Endobronchial ultrasound-guided transbronchial needle aspiration can improve the diagnostic accuracy of positron emission tomography/computed tomography in hilar and/or mediastinal lymphadenopathy

ABSTRACT

Context: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and positron emission tomography/computed tomography (PET/CT) are the two most extensively used methods for the diagnosis and staging of lung cancer.

Aims: The present study was designed to compare the diagnostic performance of EBUS-TBNA with that of PET/CT in patients with hilar and/or mediastinal lymphadenopathy.

Settings and Design: We compared the accuracy of EBUS-TBNA with that of PET/CT in the diagnosis of hilar and/or mediastinal lymphadenopathy and evaluated the diagnostic utility of EBUS-TBNA in patients with PET/CT false-positive and false-negative findings.

Methods: This study retrospectively analyzed 85 patients with hilar and/or mediastinal lymphadenopathy who underwent EBUS-TBNA and PET/CT between January 2014 and December 2017. The accuracy of EBUS-TBNA histopathology and cytopathology was evaluated and compared with PET/CT scan findings.

Results: The diagnostic accuracy of EBUS-TBNA combined with PET/CT was significantly higher than that of the single diagnostic method (P < 0.001). Among PET/CT-negative lymph nodes, 4 of 9 (44.4%) malignant lymph nodes were identified by EBUS-TBNA. Among PET/CT-positive lymph nodes, 43 of 47 (91.5%) benign lymph nodes were diagnosed by EBUS-TBNA.

Conclusions: EBUS-TBNA combined with PET/CT could effectively reduce false-positive and false-negative rates in the diagnosis of hilar and mediastinal lymphadenopathy, which might provide accurate staging, determine optimum therapeutic strategy and improve survival in patients with lung cancer.

KEY WORDS: Endobronchial ultrasound-guided transbronchial needle aspiration, lung cancer, lymphadenopathy, positron emission tomography/computed tomography

INTRODUCTION

Mediastinal lymph node (LN) metastases are diagnosed in approximately 28%–38% of patients with lung cancer.[1] Accurate staging is crucial for selecting the optimum treatment strategy and determining the prognosis of patients with lung cancer.[2,3] Positron emission tomography/computed tomography (PET/CT) is the most widely employed noninvasive imaging modality for clinical staging of lung cancer. Previous studies have indicated benefits of PET/CT in detecting LN metastases.[4] However, due to lacking of pathological diagnosis in the evaluation of mediastinal LN metastases by imaging, misdiagnosis often occurs.[5] Therefore, histological
confirmation of mediastinal LN metastases is still necessary for accurate staging. Owing to its high accuracy, minimal invasiveness, and safety, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has emerged as the most effective tool for the diagnoses of enlarged LNs and masses near the trachea and bronchus.\[5,6\] Furthermore, it has been recommended by international guidelines,\[2,3,7\] Several studies have demonstrated application of EBUS-TBNA and PET/CT in the assessment of mediastinal LN metastases from lung cancer.\[8,9\] However, there is a paucity of literature providing histopathologic and cytopathologic evidence of hilar and/or mediastinal lymphadenopathy based on EBUS-TBNA. Therefore, the present study retrospectively analyzed the diagnostic significance of EBUS-TBNA histopathology and cytopathology for the diagnosis of hilar and/or mediastinal lymphadenopathy. Furthermore, the diagnostic utility of EBUS-TBNA was compared with that of PET/CT in the diagnosis of mediastinal lymphadenopathy.

**METHODS**

This retrospective study included a total of 85 patients with hilar and/or mediastinal lymphadenopathy who underwent EBUS-TBNA and PET/CT at the First Affiliated Hospital of Soochow University between January 2014 and December 2017 (Table 1). The patients included 55 and 30 with malignant and benign diseases, respectively (Table 2). At least one enlarged mediastinal or hilar LN measuring ≥1 cm on the short axis was observed in all patients in chest CT. All patients underwent PET/CT examination first and followed by EBUS-TBNA. Written informed consent was obtained from each patient. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University.

**Positron emission tomography with computed tomography acquisition**

18F-fluorodeoxyglucose (FDG) PET/CT scans were obtained using an advanced Discovery STE PET/CT scanner (General Electric Medical Systems, Milwaukee, WI, USA). The patients fasted for at least 6 h before the PET/CT examination. Blood glucose was measured in all patients to ensure that the value was <11 mmol/L. Imaging was performed after intravenous injection of 18F-FDG (dose of 0.12 mCi/kg) tracer for 60 min. A whole-body emission scan in three-dimensional mode was obtained from the base of the skull to the mid-femur, 2–3 min per bed position. The PET/CT images were reconstructed using an ordered-subset expectation maximization iterative reconstruction algorithm. Attenuation correction and image fusion were performed using low-dose CT data. A maximum standardized uptake value (SUV\(_{\text{max}}\)) ≥2.5 was used as the cut-off for malignancy.\[9\]

**Endobronchial ultrasound-guided transbronchial needle aspiration**

The patients kept fast for at least 4 h before the procedure. Before commencing the bronchoscopy, Local anesthesia was administered with 2% lidocaine. Some patients received an intravenous bolus injection of midazolam and/or fentanyl for conscious sedation. Initially, conventional flexible bronchoscopy (BF-260, Olympus, Tokyo, Japan) was performed in each patient to examine the tracheobronchial tree, followed by an EBUS with a dedicated convex probe (BF-UC260FW, Olympus or Fujifilm EB-530US, Fujifilm, Tokyo, Japan). All EBUS-TBNA procedure was performed using a 21G needle (NA-201SX-4021, Olympus) under real-time ultrasound guidance through the working channel of the EBUS bronchoscope. Scanning was performed at a frequency of 7.5 MHz and images were processed using an Olympus ultrasound processor (EU-ME1, Olympus or SU-8000, Fujifilm), which scans in a direction parallel to the insertion of the bronchoscope to visualize the surrounding vascular structure. Once the target LN was located, the needle was advanced into the target lesion. An average of five punctures per LN was obtained. The locations of the LNs were classified according to the International Association for the Study of Lung Cancer LNs map criteria.\[10\] No rapid on-site cytological evaluation was performed. Part of the aspirated materials were immediately immersed and rinsed in a vial containing Thinprep PreservCyt

### Table 1: Patients’ characteristics

| Gender   | n (%)   |
|----------|---------|
| Male     | 60 (70.6) |
| Female   | 25 (29.4) |

### Table 2: Summary of the diagnoses of the patients

|                      | Patients, n (%) | Total LNs | Malignant LNs | Benign LNs |
|----------------------|----------------|-----------|---------------|------------|
| Malignant            |                |           |               |            |
| Pulmonary SCC        | 7 (8.2)        | 10        | 8             | 2          |
| Pulmonary ADC        | 26 (30.6)      | 48        | 41            | 7          |
| SCLC                 | 9 (10.6)       | 15        | 13            | 2          |
| NSCLC-NOS            | 5 (5.9)        | 6         | 6             | 0          |
| B cell lymphoma      | 2 (2.4)        | 3         | 3             | 0          |
| NHL                  | 2 (2.4)        | 6         | 6             | 0          |
| T cell lymphoma      | 1 (1.2)        | 1         | 1             | 0          |
| HL                   | 1 (1.2)        | 1         | 1             | 0          |
| IMT                  | 1 (1.2)        | 1         | 1             | 0          |
| Cervical SCC         | 1 (1.2)        | 1         | 1             | 0          |
| Suspicious of malignancy* | 1 (1.2)    | 2         | 2             | 0          |
| Benign               |                |           |               |            |
| Reactive             | 19 (22.4)      | 39        | 0             | 39         |
| Granuloma            | 6 (7.1)        | 13        | 0             | 13         |
| Tuberculosis         | 4 (4.7)        | 5         | 0             | 5          |
| Total                | 85 (100)       | 151       | 83            | 68         |

*Cases were considered suspicious of malignancy if disease progression was identified in follow-up images, but evidence was insufficient for malignant diagnosis. LNs=Lymph nodes, SCC=Squamous cell carcinoma, ADC=Adenocarcinoma, SCLC=Small cell lung cancer; NSCLC-NOS=Non-small cell lung cancer not otherwise specified; IMT=Inflammatory myofibroblastic tumor; NHL=Non-Hodgkin lymphoma; HL=Hodgkin lymphoma
solution (Hologic Ltd., Massachusetts, USA). The preservCyt vial was placed into Thinprep 2000 (Hologic Ltd., USA) for preparation for liquid-based cytological analysis. Other aspirated samples were discharged onto glass slides, smeared, fixed in 95% (v/v) ethanol, and sent for cytological examination. Specimens from both conventional smears and liquid-based cytology were stained with hematoxylin and eosin (H and E). EBUS-TBNA specimens were classified as “positive” if malignant cells were observed and “negative” if no malignancy was found. The staining results appearing atypical cells were also considered as negative. Aspired histologic materials, including tissue cores or fragments, were immediately fixed in 10% formalin, paraffin-embedded, sliced, H and E-stained, or further immunostained.

### Diagnostic criteria
A true negative was defined as no evidence of malignancy on EBUS-TBNA and at least 6 months of clinical follow-up documenting no radiological progression of the disease. Histopathologic finding of malignancy in samples obtained by EBUS-TBNA was considered as a true positive. A false negative was defined as histopathological finding providing no evidence of malignancy in EBUS-TBNA samples and surgical confirmation of malignancy or obvious progression of lesions within 6 months of follow-up images.

### Statistical analysis
The sensitivity, specificity, positive predictive value, negative predictive value and accuracy between EBUS-TBNA and PET/CT in the diagnoses of hilar and/or mediastinal lymphadenopathy were compared by McNemar’s method or Fisher’s exact test. Unpaired Student’s t-tests were used to compare SUV max between the EBUS-TBNA false-negative group and the EBUS-TBNA true-positive group. Statistical analysis was performed using the SPSS for Windows, version 16.0 (SPSS, Chicago, IL, USA). P < 0.05 was considered as statistically significant.

### RESULTS
The diagnostic utility of EBUS-TBNA and PET/CT for lung cancer were shown in Table 3. The histopathological and cytopathological findings of 151 LNs were summarized in Tables 4-6. The most frequently sampled LN stations were 4R (26.5%), 7 (29.1%), and 1R (17.2%). During EBUS-TBNA, several patients experienced bleeding, which was effectively managed. There were 23 EBUS-TBNA false-negative LNs (13 patients). Of these, 22 LNs were confirmed to be malignant by surgery, and one LN was considered suspicious for malignancy in subsequent follow-up. The mean SUV max of the EBUS-TBNA false-negative LNs (5.7, range, 1.4–25.6; n = 23) was significantly lower than that of the true-positive LNs diagnosed by EBUS-TBNA (7.8, range, 1.5–15.7; n = 60) (P < 0.05).

Table 7 presented the pathological diagnoses of PET/CT-positive and PET/CT-negative LNs. Of the 46 PET/CT-positive benign LNs, 29 were reactive and diagnosed by EBUS-TBNA. A representative case was shown in Figure 1. Eleven of 13 (84.6%) granulomas and 3 of 4 (75%) TB cases were diagnosed by EBUS-TBNA. Among the 74 PET/CT-positive malignant LNs, 8 of 9 (88.9%) metastatic LNs of squamous cell carcinoma were diagnosed by EBUS-TBNA. Thirty-two of 36 (88.9%) metastatic LNs of adenocarcinoma, 11 of 12 (91.7%) metastatic LNs of small cell lung cancer, 4 of 6 (66.7%) metastatic LNs of non-small cell lung cancer not otherwise specified, and 1 of 5 (20%) non-Hodgkin lymphoma LNs were diagnosed by EBUS-TBNA. However, three B-cell lymphoma LNs and one Hodgkin lymphoma LN were not detected by EBUS-TBNA and were diagnosed by surgical biopsy.

Among the PET/CT-negative LNs, 21 reactive LNs and one case of TB were diagnosed by EBUS-TBNA. Two of 5 (40%) metastatic LNs of adenocarcinoma, 1 metastatic LN of small cell lung cancer and 1 non-Hodgkin lymphoma LN were detected by EBUS-TBNA. One T-cell lymphoma LN was not detected by EBUS-TBNA and was diagnosed by surgical biopsy.

The sensitivity of EBUS-TBNA for the histopathological and cytopathological diagnoses of hilar and/or mediastinal LN malignancies was 72.3%, and 61.4% and the negative predictive value were 74.5% and 68%, respectively. The specificity and positive predictive value of both tests were

### Table 3: Diagnostic value of PET/CT and EBUS-TBNA in the detection of mediastinal metastases of lung cancer

|                | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|----------------|----------------|-----------------|---------|---------|--------------|
| ADC PET/CT     | 87.8           | 57.1            | 92.3    | 44.4    | 83.3         |
| EBUS-TBNA      | 82.9           | 100             | 100     | 50      | 85.4         |
| SCLC PET/CT    | 92.3           | -               | 85.7    | -       | 80           |
| EBUS-TBNA      | 92.3           | 100             | 100     | 66.7    | 93.3         |
| SCC PET/CT     | 100            | 100             | 100     | 100     | 100          |
| EBUS-TBNA      | 100            | 100             | 100     | 66.7    | 90.9         |
| NSCLC-NOS PET/CT | 100          | -               | 100     | -       | 100          |
| EBUS-TBNA      | 66.7           | 100             | -       | 66.7    |              |

PET/CT=Positron emission tomography/computed tomography, EBUS-TBNA=Endobronchial ultrasound-guided transbronchial needle aspiration, SCC=Squamous cell carcinoma, ADC=Adenocarcinoma, SCLC=Small cell lung cancer, NSCLC-NOS=Nonsmall cell lung cancer not otherwise specified, PPV=Positive predictive value, NPV=Negative predictive value
**Table 4: Locations of lymph nodes diagnosed as malignant lesions by EBUS-TBNA**

| Total, n (%) | SCC | ADC | SCLC | NSCLC-NOS | NHL |
|-------------|-----|-----|------|------------|-----|
| 2R          | 5 (8.3) | 0 | 3 | 1 | 1 |
| 4R          | 20 (33.3) | 2 | 13 | 3 | 1 |
| 4L          | 2 (3.3) | 0 | 1 | 1 | 0 |
| 7           | 20 (33.3) | 4* | 8 | 5 | 2 |
| 10R         | 3 (5) | 0 | 2 | 1 | 0 |
| 10L         | 1 (1.7) | 0 | 1 | 0 | 0 |
| 11R         | 8 (13.3) | 2 | 5 | 1 | 0 |
| 11L         | 1 (1.7) | 0 | 1 | 0 | 0 |
| Total, n (%) | 60 (100) | 8 (13.3) | 34 (56.7) | 12 (20) | 4 (6.7) |

*Including one cervical SCC. EBUS-TBNA=Endobronchial ultrasound-guided transbronchial needle aspiration, SCC=Squamous cell carcinoma, ADC=Adenocarcinoma, SCLC=Small cell lung cancer, NSCLC-NOS=Non-small cell lung cancer not otherwise specified, NHL=Non-Hodgkin lymphoma.

**Table 6: Summary of locations of all lymph nodes diagnosed by EBUS-TBNA cytopathology**

| Malignant, n (%) | Benign, n (%) |
|-----------------|---------------|
| 2R              | 5 (9.8)       | 5 (5)        |
| 4R              | 20 (39.2)     | 20 (20)      |
| 4L              | 1 (2)         | 8 (8)        |
| 7               | 14 (27.5)     | 30 (30)      |
| 10R             | 2 (3.9)       | 10 (10)      |
| 10L             | 0             | 2 (2)        |
| 11R             | 8 (15.7)      | 18 (18)      |
| 11L             | 1 (2)         | 7 (7)        |
| Total, n (%)    | 51 (100)      | 100 (100)    |

**Table 7: Summary of histopathological diagnosis of PET/CT-positive and -negative lymph nodes**

| PET/CT-positive LNs, n (%) | PET/CT-negative LNs, n (%) |
|---------------------------|---------------------------|
| SCC                       | 9 (7.5)                   | 0                          |
| ADC                       | 36 (30)                   | 5 (16.1)                   |
| SCLC                      | 12 (10)                   | 1 (3.2)                    |
| Suspicious of malignancy* | 1 (0.8)                   | 1 (3.2)                    |
| NSCLC-NOS                 | 6 (5)                     | 0                          |
| Granuloma                 | 29 (24.2)                 | 21 (67.7)                  |
| Tuberculosis              | 13 (10.8)                 | 0                          |
| B cell lymphoma           | 4 (3.3)                   | 1 (3.2)                    |
| NHL                       | 5 (4.2)                   | 1 (3.2)                    |
| T cell lymphoma           | 0                         | 1 (3.2)                    |
| HL                        | 1 (0.8)                   | 0                          |
| IMT                       | 1 (0.8)                   | 0                          |
| Total, n (%)              | 120 (100)                 | 31 (100)                   |

*Cases were considered suspicious of malignancy if disease progression was identified in follow-up images but the evidence was insufficient for malignant diagnosis. PET/CT=Positron emission tomography/computed tomography, SCC=Squamous cell carcinoma, ADC=Adenocarcinoma, SCLC=Small cell lung cancer, NSCLC-NOS=Non-small cell lung cancer not otherwise specified, IMT=Inflammatory myofibroblastic tumor, NHL=Non-Hodgkin lymphoma, HL=Hodgkin lymphoma.

**DISCUSSION**

PET/CT is a noninvasive technique that cannot provide tissue samples for pathological diagnosis. Moreover, it is not sufficiently sensitive and specific to determine hilar or mediastinal LN involvement, which leads to potential false-positive findings. For patients with suspected malignant mediastinal LNs, tissue specimens should be extracted for pathological diagnosis and accurate staging to determine prognosis.\[2,3,7,11,12\]

In this study, among the PET/CT-positive LNs, 46 (38.3%) were benign LNs, most of which were granulomatous inflammation and reactive lymphoid hyperplasia. Mediastinal lymphadenopathy in some patients with lung cancer may be attributed to a hypersensitivity reaction induced by the tumor.\[13,14\]

Among the PET/CT-negative LNs, 8 was diagnosed as malignant by EBUS-TBNA or surgery, and one LN was suspected to be malignant in follow-up. Among PET/CT-negative LNs, 17.6% were diagnosed as malignant by EBUS-TBNA.\[15\] A previous study reported that among 104 patients staged N0 by PET/CT before surgery, 27 (26.0%) were false-negative findings,\[16\] which may be associated with micrometastases.\[17\]

Due to the high false-negative rate, PET/CT could not reliably determine which patient had a chance of surgery.\[17\]
A previous review indicated a significant decrease in the sensitivity of PET/CT when evaluating metastatic LNs of adenocarcinoma. Consistent with this finding, in our study, 5 PET/CT-negative LNs of 3 patients were confirmed to be metastatic LNs. Similarly, Herth et al.[19] showed that 6 of 100 NSCLC patients without mediastinal PET activity had Stage N2 or N3 disease, of which all were identified by EBUS-TBNA. These findings may be attributed to the most frequent prevalence of mediastinal LN metastases in adenocarcinoma[20] and may also be related to the reduced uptake of FDG in LNs of patients with adenocarcinoma.[21]

The findings of the present study revealed the high sensitivity, specificity, and accuracy of cytopathology in differentiating benign from malignant LNs, suggesting its potential in lung cancer staging. Histopathology combined with cytopathology was superior to the single diagnostic method in terms of diagnostic sensitivity, negative predictive value, and accuracy. Vaidya et al.[22] also found that the histopathology and cytopathology and cytology of EBUS-TBNA could improve diagnostic efficacy.

This study had several limitations. First, our findings were based on a retrospective analysis of data obtained from a single center. Second, only a few EBUS-TBNA negative patients were confirmed histopathologically by surgical sampling. Despite these limitations, our findings suggested that EBUS-TBNA histopathology and cytopathology could significantly improve the diagnostic accuracy of PET/CT for the diagnosis of mediastinal lymphadenopathy.

CONCLUSIONS

EBUS-TBNA combined with PET/CT could effectively reduce false-positive and false-negative rates in the diagnosis of hilar and mediastinal lymphadenopathy to provide accurate staging and determine optimum therapeutic strategy, which might improve survival in patients with lung cancer.

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Conflicts of interest

There are no conflicts of interest.

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