Original Article on Transbronchial Needle Aspiration (TBNA)

Standardized transbronchial needle aspiration procedure for intrathoracic lymph node staging of non-small cell lung cancer

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Background: Thoracic lymph node (LN) metastasis is the determining factor for NSCLC staging. However, enlargement in thoracic LNs, which can be detected by chest computed tomography (CT), may not be adequate for NSCLC staging. This study aimed to investigate the effectiveness of a new transbronchial needle aspiration (TBNA) procedure to improve the sensitivity and accuracy of lung cancer diagnosis and staging.

Methods: A standardized TBNA procedure was performed on enlarged and non-enlarged LNs in the order of N3 to N1 station according to Wang's LN map. The status of LN metastasis determined by the standardized TBNA procedure was compared with the results from CT scan.

Results: The TBNA biopsy revealed that 21.43% of non-enlarged LNs were malignant. Compared with chest CT, the standardized TBNA procedure improved the accuracy of LN metastasis staging and discovered skip LN metastasis.

Conclusions: The standardized TBNA procedure of this study may be recommended to be used as a routine TBNA procedure, in which LNs should be biopsied in the order of N3 to N1 station and both enlarged and non-enlarged LNs should be included to improve the accuracy of lung cancer staging.

Keywords: Lung cancer; staging; standardized; transbronchial needle aspiration (TBNA)

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Introduction

Lung cancer is the leading cause of cancer-related motility and mortality worldwide, according to the latest data released by International Agency for Research on Cancer (IARC) (1). Early detection and precise staging are critical for clinical management of lung cancer. Metastasis in the intrathoracic lymph nodes (LNs), which is represented by the designator N in the TNM staging system, is usually a determining factor for therapeutic strategy for lung cancer. Computed tomography (CT) to determine LN staging of lung cancer relies on the size of malignant LNs and may only accurately detect malignant LNs that are larger than normal LNs. Toloza *et al*. found that 18% of the non-enlarged LNs that were detected by chest CT turned out to be malignant LNs after pathological examination (2),

suggesting that LN size may not be a reliable parameter for evaluation of LN metastasis in patients with non-small cell lung cancer (NSCLC). In addition, mediastinoscopy, which shows a diagnostic sensitivity of 90-95%, is traditionally considered as the gold standard for mediastinal staging of NSCLC (3). However, nowadays, mediastinoscopy is no longer the first choice for lung cancer diagnosis and staging owing to the limitations in assessment and high invasiveness and risk (4,5).

Transbronchial needle aspiration (TBNA), which is considered as a remarkably invaluable and minimally invasive technique, has been widely used for the diagnosis and staging of mediastinal adenopathy and masses (6). LN staging may be misdiagnosed based on the assumption that the metastatic LNs usually present as enlarged LNs. Accumulating evidence support that endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can improve the accuracy of diagnosis, but the procedure for EBUS-TBNA usually requires general anesthesia or conscious sedation, a second survey scope, and high expense (7-11). Most importantly, the misdiagnosis issue, which mentioned above, remains unsolved.

Here, we aim to address the misdiagnosis issue and investigate the effectiveness of a modified TBNA procedure to improve diagnostic sensitivity and accuracy in patients with NSCLC. We designed a standardized TBNA procedure and evaluated the effectiveness of the procedure. The standardized TBNA was performed in the order of N3-N2-N1 LN stations according to Wang's LN map (12) and all LNs, including non-enlarged LNs on CT scan, were examined by TBNA.

Materials and methods

Patients

Participating patients were diagnosed with NSCLC between December 2014 and March 2015 by transbronchial biopsy, bronchial brushing, or CT-guided percutaneous needle aspiration with at least one LN station enlargement. Electronic bronchoscope (Olympus Corporation, CV-260SL, Tokyo, Japan) and Wang needle (MW-122) were used in this current study. The operations were performed under local anesthesia or concise sedation. This study was reviewed and approved by the Institutional Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. Informed consent was obtained from each patient.

Radiological assessment

High resolution CT (HRCT) was performed before bronchoscopy, and the results were reviewed by an experienced radiologist blindly. The cutoff diameter for enlarged LNs was 10 mm. A LN with a diameter >10 mm was considered as an enlarged LN. TNM staging of each patient was determined.

Standardized TBNA procedure

TBNA was carried out in the order of N3 to N1 LN station in each patient according to Wang's LN map. Three passes were performed in each station. Specifically, the pass started from N3 stations (contralateral 2, 4, 10, and 11 stations), then N2 stations (ipsilateral 2, 4, 7, and 8 stations), eventually N1 stations (ipsilateral 10 and 11 stations). A small amount of the LN specimens was fixed in 95% ethanol and stained with H&E, and the remaining specimens were fixed in 10% formalin, embedded in paraffin, and stained with H&E. The H&E staining was reviewed by pathologists. TBNA was considered successful when the number of lymph cell was ≥40 per high power field or positive malignant lymph cells were detected. Positive diagnosis was defined as the detection of malignant lymph cells, and negative diagnosis was defined as the absence of malignant lymph cells.

Statistical analysis

Statistical analysis was performed using the statistical analysis software SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation (SD). Metastatic rate and the success rate of biopsy are presented as rate ± standard error (SE). χ^2 test was used to compare values of different groups. $P<0.05$ was considered statistically significantly different.

Results

TBNA results

A total of 53 patients, including 41 men and 12 women, participated in this study. The age of the patients was between 39 and 78 years, and the mean age was 62±10 years. Overall, 226 LNs from the 53 patients were sampled and 192 were biopsied successfully, representing a success rate of 84.96%. There were 116 LN metastasis, including 107 enlarged and 9 non-enlarged LNs. The metastatic rate for enlarged and non-enlarged LNs was 64.85% and 21.43%,

Table 1 Results of the standardized TBNA procedure in 53 patients with non-small cell lung cancer

Procedures	Location									Total
	11R	10R	4R	2R	7	8	4L	10L	11L	
Total nodes sampled (nodes biopsied successfully)	10 [8]	25 [16]	52 [46]	2 [2]	53 [50]	5 [4]	49 [46]	23 [15]	7 [5]	226 [192]
Total nodes sampled (metastatic lymph nodes)	10 [6]	25 [7]	52 [28]	2 [1]	53 [33]	5 [4]	49 [27]	23 [7]	7 [3]	226 [116]
Nodes biopsied successfully (metastatic lymph nodes)	8 [6]	16 [7]	46 [28]	2 [1]	50 [33]	4 [4]	46 [27]	15 [7]	5 [3]	192 [116]
Enlarged nodes sampled (metastatic lymph nodes)	8 [6]	13 [7]	42 [25]	1 [1]	44 [30]	5 [4]	36 [25]	11 [6]	5 [3]	165 [107]
Non-enlarged nodes sampled (metastatic lymph nodes)	2 [0]	12 [0]	10 [3]	1 [0]	9 [3]	0 [0]	13 [2]	12 [1]	2 [0]	61 [9]
Non-enlarged nodes biopsied successfully (metastatic lymph nodes)	0 [0]	7 [0]	8 [3]	1 [0]	7 [3]	0 [0]	12 [2]	7 [1]	0 [0]	42 [9]

Location of intrathoracic lymph nodes (UICC 2009). 11R, interlobar [right]; 10R, hilar [right]; 4R, lower paratracheal [right]; 2R, upper paratracheal [right]; 7, subcarinal; 8, paraesophageal [below carina]; 4L, lower paratracheal [left]; 10L, hilar [left]; 11L, interlobar [left].

Table 2 Comparison of the proportion of metastatic lymph nodes and success rate of biopsy in non-enlarged LNs in different regions

Variables	Hilar region (11R + 10R + 10L + 11L) (%)	Mediastinal region (2R + 4R + 4L + 7 + 8) (%)	P
Metastatic lymph nodes/non-enlarged nodes sampled (proportion of metastatic lymph node)	1/28 (3.57)	8/33 (24.24)	0.031
Successfully biopsied nodes/non-enlarged nodes sampled (success rate)	14/28 (50.00)	28/33 (84.84)	0.003

P<0.05 was considered significantly different. The proportion of metastatic lymph nodes in non-enlarge lymph nodes in the mediastinal region was significantly higher than that in the hilar region (P=0.031). The success rate of biopsy of the non-enlarged lymph nodes in the mediastinal region was significantly higher than that in the hilar region (P=0.003).

respectively. The malignant non-enlarged LNs were at 4R, 7, 4L, 10L station (*Table 1*).

Comparison of metastatic rate in different regions

The LN stations, 2R, 4R, 4L, 7, and 8 were grouped into the mediastinal region, and 11R, 10R, 10L, 11L were considered in the hilar region. The proportion of metastatic LNs in non-enlarged LNs in the mediastinal region was significantly higher than that in the hilar region (24.24% *vs.* 3.57%, P=0.031). The success rate of TBNA in non-enlarged LNs was also dramatically higher in the mediastinal region than in the hilar region (84.84% *vs.* 50.00%, P=0.003) (*Table 2*).

The effect of non-enlarged LNs on lung cancer staging

Compared with chest CT scan, TBNA detected 9 malignant non-enlarged LNs. Because of the detection of these malignant LNs by TBNA, the N staging was changed from N2 to N3 in 5 patients and from N1 to N2 in 3 patients (*Table 3*).

Skip LN metastasis

Of the 53 patients, 23 exhibited skip LN metastasis, including 1 solitary heterolateral hilar LN metastasis (4.35%), 8 solitary ipsilateral hilar LN metastasis (34.78%), 1 ipsilateral and heterolateral hilar without mediastinum nodal metastasis (N1 + N3, 4.35%), and 13 heterolateral

Table 3 Comparison of lymph node metastasis staging determined by CT scan *vs.* by the standardized TBNA procedure in the 9 patients with malignant non-enlarged LNs

Patient No.	Primary tumor location	Lymph node metastasis staging of TNM			
		Enlarged LNs in CT scan	Staging from CT scan	Metastatic LNs in TBNA	Staging from TBNA
1	Right upper lobe	N1	N1	N2 + N1	N2
2	Right inferior lobe	N2 + N1	N2	N3 + N2 + N1	N3
3	Right inferior lobe	N2	N2	N3 + N2	N3
4	Right inferior lobe	N1	N1	N2 + N1	N2
5	Left upper lobe	N1	N1	N2	N2
6	Left upper lobe	N2 + N1	N2	N3 + N2 + N1	N3
7	Left inferior lobe	N2	N2	N2 + N1	N2
8	Left inferior lobe	N2	N2	N3 + N2	N3
9	Left main bronchus	N2	N2	N3 + N2	N3

Intrathoracic N staging (UICC 2009). N0, no metastasis to lymph node(s); N1, metastasis to ipsilateral hilar or intrapulmonary lymph node(s); N2, metastasis to ipsilateral mediastinal lymph nodes and paratracheal and paraesophageal lymph nodes; N3, metastasis to contralateral intrathoracic lymph node(s).

Table 4 Skip lymph node metastasis

Primary tumor location	Number of case	Number of case from CT scan [No. of case from TBNA]							
		N0	N3	N2	N1	N2 + N1	N3 + N1	N3 + N2	N3 + N2 + N1
Right upper lobe	7	0 [0]	0 [0]	0 [0]	1 [0]	1 [2]	0 [0]	3 [3]	2 [2]
Right middle lobe	4	0 [1]	0 [0]	1 [1]	0 [0]	1 [1]	0 [0]	1 [0]	1 [1]
Right inferior lobe	16	0 [3]	0 [0]	4 [3]	3 [0]	3 [3]	0 [0]	1 [2]	5 [5]
Left upper lobe	9	0 [1]	0 [0]	1 [2]	2 [1]	1 [0]	0 [1]	2 [2]	3 [2]
Left inferior lobe	12	0 [2]	0 [0]	2 [1]	1 [1]	3 [2]	0 [0]	2 [3]	4 [3]
Left main bronchus	3	0 [0]	0 [0]	1 [1]	0 [0]	0 [0]	0 [0]	1 [2]	1 [0]
Right main bronchus	2	0 [1]	1 [1]	0 [0]	0 [0]	0 [0]	0 [0]	0 [1]	1 [0]
Total	53	0 [8]	1 [1]	9 [8]	7 [2]	9 [8]	0 [1]	10 [13]	17 [13]

hilar and mediastinum metastasis without affecting ipsilateral hilar LN (N3 + N2, 56.52%) (*Table 4*).

Complication

The 53 patients did not develop severe complications, such as hemorrhage, pneumothorax, pneumomediastinum, hematoma, or infection during the TBNA procedure.

Discussion

In this current study, we detected malignant metastasis in non-enlarged LNs by using a standardized TBNA procedure. Based on Wang's LN map, we successfully biopsied 42 out of 61 non-enlarged LNs by the TBNA procedure and found that 9 out of the 42 LNs were metastatic LNs. This metastatic rate is consistent with the results from surgery (3-5,13). The slightly higher metastatic rate in this current study might be related with patient selection. Notably, 8 patients, who had non-enlarged LNs that were diagnosed as metastatic LNs by TBNA, eventually were re-staged to a more advanced LN metastasis stage, suggesting that detection of malignant non-enlarged LNs may be critical for lung cancer staging. Thus, we believe the standardized TBNA procedure in our current study may reduce misdiagnosis rate and improve the accuracy of LN metastasis staging in NSCLC.

Lymph drainage is the most common pathway for lung

cancer metastasis. The hilar LNs are usually at the upstream of mediastinal LNs (14). However, mediastinal N2 LN metastasis may occur without the involvement of LNs in the hilar region, and these phenomena is called skip LN metastasis (15). In this current study, we detected skip LN metastasis by using the standardized TBNA procedure. Thus, our results indicate that N2 and N3 LNs should be examined for malignancy although N1 LNs present negative malignancy.

The proportion of metastatic LNs in non-enlarged LNs in the mediastinal region was approximately 7 times of that in the hilar region, and the success rate of TBNA in the mediastinal region was also dramatically higher than that in the hilar region. The low proportion of metastatic LNs in non-enlarged LNs in the hilar region may be associated with the poor success rate of TBNA, which was only 50%, in the hilar region. In addition, according to the principle of TNM staging in NSCLC, LN metastasis is defined based on the status of the contralateral LN but not the ipsilateral LNs. Thus, according to the operation duration of TBNA and patient tolerance, biopsy of non-enlarged LNs in the hilar region may be skipped without substantial effects on cancer staging.

High false negative rate is one of the disadvantages associated with TBNA for NSCLC staging. Previous studies showed that EBUS-TBNA presented a higher sensitivity (79-95%) with a lower false negative rate (1-37%) compared with conventional TBNA (13,16-20). The great variation (1-37%) in the false negative rate of the previous studies may be related with study design heterogeneity, LN size and station, TBNA method and passes, and the skill of the person who performed TBNA. False negative rate may be reduced by using the standardized TBNA procedure of this current study to decrease heterogeneity of TBNA.

Limitation

Positive results from TBNA usually do not require confirmation by surgery. Thus, the positive predictive value of the standardized TBNA procedure is 100%. However, negative results from TBNA need to be confirmed by surgery. Because the gold criteria by surgery were lacking in our study, we were unable to report the precise sensitivity and specificity of the standardized TBNA procedure.

Conclusions

In summary, we recommend the standardized TBNA procedure for LN biopsy. In this procedure, LNs should be biopsied in the order of N3 to N1 and both enlarged and non-enlarged LNs should be included to achieve accurate staging of lung cancer.

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Footnote

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

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