


ORIGINAL ARTICLE

Intrapulmonary lymph node metastasis is common in clinically staged IA adenocarcinoma of the lung

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Introduction

Non-small cell lung cancer (NSCLC) accounts for > 80% of all lung cancer cases, and adenocarcinoma has become the most common histological type. Different therapeutic approaches should be applied for NSCLC of different stages. The most widely used staging system for NSCLC is the International Association for the Study of Lung Cancer (IASLC) Tumor Node Metastasis (TNM) staging system,

Abstract

Background: Intrapulmonary lymph nodes (LNs, stations 11–14) are usually omitted in postoperative pathological examination. Some non-small cell lung cancer (NSCLC) patients with intrapulmonary LN metastasis are incorrectly diagnosed as N0 cases. Furthermore, underestimation of intrapulmonary LN involvement in clinically early stage NSCLC may lead to the incorrect choice of surgical procedure: lobectomy or sublobar resection. This study was conducted to determine the status of intrapulmonary LN involvement in clinically staged IA (c-T1N0M0) peripheral adenocarcinoma of the lung.

Methods: Seventy-five lobectomy specimens of c-T1N0M0 peripheral adenocarcinoma of the lung were carefully dissected to find intrapulmonary LNs. The longest diameter of each intrapulmonary LN was measured and sent for pathological examination, together with hilar and mediastinal LNs, to investigate the relationship between LN metastasis and primary tumor size.

Results: Intrapulmonary LN metastasis was detected in 22.7%(17/75) of patients. Positive LNs were detected in 21.7% (10/46) of T1b patients and 45% (11/24) of T1c patients, while no metastasis (0/5) was observed in T1a patients ($P = 0.036$). The mean longest diameter of the 17 involved intrapulmonary LNs was only 6.5 ± 2.1 mm, which was not significantly different to the size of negative intrapulmonary LNs (5.2 ± 1.4 mm).

Conclusions: Intrapulmonary LN metastasis is common in clinically staged IA peripheral adenocarcinoma of the lung. LN metastasis is related to tumor size, and this should be taken into account to determine appropriate surgical procedures and postoperative treatment. Computed tomography is not a reliable method to judge LN metastasis, particularly intrapulmonary LN metastasis.

which is currently in its 8th edition (adopted January 2017).¹

Determination of regional lymph node (LN) status is one of the key factors used to accurately stage NSCLC and subsequently decide the appropriate therapeutic modality. Most N0–1 stage patients without distant metastasis (M0) are principally candidates for surgical treatment alone or surgery followed by adjuvant chemotherapy. Surgical treatment for N2 (mainly IIIA) patients is controversial. Surgical

[Correction added on 4 February 2019, after first online publication: Daxin Zhu, Changlong Qin, Jingsi Dong, Xiaoming Qiu and Mingyu Fan have been added as co-authors. Also, QingHua Zhou has been made a co-corresponding author.]

procedures do not benefit N3 and M1 patients; chemotherapy or radiochemotherapy are the optimal treatments.² When a patient is suspected or confirmed with NSCLC, clinical TNM staging mainly based on imaging studies should be conducted to determine if surgery should be considered and what type of surgical procedure (lobectomy or sublobar resection) is preferred. Clinical N stage (cN stage) is established by imaging studies, usually with contrast-enhanced computed tomography (CT) or positron emission (PET)-CT. However, the accuracy of cN staging by imaging studies is limited and is often revised according to the results of pathological examinations after surgery (pN stage).^{3–5} pN stage is the main determinant factor for postoperative treatment and prognosis of NSCLC patients. For stage IA (c-T1N0M0) peripheral NSCLC patients, postoperative adjuvant therapy is seldom needed. However, if positive LNs are found during pathological examination, adjuvant therapy is indicated, as a large number of patients may benefit from such therapy.^{6,7} Furthermore, pN stage is a determinant prognostic factor of NSCLC. The five-year survival rate varies from about 60% in pN0 patients to < 10% in pN3 patients.⁸ Accurate pN staging relies on intra-operative collection of LNs in different stations by surgeons and precise examination of LNs in a pathological laboratory. Regularly, the hilar (station 10) and mediastinal (stations 2–9) LNs are collected for pathological examination, and provide the basis for pN staging. Intrapulmonary LNs (stations 11–14) are usually ignored because they are generally sent to the pathological laboratory within the resected lung specimen and are very rarely intentionally extracted for pathological investigation.^{9,10} As a result, some patients with positive intrapulmonary LNs (actually N1) are likely to be misdiagnosed as N0. This may cause negative effects on reasonable postoperative treatment and prognosis. In the present study, we collected pathological data of 75 patients with adenocarcinoma of the lung who were clinically diagnosed as stage IA (c-T1N0M0), in order to evaluate the accuracy of cN stage using contrast enhanced CT scan, and to obtain information about intrapulmonary LN metastasis in patients with clinically staged IA peripheral adenocarcinoma of the lung.

Methods

Patient population

Samples from 75 patients (34 men, 41 women) with peripheral adenocarcinoma of the lung who underwent lobectomy at the Lung Cancer Center, West China Hospital of Sichuan University from September 2015 to December 2016 were included in the study. Their age ranged from 35 to 82 (61.3 ± 10.2) years. All patients were clinically diagnosed or suspected with stage IA (c-T1N0M0) peripheral lung cancer, and were pathologically confirmed

to have adenocarcinoma after surgery. All patients received a contrast-enhanced high-resolution CT scan of chest, with a slice thickness of 1 mm, so that the size of the primary tumor and regional LNs could be accurately measured. Enhanced magnetic resonance image scanning of the head, enhanced CT scan of the abdomen, and Tc-99m methylene diphosphonate single photon emission tomography (SPECT) bone imaging were routinely performed to exclude distant metastasis. Other preoperative tests, including pulmonary function tests, blood tests, and electrocardiograms were also routinely performed to confirm that patients could tolerate the planned lobectomy.

Intra-operative collection of lymph nodes (LNs)

A lobectomy was directly performed in 39 patients. Twelve had preoperative pathological evidence of lung cancer through bronchoscopy or percutaneous transthoracic needle biopsy, and 27 cases were undiagnosed nodes located near hilar structures and thus unsuitable for wedge resection or segmentectomy. Wedge resection following lobectomy was performed in the remaining 36 cases with undiagnosed nodes located in peripheral areas verified as lung cancer by intra-operative frozen section. Systemic LN resection was performed in all 75 cases. Generally, station 2, 3, 4, 7, 9, and 10 LNs were resected in patients with lesions in the right lung; and station 5, 6, 7, 9, and 10 LNs were resected in patients with lesions in the left lung. After the lobectomy was completed, the lung specimen was carefully dissected to extract intrapulmonary LNs, primarily station 11 (interlobar) and station 12 (segmental) LNs. Occasionally, enlarged station 13 or 14 (subsegmental) LNs were also collected. The longest diameter of each LN was recorded and the specimen was placed in a bag marked with a serial number (Fig 1).

Pathological investigation of LNs and relation to clinical N stage

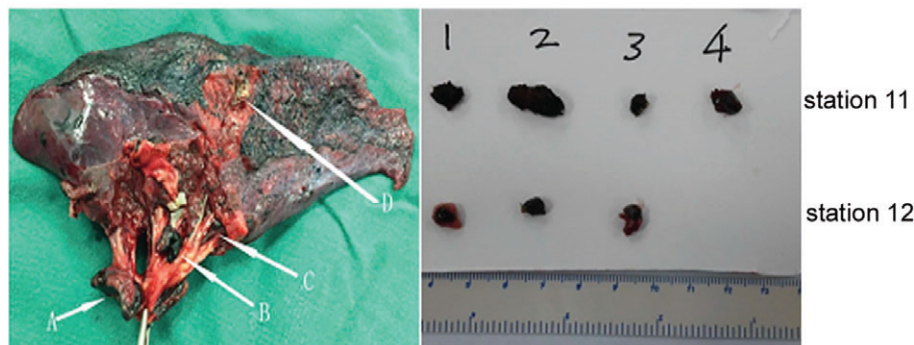
Hematoxylin-eosin (HE) staining was used for the pathological examination of LNs. Experienced pathologists examined every pathological LN slide for possible metastasis. The cN stage was revised according to the results of pathological examinations and the accuracy of cN stage was analyzed via contrast-enhanced CT scan.

Results

Positive LN counts

A total of 1464 LNs were collected, with an average number of 19.4 LNs per patient. The total positive rate of LNs was 4.9% (72/1464). The positive rates of intrapulmonary

Figure 1 Intrapulmonary lymph node (LN) lung specimens and their sizes (A, station 11; B, station 12; C, station 13; D, primary tumor).



LNs, hilar LNs (station 10), and mediastinal LNs (stations 2–9) were 6.5% (41/628), 2.3% (6/258), and 4.3% (25/578), respectively.

Revision of tumor node metastasis stage of clinically diagnosed N0 patients

Twenty-eight percent (21/75) of the preoperative N0 patients were confirmed as N1 or N2 stage via postoperative pathological examination. The sensitivity of cN stage using contrast-enhanced chest CT scan was 72% (54/75). Positive intrapulmonary, hilar, and mediastinal LNs were detected in 22.7% (17/75), 5.3% (4/75), and 13.3% (10/75) of patients, respectively. Eleven patients were re-diagnosed as N1 from N0, and the final aggregate stage was revised from stage IA to IIB; 10 patients were re-diagnosed as N2 from N0, and 9 from stage IA to IIIA. The remaining patient was revised from stage IA to IVA after pleural metastasis was confirmed during surgery (Table 1).

Relationship between LN metastasis and size of primary tumor

In the 8th edition TNM staging system for NSCLC, an additional subdivision within the T1 was defined according to the size of the primary tumor: T1a ($T \leq 1$ cm), T1b

($1\text{ cm} < T \leq 2$ cm), and T1c ($2\text{ cm} < T \leq 3$ cm). We investigated the relationship between the size of the primary tumor and LN metastasis. Positive LNs were detected in 21.7% (10/46) T1b patients and 45% (11/24) T1c patients, and were not observed in T1a patients (0/5; $P = 0.036$) (Table 2).

Size of positive intrapulmonary LNs

We measured the longest diameter of each intrapulmonary LN in each patient to investigate the relationship between LN metastasis and size. The average longest diameter of positive intrapulmonary LNs was 6.5 ± 2.1 mm, which was not significantly different to negative intrapulmonary LNs (5.2 ± 1.4 mm) (Table 3).

Discussion

Regional LN metastasis (N stage) is an essential component of NSCLC staging. It is also a determinant factor for prognosis and treatment decisions. When pathological examination is not available, N stage is usually established through imaging studies. A contrast-enhanced chest CT scan is the most commonly used noninvasive method to

Table 1 Intrapulmonary, hilar, and mediastinal LN metastasis in patients with clinical stage IA (c-T1N0M0) peripheral adenocarcinoma of the lung

No. of cases	Intrapulmonary LN	Hilar LN	Mediastinal LN
54	–	–	–
10	+	–	–
1	–	+	–
1	–	–	+
2	–	+	+
6	+	–	+
1	+	+	+
Total	17	4	10

LN, lymph node.

Table 2 Relationship between LN metastasis and primary tumor size

T stage	LN metastasis		P
	Yes	No	
T1a	0	5	0.036
T1b	10	36	
T1c	11	13	

LN, lymph node.

Table 3 Relationship between metastatic intrapulmonary LNs and size

Status of LNs	Diameter (mm)	P
Positive	6.5 ± 2.1	0.576
Negative	5.2 ± 1.4	

LNs, lymph nodes.

determine N stage, assessing LN metastasis by size. LNs with a shorter axis > 1 cm on CT are usually considered positive.¹¹ However, clinical data has shown that CT scanning is not a reliable method for N staging, with low sensitivity (approximately 60%) and low specificity (approximately 70%).^{12,13} Although PET-CT and mediastinoscopy are reported to be more accurate methods for N staging, invasiveness and high expense prevent routine use.¹⁴ In the present study, 28% (21/75) of patients with peripheral adenocarcinoma of the lung staged as N0 by CT scan before surgery were confirmed to have metastatic LNs (N1 or N2) in postoperative pathological examination. Of the 21 patients, 11 were upstaged from stage IA to IIB (with positive hilar or/and intrapulmonary LNs), 9 were upstaged from IA to IIIA (with positive mediastinal LNs), and one from stage IA to IVA, because pleural metastasis as well as positive mediastinal LNs were confirmed. Most positive intrapulmonary LNs were < 1 cm at the longest axis, and the average longest diameter was only 6.5 mm; LNs of this size cannot be diagnosed by CT scan.

Pathological examination is the most accurate means of N staging (pN stage) for NSCLC and the most important factor for determining prognosis and making postoperative treatment decisions. However, the accuracy of pN stage is also impacted by various factors. Adequate numbers of stations and LNs need to be collected during surgery, correctly labeled, and sent for pathological examination.^{15,16} In the pathological laboratory, the LNs of various stations should be routinely examined, including intrapulmonary LNs. In most cases, however, only the hilar and mediastinal LNs of lung cancer patients are routinely examined after surgery. Intrapulmonary LNs are usually not considered because they are located deep in the pulmonary parenchyma and are rarely isolated for pathological examination.¹⁷ But intrapulmonary LN metastasis, like hilar metastasis, is also defined as stage N1. For N1 patients, postoperative adjuvant chemotherapy is principally recommended, while adjuvant chemotherapy is not indicated for T1N0M0 patients. Therefore, patients with positive intrapulmonary LNs misdiagnosed as N0 might lose the opportunity for optimal postoperative treatment. Accurate pN staging of peripheral NSCLC is also important to make a rational choice of surgical procedure for future patients. Lobectomy has been the standard surgical procedure for operable lung cancer patients for the past decades. However, more and more patients are being diagnosed at early stages as a result of the extensive application of CT screening. Sublobar resection, which mainly includes segmentectomy and wedge resection, is more frequently applied in order to reduce pulmonary function loss. However, higher local recurrence has been reported in sublobar resected peripheral NSCLC patients compared to those who underwent lobectomy.¹⁸ Although the accurate

mechanism for this clinical finding requires further research, it may partly be attributed to undetected positive intrapulmonary LNs. Thus, it is clinically meaningful to reveal the regularity of intrapulmonary LN metastasis in order to choose the optimal surgical procedure for peripheral NSCLC.

A previous study reported that tumor size is related to occult LN metastasis in peripheral NSCLC.¹⁹ In the present study, 17 of the 75 patients with peripheral adenocarcinoma of the lung staged as N0 via contrast enhanced chest CT scan before surgery were found to have intrapulmonary LNs metastasis (N1) by postoperative pathological examination. Ten of the 17 patients only had intrapulmonary LN metastasis without hilar or/and mediastinal LN metastasis. These N1 patients would have been misdiagnosed as N0 if only the hilar and mediastinal LNs were pathologically examined. We also observed a linear relationship between T stage (tumor size) and LN metastasis in NSCLC patients. No positive LNs were detected in the five T1a ($T \leq 1$ cm) cases, while 21.7% of T1b ($1 \text{ cm} < T \leq 2$ cm) and 45% of T1c ($2 \text{ cm} < T \leq 3$ cm) cases were confirmed to have positive LNs. This finding serves as a reminder to surgeons to carefully consider surgical choices for operable peripheral NSCLC patients, such as whether wedge resection or segmentectomy is adequate in T1a cases with a cut edge 2 cm away from the border of the tumor. Sublobar resection must be very cautiously applied in T1b cases, because more than one fifth of such cases actually have positive LNs. In consideration of the high positive rate of LNs, sublobar resection should be avoided in T1c patients if their pulmonary function is adequate to tolerate lobectomy.

Disclosure

No authors report any conflict of interest.

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