the patients of the opportunity to obtain radical treatment. It may also lead to biased staging, causing inappropriate comparison, treatment failure, and incorrect survival statistics.[31] Therefore, the separate dissection and pathological examination of the intrapulmonary lymph nodes can not only improve the accuracy of clinical staging for patients with lung cancer but also have great significance in guiding patients' postoperative comprehensive treatment.

This study has some limitations. As a retrospective study, there may have been some bias in the inclusion of the patients. The patients were all from one surgical department in one hospital, so the number of subjects was quite small. The patients were heterogeneous with respect to cancer staging and subtypes of NSCLC, which might influence the outcomes. Larger studies from multiple centers will add evidence to these results. In further clinical work, it would be necessary to analyze the effect of lymph node metastasis on postoperative survival, thus further demonstrating the research value of intrapulmonary lymph nodes.

In summary, there are few prospective, large-sample studies on clinical data of intrapulmonary lymph nodes of stations 13 and 14 at home and abroad. However, this retrospective single-center study suggests that it is important to dissect the intrapulmonary lymph nodes, which can generate accurate pathological staging for patients, enable them to receive appropriate adjuvant therapy after surgery, correctly count the survival rate of patients with stage I lymph node metastasis, and provide peripheral NSCLC patients with optimal treatment for lymph node dissection. In the present study, 4% of the patients would have been staged as 1A instead of IIA if stations 13 and 14 had not been sampled.

Author contributions

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Project administration: Mingjian Ge.
Writing – original draft: Lei Bi.
Writing – review & editing: Lei Bi, Hong Zhang, Mingjian Ge.

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