Efficacy of Convex Probe Endobronchial Ultrasound (CP-EBUS) Assisted Transbronchial Needle Aspiration for Mediastinal Staging in Non-small Cell Lung Cancer Cases with Mediastinal Lymphadenopathy

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Background and Objective: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a sampling method for the patients with Non-small cell lung cancer (NSCLC) that have enlarged mediastinal lymph nodes that are detected with computed tomography (CT). We aimed to investigate the value of EBUS-TBNA in sampling enlarged mediastinal lymph nodes in the patient with NSCLC.

Patients and method: From January 2007 to May 2009, patients were diagnosed NSCLC with CT scans showing enlarged lymph nodes (node >1 cm) or a positron emission tomography (PET/CT) finding of the mediastinum underwent EBUS-TBNA.

Results: EBUS-TBNA was successfully performed in all 52 patients (mean age, 52 years; 45 men) from 93 mediastinal lymph nodes. EBUS detected lymph node metastasis in 40 patients (77%). 12 patients (23%) with negative lymph node samples were underwent mediastinoscopy. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EBUS-TBNA in the detection of mediastinal metastasis were 95 %, 100%, 100%, 83%, and 96%, respectively. EBUS-TBNA was uneventful, and there were no complications.

Conclusion: EBUS-TBNA is an effective, safe and minimally invasive procedure following PET/CT or CT scanning in the mediastinal staging of potentially operable NSCLC.

Key words: endobronchial ultrasound, non-small cell lung cancer, mediastinal staging, mediastinal lymphadenopathy, transbronchial needle aspiration

Introduction

Non-small cell lung cancer (NSCLC) accounts for one of the most common causes of malignity related deaths. \(^1\) Mediastinal lymph node metastasis (MLNM) is the most important prognostic factor in NSCLC patients without distant metastasis and also it is significant in determining treatment methods. \(^2,3\) This is why it is essential to make the correct mediastinal staging. Mediastinal lymph node staging can be performed with non-invasive (imaging) and invasive approach. CT, positron emission tomography (PET), and PET-CT are used as non-invasive techniques. CT imaging for detecting mediastinal lymph node metastasis has sensitivity and specificity of 51% (95% CI, 47–54%) and 85% (95% CI, 84–88%), respectively, demonstrating that CT scanning has limited ability to diagnose or to exclude mediastinal metastasis. \(^4\) PET scanning for detecting mediastinal metastasis has sensitivity and specificity of 74% (95% CI, 69–79%) and 85% (95% CI, 82–88%), respectively. \(^4\) According to these data PET is more accurate than CT but these technologies can be misleading and for all abnormal imaging findings cytological or histological confirmation of malignancy must
be performed so that patients are not staged incorrectly and deprived appropriate treatment. More so, PET has limited spatial resolution and certain disadvantages have been reported including the failure to identify metastasis in small lymph nodes and differentiate between lymph nodes with non-tumour related involvement and tumour metastasis. This is why the effectiveness of PET in intrathoracic staging is still a matter of discussion.

Invasive surgical methods like mediastinoscopy are frequently used to eliminate or verify MLNM due to the limitations of CT and PET, especially for patients who are candidates for surgical resection. However, although very rare, mediastinoscopy can be accompanied by complications (2%-3%) and surgical mortality (0.1%). This is why various minimal invasive methods have been tried for tissue sampling. Bronchoscopy assisted transbronchial needle aspiration (conventional TBNA) is a frequently used minimally invasive method and has been used with variable and a wide spectrum of diagnostic success rates (i.e. 20%-89%) in mediastinal staging. In addition, Conventional TBNA is a blind procedure and important factors that can influence the results of TBNA are established lymph node enlargement on CT, the lymph node size, site of the lymph node, the kind of needle used, number of aspirates performed, the ability and the experience of the operators, and the availability of rapid on site evaluation (ROSE).8

Recently, there has been significant interest in imaging-assisted TBNA. Procedure guidance with the aid of CT fluoroscopy, as well as endobronchial ultrasound (EBUS), has been shown to be feasible and simple to perform.9, 10 In previously published studies, it was shown that EBUS with TBNA was highly accurate and cost effective as a diagnostic tool.11 There are two forms of EBUS, radial and linear (convex). Initially, EBUS procedures were performed using a radial probe. Compared to conventional TBNA, although it is not a real-time procedure, this probe increases diagnostic efficiency, especially in stations other than the subcranial area.12 Recently, there are a number of recent studies focusing on the value of CP-EBUS assisted TBNA in mediastinal staging of NSCLC cases that have reported a high rate of diagnosis.13-23 However, these studies originate from a couple of centres so, to get a clearer idea on the diagnostic accuracy of convex probe endobronchial ultrasound (CP-EBUS) assisted TBNA in mediastinal staging of NSCLC cases, there is obvious need for more studies coming from different institutes. Based on this vision, in this study we intended to examine the diagnostic success of EBUS assisted TBNA in mediastinal staging of NSCLC cases identified to have mediastinal lymphadenopathy by thoracic CT and/or PET-CT, as well as factors affecting diagnostic success rate.

Patients and Method

The real time, CP-EBUS assisted TBNA procedure was performed at our clinic between January 2007 and May 2009 for staging purposes on 52 successive patients diagnosed with NSCLC, considered suitable for operation according to metastatic screening (Thoracic CT, PET/CT, Pulmonary Function Tests, Brain MRI), presenting with enlarged (short axis >1 cm) mediastinal lymph nodes in thoracic CT results and/or revealing positive mediastinal involvement (defined as standardized uptake value; SUV-max >2.5) according to PET-CT examination results. This was a prospective study. All patients were informed about the procedure and provided written confirmation for the operation. Our hospital’s Ethics Board approved the study.

Patients were subject to the procedure after at least 4 hours of fasting. Xylocaine (maximum 8 mg/kg) was used for topical anaesthesia and midazolam (0.05 mg/kg) for conscious sedation. This was followed by EBUS procedure. Procedure was performed using a fiberoptic-ultrasound bronchoscope (CP-EBUS; XBF-UC 160F-OL8; Olympus Medical Systems, Tokyo, Japan) featuring a 7.5 MHz convex linear ultrasonic transducer on the distal tip wrapped with a water-inflatable balloon. Olympus image processor was used to process the images transmitted by the bronchoscope (EU-60). The location, shape and structure of lymphadenopathy were examined with ultrasound. We started with the lymph node stations presenting worst prognosis if there were multiple lymph node involvements in the performed TBNA. In other words, we used the same needle to sample N3 prior to N2. Therefore, even if the N2 lymph node sampled were subsequently contaminated in a N3 lymph node positive patient, this contamination would be insignificant since N3 is more important prognostically. The aim of adopting this method was to perform an all-inclusive healthy staging procedure with a single TBNA needle. The bronchoscope was directed towards the lymph nodes area targeted for biopsy sampling. A specially developed 22-gauge biopsy needle (XNA-202C) was pushed upwards from the distal tip of the bronchoscope as the real time imaging continued. The outer sleeve on the needle was opened, and the needle was penetrated inside the lymph nodes (Fig. 1). Jabbing and coughing method was used most frequently to
ensure needle penetration through the bronchial wall. A syringe was attached to the proximal end to perform aspiration through the needle. Tissue samples were collected from the lymph node in the shape of cells or tissue fragments by back and forth motion as the aspiration continued. A single bronchoscope was used for all the procedures (E.C). There was no pathologist present during the procedure for ROSE. This is why it was impossible to determine whether material contained adequate number of cells during the procedure. Depending on the amount of collected material, the bronchoscopist assessed the adequacy for each sample and if it was necessary, he repeated the TBNA procedure from the same area until enough material was collected. On average, the TBNA procedure was repeated 2.27 times for each station (min: 1, max: 4). None of the patients developed any procedure-related serious complications. A part of the material collected from each area was smeared and left to dry in the air after being fixated with 90% alcohol. Some of the material, on the other hand, was squirted into 3 ml bottles containing ethyl alcohol and formaldehyde mixture to form a cellblock. Materials (lamellas and cell block bottles), for each sampled lymph node, were prepared separately, numbered and send to the pathology laboratory.

Material collected with TBNA was separated into two groups, pathologically adequate and inadequate samples. Preparations diagnosed with definite malignity were considered adequate positive, preparations containing plenty of lymphocytes but no malignities were considered adequate negative and suspicious preparations containing bronchial epithelium or cellular atypia were considered inadequate samples. None of the cases was reported as an inadequate sample. Based on LN stations, adequate material was collected from 89 (95%) out of 93 lymph node stations.

Mediastine was resampled by performing invasive diagnostic procedures from the mediastinal lesion on all 12 patients without malignity diagnosis, even when the collected material was adequate. These samples were examined histopathologically. Results using this approach were later compared with TBNA results. CP-EBUS guided TBNA procedure was considered to be a false negative when malignity was found as a result of invasive procedures. On the other hand, if invasive procedures cannot identify malignity the CP-EBUS, TBNA was considered to be a true negative.

Statistical Analysis

Diagnostic success was calculated based on each patient and lymph node. The procedure’s rates of diagnostic accuracy, sensitivity, specificity, positive and negative predictive values were calculated using standard formulations. Chi-Square or Fisher’s Exact was used for frequency comparison amongst subgroups whilst Student’s t-test was used for comparison of averages.

Results

CP-EBUS- TBNA was performed in all 52 patients to obtain samples from mediastinal lymph nodes (93 nodes). The procedure was uneventful, and there were no complications. 40 (77 %) patients were diagnosed with MLNM according to the CP-EBUS guided TBNA (Table 1). It was considered that the procedure outcome was diagnostic and true positive for these patients. Mediastinoscopy was performed on 12 cases considered having an adequate, negative EBUS-TBNA result. Ten (83%) cases were considered to be true negatives, and 2 (17%) cases were considered as false negatives. Overall, 35 patients had stage N2 disease, of which 34 cases (97%) were identified from EBUS-TBNA, and 7 patients had stage N3 disease, of which 6 cases (86%) were identified by EBUS-TBNA (Table 1). Hence, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy rate of CP-EBUS-TBNA in diagnosing MLNM of patients with NSCLC based on cases for EBUS were respectively 95%, 100%, 83%, 100% and 96% (Table 2).

TBNA was performed on a total of 93 mediastinal lymph node stations in fifty-two cases (34 in the subcarinal station, 4 in the right upper paratracheal station, 38 in the right lower paratracheal station, 1 in the left upper paratracheal station and 16 in the left lower paratracheal station) (Table 3). The average lymphadenopathy diameter
Maximum effort is required for accurate staging since mediastinal staging is the most important treatment selection criteria and prognostic indicator in NSCLC without distant metastasis. Many non-invasive and invasive methods presenting various advantages and disadvantages are utilised for this purpose. The sensitivity and specificity levels of thoracic CT, the most easily obtained non-invasive method, falls weak in identifying MLNM. A mediastinoscopy, on the other hand, the method with best sensitivity and specificity is an invasive method and, although small, presents the risk of morbidity and mortality. This is why a specific method to identify MLNM looks rather appealing. However, the chosen method must be universal with high sensitivity in metastasis suspected patients, high specificity in early stage patients and a high degree of accuracy in all patient groups. Initial studies on the EBUS-TBNA method, used recently for this purpose appear very promising. Current discussions are focused on whether EBUS-TBNA will replace mediastinoscopy, an invasive method, in identifying MLNM. In our study, we performed CP-EBUS guided transbronchial needle aspiration (TBNA) procedure on 52 successive patients diagnosed with NSCLC, considered suitable for operation according to metastatic screening and studied its value in staging. Similar to studies in published literature, we reached high rate of diagnosis (96%) and rendered invasive staging redundant in a high degree of patients (77%).

Thoracic CT did not identify LN in 27 of the 93 mediastinal lymph nodes subject to EBUS-TBNA. PET/CT scan did not determine the involvement in 8 of the 27 lymph nodes. Despite negative CT and PET/CT scan results, EBUS-TBNA of mediastinal lymph nodes was positive for metastatic disease in five lymph stations. The stage changed from N2 to N3 disease in three patients.

**Discussion**

Maximum effort is required for accurate staging since mediastinal staging is the most important treatment selection criteria and prognostic indicator in NSCLC without distant metastasis. Many non-invasive and invasive methods presenting various advantages and disadvantages are utilised for this purpose. The sensitivity and specificity levels of thoracic CT, the most easily obtained non-invasive method, falls weak in identifying MLNM. A mediastinoscopy, on the other hand, the method with best sensitivity and specificity is an invasive method and, although small, presents the risk of morbidity and mortality. This is why a specific method to identify MLNM looks rather appealing. However, the chosen method must be universal with high sensitivity in metastasis suspected patients, high specificity in early stage patients and a high degree of accuracy in all patient groups. Initial studies on the EBUS-TBNA method, used recently for this purpose appear very promising. Current discussions are focused on whether EBUS-TBNA will replace mediastinoscopy, an invasive method, in identifying MLNM. In our study, we performed CP-EBUS guided transbronchial needle aspiration (TBNA) procedure on 52 successive patients diagnosed with NSCLC, considered suitable for operation according to metastatic screening and studied its value in staging. Similar to studies in published literature, we reached high rate of diagnosis (96%) and rendered invasive staging redundant in a high degree of patients (77%).

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N3 or N2, eliminating the need for advanced invasive staging. 12 (23%) cases presenting negative aspirate in terms of malignity were subject to mediastinoscopy. Considered together with mediastinoscopy results C-EBUS guided TBNA’s rate of sensitivity, specificity, false positivity, false negativity and accuracy in staging NSCLC was respectively 95%, 100%, 0%, 17% and 96%. Results obtained in our study show coherence with most studies published on this subject (Table 4). However, our study differed from most other studies in terms of smaller case group and the absence of negative cases in CT and PET/CT. Nonetheless, regardless of these differences, the high degree of diagnosis identified in our study proves the effectiveness of CP-EBUS method in mediastinal staging.

EBUS is generally a method used during mediastinal staging for sampling lymph node over 1 cm that are observed in CT examinations. A recent study by Herth et al. was conducted to investigate EBUS-TBNA’s diagnostic value in 1 cm or smaller mediastinal lymph nodes performed EBUS-TBNA on 100 NSCLC cases where CT failed to determine lymph node enlargement. The study demonstrated that EBUS-TBNA offered correct diagnosis even in 1 cm or smaller lymph nodes as it prevented unnecessary surgical procedures in 1 out of 6 NSCLC patients failing to reveal mediastinal involvement in CT examinations. Although there were cases identified to have pathological lymph node according to CT and PET-CT in our study, EBUS identified pathological lymph node obtaining malignity diagnosis in 8 lymph node stations of 5 cases even though there was no such indication in CT and PET-CT examinations. As a result, 3 cases were identified to have progressed from N2 stage to N3 stage. This is why we believe EBUS evaluation will offer certain contribution in excluding unexpected N2-N3 illness prior to planned surgical resection in patients with normal mediastine according to CT.

Although PET is significantly superior to CT in detecting mediastinal involvement and may be useful to detect distant metastases, inflammatory reactions of lymph nodes may lead to accumulation of FDG, resulting in false-posi-

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**Table 3**  Localizations, sizes, sampling numbers and results of the lymph nodes on CT, PET, and EBUS-TBNA

<table>
<thead>
<tr>
<th>LN</th>
<th>CT n</th>
<th>LN diameter (mm)</th>
<th>PET-CT n</th>
<th>SUV value</th>
<th>CT n</th>
<th>LN diameter (mm)</th>
<th>CP-EBUS AD</th>
<th>SN (n)</th>
<th>MLNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>2R</td>
<td>3</td>
<td>16 ± 7a</td>
<td>4</td>
<td>11 ± 0.3a</td>
<td>4</td>
<td>14 ± 2a</td>
<td>4 (100%)</td>
<td>0</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>4R</td>
<td>33</td>
<td>14 ± 11b</td>
<td>34</td>
<td>8 ± 4a</td>
<td>38</td>
<td>13 ± 6a</td>
<td>36 (94%)</td>
<td>2</td>
<td>33 (87%)</td>
</tr>
<tr>
<td>2L</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>-</td>
<td>1</td>
<td>10</td>
<td>1 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4L</td>
<td>5</td>
<td>16 (3–27)b</td>
<td>14</td>
<td>8 ± 3a</td>
<td>16</td>
<td>13 ± 6a</td>
<td>16 (100%)</td>
<td>2.3 ± 0.8</td>
<td>14 (88%)</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>15 (10–25)b</td>
<td>30</td>
<td>10 ± 4a</td>
<td>34</td>
<td>18 ± 9a</td>
<td>32 (94%)</td>
<td>2.2 ± 0.7</td>
<td>31 (91%)</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>12 (10–20)b</td>
<td>82</td>
<td>9.3 ± 4.5a</td>
<td>93</td>
<td>15 ± 7a</td>
<td>89 (95%)</td>
<td>2.2 ± 0.7</td>
<td>82 (88%)</td>
</tr>
</tbody>
</table>

a results were given as Mean ± SD; b results were given as median (quarter intervals)
MLNM, mediastinal lymph node metastasis; LN, lymph node; SN, sampling number; AD, Adequate material
7; subcarinal, 2R; right upper paratracheal, 4R; right lower paratracheal, 2L; left upper paratracheal, 4L; left lower paratracheal

**Table 4**  Results of studies investigating role of C-EBUS-TBIA for mediastinal staging in NSCLC patients

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Patients (n)</th>
<th>Stage</th>
<th>Technique</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>FP %</th>
<th>FN %</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yasufuku, et al/2004</td>
<td>70</td>
<td>II–III</td>
<td>RT-22 ga</td>
<td>95</td>
<td>100</td>
<td>0</td>
<td>10</td>
<td>67</td>
</tr>
<tr>
<td>Yasufuku, et al/2005</td>
<td>108</td>
<td>II–III</td>
<td>RT-22 ga</td>
<td>95</td>
<td>100</td>
<td>0</td>
<td>11</td>
<td>69</td>
</tr>
<tr>
<td>Rintoul, et al/2005</td>
<td>20</td>
<td>II–III</td>
<td>RT-22 ga</td>
<td>95</td>
<td>100</td>
<td>0</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Vilmann, et al/2005</td>
<td>31</td>
<td>II–III</td>
<td>RT-22 ga</td>
<td>95</td>
<td>100</td>
<td>0</td>
<td>28</td>
<td>65</td>
</tr>
<tr>
<td>Herth, et al/2006</td>
<td>100</td>
<td>I</td>
<td>RT-22 ga</td>
<td>94</td>
<td>100</td>
<td>0</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Yasufuku, et al/2006</td>
<td>102</td>
<td>I–III</td>
<td>RT-22 ga</td>
<td>92</td>
<td>100</td>
<td>0</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>Vincent, et al/2008</td>
<td>152</td>
<td>I–III</td>
<td>RT-22 ga</td>
<td>99</td>
<td>100</td>
<td>0</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>Bauwens, et al/2008a</td>
<td>106</td>
<td>I–III</td>
<td>RT-22 ga</td>
<td>95</td>
<td>97</td>
<td>0</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>Herth, et al/2008b</td>
<td>100</td>
<td>I–III</td>
<td>RT-22 ga</td>
<td>89</td>
<td>100</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Bin, et al/2009</td>
<td>117</td>
<td>II–III</td>
<td>RT-22 ga</td>
<td>90</td>
<td>100</td>
<td>0</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>Current series/2010</td>
<td>52</td>
<td>II–III</td>
<td>RT-22 ga</td>
<td>95</td>
<td>100</td>
<td>0</td>
<td>17</td>
<td>77</td>
</tr>
</tbody>
</table>

RT-US, bronch-real-time ultrasound bronchoscope; n, number of cases; FP, false positive; FN, false negative

a Increased activity in mediastinum in PET scan, b Nodes <1 cm, negative mediastinal activity in PET scan.

Excluded from calculations because NPV is relatively less reliable with a prevalence of >90%.
tive results. Therefore, false positive PET findings in the mediastine may be frequently seen, and many authors\textsuperscript{20–22) have suggested that tissue confirmation is necessary before denial of surgery. Our data support the suggestions from these authors.\textsuperscript{25–27) In the present study, there were 10 false-positive cases (20\%) that were all correctly diagnosed as false positive by EBUS-TBNA prior to surgery.

Although the diagnostic yield is high, the potential of false negative results in the few patients returning negative result with EBUS-TBNA still remains an important problem. This is why such patients should be referred to additional invasive procedures. False negativity of mediastinoscopy, an invasive procedure, is substantially lower. Lemaire et al. reported the false-negative rate for lymph node metastasis to be 5.5\% (56 of 1,019) among patients with lung cancer undergoing resection.\textsuperscript{28) In our study, twelve patients with negative EBUS-TBNA underwent a surgical staging procedure (mediastinoscopy). Of these, the final diagnosis was positive in two patients (17\%). A similar rate of false negativity was obtained in our study and other studies, (Table 4) demonstrating significantly higher false negativity compared to mediastinoscopy.

Another disadvantage of TBNA is false positive results. The significance of a false positive result is that the case might lose the chance of operation due to incorrect staging. When performing a biopsy from the airway, there always remains the possibility of a false positive result. It is safe to say that cytology and/or histology positive for malignancy is a true positive. Therefore, a false positive is usually related to a contaminant in the TBNA process. In our study, there are several lines of evidence against contamination during the process. First of all, there were no changes in the bronchial airway at the site of puncture. Since the lymph nodes are adjacent to the bronchial wall, there is a low possibility of contamination. Secondly, the dedicated 22-gauge needle is equipped with an internal sheath that is withdrawn after the puncture of the bronchus. This sheath allows for the prevention of contamination.

Certain studies demonstrate practicing ROSE in NSCLC Staging increases TBNA's rate of diagnosis.\textsuperscript{29) We were unable to perform ROSE in our study, during the TBNA procedure, as there was no pathologist within the bronchoscopy unit. It was the bronchoscopist that decided on the adequacy of performed aspirations. Our study's material adequacy remained at hundred percent. This could be attributed to the efficient EBUS assisted lymph node localisations. We believe that specialists' conventional TBNA experience played a role in the high degree of material adequacy. Hence it is obvious that ROSE will not offer additional advantages.

EBUS offers a unique way of imaging airways and parabronchial structures during bronchoscopy procedures.\textsuperscript{30} The procedure is safe, minimally invasive, and it does not require general anaesthesia or hospitalization. The complication rate is extremely low, nearly next to nil.\textsuperscript{31, 32) This is why CP-EBUS guided TBNA at the same time appears to be a very reliable method. In our study, the procedure was completed in nearly all of the patients without significant complications.

Our study has existing limitations such as it has been composed with cases who were diagnosed with NSCLC and had pathological mediastinal lymph nodes that were only examined with Chest CT and/or PET-CT and in contrast to many of the other studies a smaller number of cases were included. Although our results resemble the common outcome of previous studies, it differs from other multicentre studies as it is the only single centre study, and it is the first study from our country.

In conclusion, CP-EBUS guided TBNA ensures safe practice of the procedure with its high degree of sensitivity, specificity and accuracy in mediastinal staging of NSCLC and to a great extent renders advanced invasive procedures thanks to its high diagnostic yield. Potentially operable patients with mediastinal involvement on computed tomography or PET may benefit from pre-surgical endobronchial ultrasound-guided transbronchial needle aspiration and staging.

Conflicts of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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