

The Efficacy of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in Mediastinal Staging of Non-Small Cell Lung Cancer in a University Hospital

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Background: In mediastinal lymph node sampling in non-small cell lung cancer (NSCLC) it is important to determine the appropriate treatment as well as to predict an outcome. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a recently developed, accurate, safe technique in patients with NSCLC for sampling mediastinal lymph nodes. We sought to determine the usefulness of EBUS-TBNA in mediastinal staging with NSCLC considered to be operable.

Methods: We retrospectively reviewed the records of 142 patients who underwent EBUS-TBNA for mediastinal staging in the Asan Medical Center, Korea from July 2008 to July 2010. If patients were in an operable state, they underwent subsequent surgical staging. Diagnoses based on biopsy results were compared with those based on surgical results.

Results: We performed EBUS-TBNA in 184 mediastinal lymph nodes in 142 NSCLC patients. Almost all of the EBUS-TBNA samples were from the lower paratracheal (112, 60.9%) and subcarinal (57, 31.0%) lymph nodes. In 142 patients, 51 patients (35.9%) were confirmed with malignant invasion of the mediastinal lymph node by EBUS-TBNA and 91 (64.1%) patients were not confirmed. Among the 91 patients, 64 patients (70.3%) underwent surgical staging. 3 patients (4.7%) who were misdiagnosed by the EBUS-TBNA were confirmed by surgery. After Diagnostic sensitivity of EBUS-TBNA, the prediction of mediastinal metastasis was 94.4% and specificity was 100%. The procedures were performed safely and no serious complications were observed.

Conclusion: We demonstrated the high diagnostic value of EBUS-TBNA for mediastinal staging.

Key Words: Bronchi; Ultrasonography, Interventional; Biopsy, Fine-Needle; Mediastinum; Lymphatic Metastasis; Carcinoma, Non-Small-Cell Lung

Introduction

Accurate disease staging is an important factor not only for determining a treatment method but also for predicting prognosis in patients diagnosed with lung cancer. In particular, mediastinal lymph node invasion

should be examined in patients with non-small cell lung cancer for lymph node staging. Many studies have reported that chest computed tomography (CT), which is one of methods that identify mediastinal lymph node invasion, has low sensitivity and specificity¹. Positron emission tomography has been also known as a method to identify mediastinal lymph node invasion, but has a limitation in that it has false negativity in slowly progressed cancer such as bronchioloalveolar carcinoma, and false positivity in granuloma or inflammatory lymph node diseases^{2,3}. According to the guideline of American College of Chest Physicians (2007), it describes that

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a pathological examination should be conducted if central lung cancer or mediastinal lymph node invasion is suspected. Until now, mediastinoscopic biopsy has been conducted as a standard examination⁴. However, mediastinoscopic biopsy has a limitation in that it is an invasive procedure that requires general anesthesia.

Endobronchial ultrasound-guided transbronchial needle aspiration is a non-invasive procedure where needle aspiration is conducted while watching ultrasonogram during the conduct of bronchoscopy. Its usefulness in mediastinal lymph node examination has been frequently reported⁵. According to most studies published to date, endobronchial ultrasound-guided transbronchial needle aspiration has been reported to have sensitivity and specificity more than 90% in the examination of mediastinal lymph node invasion in lung cancer patients^{6,7}.

Accordingly, in this study, the result of examining lymph node invasion via endobronchial ultrasound-guided transbronchial needle aspiration in patients, who had been already diagnosed with non-small cell lung cancer at one Korean general hospital, and who had shown mediastinal lymph node enlargement in chest CT, and the result of pathological examination of the mediastinal lymph node obtained from primary lung cancer resection and lymphadenectomy in patients without invasion were comparatively analyzed to investigate the usefulness of endobronchial ultrasound-guided transbronchial needle aspiration.

Materials and Methods

1. Subjects

Of 770 patients who underwent endobronchial ultrasound-guided transbronchial needle aspiration at Seoul Asan hospital from July 1st 2008 to July 31st 2010, 142 patients, who had been already diagnosed with non-small cell lung cancer via percutaneous biopsy or bronchoscopy, and who had shown mediastinal lymph node enlargement with a size of more than 5 mm in chest CT, were selected as subjects. Positron emission tomography was conducted on all patients to predict mediastinal lymph node invasion and distant metastasis in

lung cancer. If the maximum standardized uptake value (SUV) was 2.5 or higher, it was considered positive. Patients, who had distant metastasis where a surgical treatment was impossible, or who had poor health status where bronchoscopy was impossible, were excluded from the subjects. Primary lung cancer resection and lymphadenectomy were conducted on the patients who had no mediastinal lymph node invasion in endobronchial ultrasound-guided transbronchial needle aspiration. After the surgery, mediastinal lymph node invasion was examined again to assess the accuracy of endobronchial ultrasound-guided transbronchial needle aspiration. This study was approved by the IRB of Seoul Asan hospital (201-0259).

2. Endobronchial ultrasound-guided transbronchial needle aspiration

Endobronchial ultrasound-guided transbronchial needle aspiration was conducted after the intravenous injection of 2.0~5.0 mg midazolam following local anesthesia with 4% lidocaine. The tracheobronchea was observed via fiberoptic bronchoscopy (BF-T160 bronchoscope; Olympus, Tokyo, Japan). Subsequently, an examination was conducted using convex probe EBUS (XBF-UC 160F; Olympus) with an ultrasonic transducer installed at the end of bronchoscopy. This endobronchial ultrasonogram was approached to the wall of the airway to examine, and a installed balloon was dilated with saline solution to obtain ultrasonographic images of the lymph node. After 22-gauge needle (NA-202C; Olympus) was inserted to the lymph node, the samples were obtained using negative pressure. Aspiration was performed at each lesion at least twice, and was continued until the tissue was obtained⁸. A pathological examination was not immediately conducted in the endoscopic lab. Instead, the samples obtained using the needle was smeared on a glass slide, and then fixed with 95% alcohol, followed by cytology. The tissue samples were immediately fixed with formaldehyde, and then transferred to the pathology lab. All endoscopic examinations and subsequent endobronchial ultrasound-guided transbronchial needle aspiration were conducted by

one conductor. Classification criteria presented by Mountain et al. was used to mark lymph node location⁹.

3. Analysis methods

The sensitivity and specificity of endobronchial ultrasound-guided transbronchial needle aspiration were examined to assess its usefulness for the examination of mediastinal lymph node invasion. The result variables were analyzed using a SPSS statistical package for social science version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Endobronchial ultrasound-guided transbronchial needle aspiration was conducted on the mediastinal lymph node of 142 patients who had been already histologically diagnosed with non-small cell lung cancer. The male subjects accounted for 110 (77.5%) patients and the median age was 63 years (range, 40~88). The histological classification of the patients with non-small cell

lung cancer consisted of adenocarcinoma in 83 patients (58.5%), squamous cell carcinoma in 42 patients (29.6%) unclassified non-small cell lung cancer in 17 patients (12.0%). The lymph node on which endobronchial ultrasound-guided transbronchial needle aspiration was conducted had a median size of 10 mm (5~50 mm), and 91.9% of the lymph node were located in lower paratracheal lesion (4L, 4R) and subcarinal lesion (Table 1)⁷.

Via endobronchial ultrasound-guided transbronchial needle aspiration, mediastinal lymph node invasion was identified in 51 patients (35.9%), of whom 15 patients (29.4%) underwent a surgery and 36 patients (70.6%) underwent chemotherapy or radiotherapy. Among 91 patients (64.1%) who had not shown mediastinal lymph node invasion in endobronchial ultrasound-guided transbronchial needle aspiration, 64 patients (70.3%) underwent a surgery. As a result of the surgery, mediastinal lymph node invasion was identified in 3 patients (4.7%), and no mediastinal lymph node invasion was found in the remaining 61 patients (95.3%). 27 patients (29.7%), who had not shown mediastinal lymph node invasion in endobronchial ultrasound-guided transbronchial needle aspiration and who had been able to undergo lung cancer surgery, actually did not undergo the surgery or were not followed up after diagnosis due to

Table 1. Characteristics of patients and lymph nodes

Variables	Data
Patients, No	142
Male	110 (77.5)
Age*, yr	63 (40~88)
Histologic diagnosis of patients, No	
Adenocarcinoma	83 (58.5)
Squamous cell carcinoma	42 (29.6)
NSCLC, nonspecified	17 (12.0)
Median size of LNs sampled by EBUS-TBNA*, mm	10 (5~50)
Location of lymph nodes targeted by EBUS-TBNA, No	
Left upper paratracheal (2L)	1 (0.5)
Right upper paratracheal (2R)	6 (3.3)
Left lower paratracheal (4L)	39 (21.2)
Right lower paratracheal (4R)	73 (39.7)
Subcarinal (7)	57 (31.0)
Lower paraesophageal (8)	8 (4.3)
Total	184

Data are presented as number (%) unless otherwise indicated. *Data are presented as median (range).

NSCLC: non-small cell lung cancer; EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; LN: lymph node.

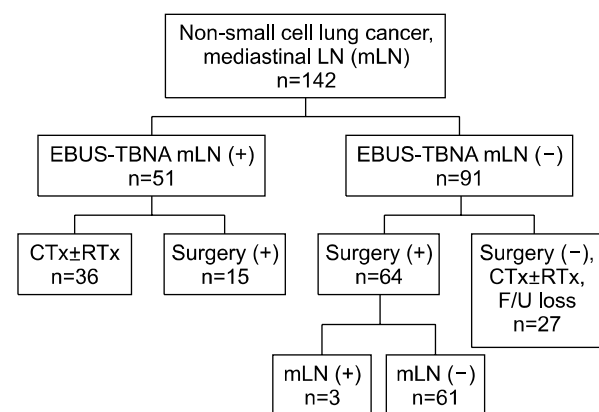


Figure 1. Clinical course of 142 patients enrolled in the study. CTx: chemotherapy; EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; F/U: follow up; LN: lymph node; RTx: radiation therapy; mLN (+): tumor invade the mediastinal lymph node.

surgery risks and postoperative health status caused by old age, decreased lung function, or cardiovascular diseases (Figure 1). Therefore, endobronchial ultrasound-guided transbronchial needle aspiration was shown to have a sensitivity of 94.4% (51/54) and a specificity of 100% (61/61) for mediastinal lymph node invasion in non-small cell lung cancer. In addition, positron emis-

sion tomography was shown to have 98.1% (53/54) sensitivity and 80.3% (49/61) specificity.

Three patients, who had not shown lymph node invasion in endobronchial ultrasound-guided transbronchial needle aspiration and who had undergone lung cancer resection and lymphadenectomy, showed lymph node invasion in the resected tissue. One patient who

Table 2. Clinical characteristics of cases misdiagnosed by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of mediastinal staging in non-small cell lung cancer (NSCLC)

Sex/Age (yr)	Histologic type	Primary tumor location	Target LN location	Size of LN (mm)	Max,SUV of LN, PET
M/57	Sarcomatoid carcinoma	RUL, RML	7	11	5.0
M/67	Squamous cell carcinoma	LLL	4L	7	2.5
M/67	Adenocarcinoma	LLL	7	9	3.6

LLL: left lower lobe; LN: lymph node; RML: right middle lobe; RUL: right upper lobe; SUV: standardized uptake value; 4L: left lower paratracheal lymph node; 7: subcarinal lymph node.

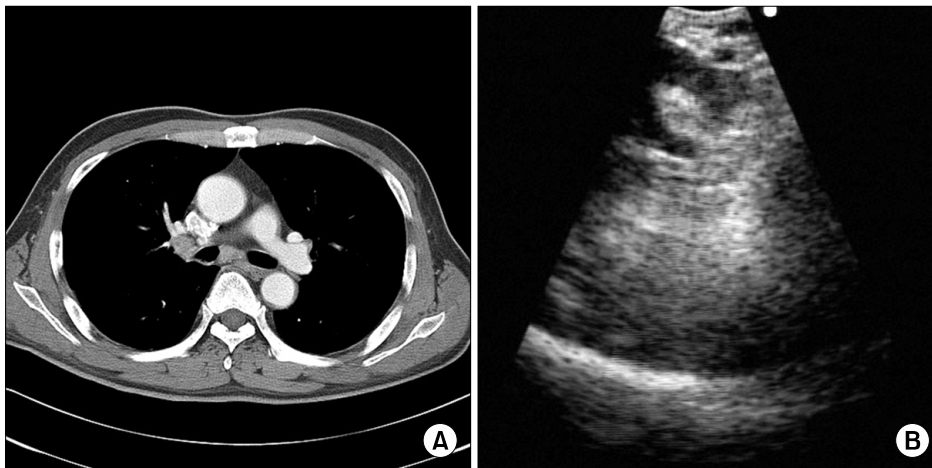


Figure 2. In a patient with right lower lobe (RLL) sarcomatoid carcinoma, nodal station 7 was assessed by EBUS-TBNA. (A) Axial CT image of stations 7. (B) EBUS image of station 7. EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; CT: computed tomography.

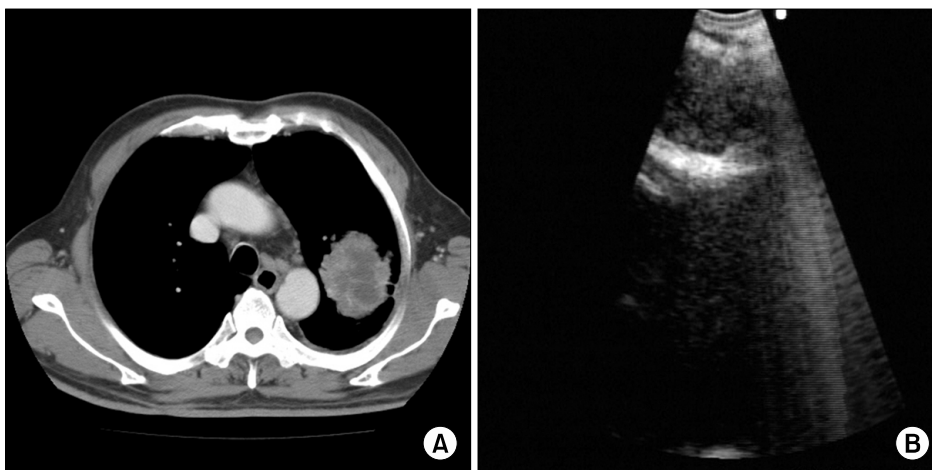


Figure 3. In a patient with left lower lobe (LLL) squamous cell carcinoma, nodal station 4L was assessed by EBUS-TBNA. (A) Axial CT image of stations 4L. (B) EBUS image of station 4L. EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; CT: computed tomography.

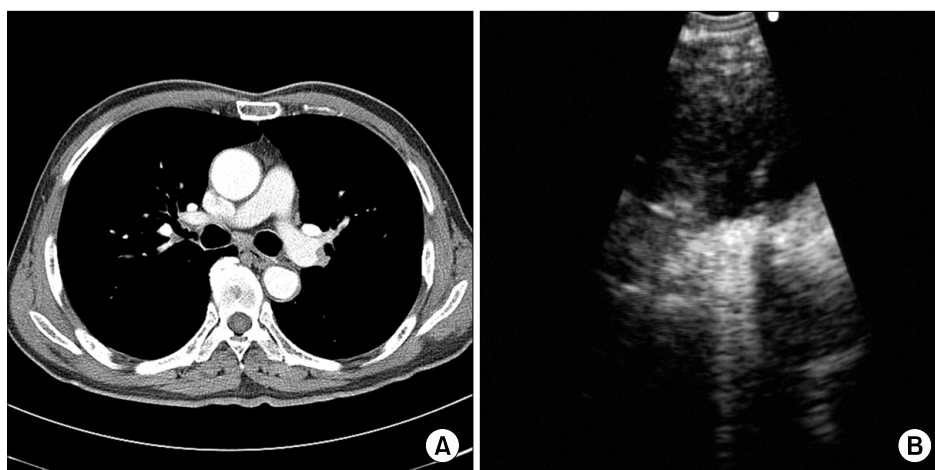


Figure 4. In a patient with Left lower lobe adenocarcinoma, nodal station 7 was assessed by EBUS-TBNA. (A) Axial CT image of stations 7. (B) EBUS image of station 7. EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; CT: computed tomography.

had been diagnosed with sarcomatoid carcinoma in a preoperative histological examination on the mass on the right upper and middle lobes and who had shown subcarinal lymph node⁷ enlargement in chest CT, underwent endobronchial ultrasound-guided transbronchial needle aspiration. Another patient, who had been diagnosed with squamous cell carcinoma in a histologic examination on the mass on the left upper lobe, underwent needle aspiration for left lower paratracheal lymph node (4L). The other patient, who had shown adenocarcinoma that had occurred around left lower bronchus underwent needle aspiration for subcarinal lymph node⁷. No lymph node invasion was found in the three patients as a result of endobronchial ultrasonogram needle aspiration. Each lymph node was shown to have the maximal SUV value of 2.5 and 3.6, respectively in positron emission tomography. The lymph node measured in endobronchial ultrasonogram was shown to have a size of 11, 7, and 9 mm, respectively, which showed no common characteristic in the three patients (Table 2, Figure 2~4).

Discussion

In this study, mediastinal lymph node invasion was examined in patients with non-small cell lung cancer via

preoperative endobronchial ultrasound-guided transbronchial needle aspiration in one university hospital. Subsequently, the mediastinal lymph node obtained from lung cancer resection and lymphadenectomy was then examined to assess the sensitivity and specificity of endobronchial ultrasound-guided transbronchial needle aspiration.

Non-small cell lung cancer accounts for approximately 85% of malignant tumors occurring in the lung. In this case, mediastinal lymph node staging is an important factor determining the resection possibility and prognosis of primary lung cancer¹⁰. Chest CT has been used for the early diagnosis and staging of lung cancer in most hospitals, but has been reported to have 51% sensitivity and 86% specificity for mediastinal lymph node invasion¹. Positron emission tomography has been also reported to have 74% sensitivity and 85% specificity for mediastinal lymph node invasion, which showed lower sensitivity than that shown in this study^{1,7}. However, positron emission tomography can not replace a pathological examination. The guideline of the US national cancer networks (2010) recommended that a pathological examination should be conducted if mediastinal lymph node invasion is suspected, and that methods such as mediastinoscopic biopsy, endobronchial ultrasound-guided transbronchial needle aspiration, and

esophagoscopy ultrasound-guided needle aspiration could be used¹¹. A pathological examination via mediastinoscopic biopsy has been known as a standard method to date. However, mediastinoscopic biopsy has been reported to be actually conducted in 27% of patients before lung cancer resection¹². Unlike the recommendation of the guideline, mediastinoscopic biopsy has not been readily conducted in actual clinical practices due to the following reasons. This is likely to be attributable to the fact that mediastinoscopic biopsy, which has been known to be a relatively safe examination, has disadvantages of adverse events related to general anesthesia, and complications such as skin incision, arrhythmia, bleeding, chest lymphatic injury, recurrent laryngeal nerve injury, and pneumonia¹³.

Endobronchial ultrasonogram can observe the tracheal wall and para-structures in a real time by adhering the tracheal wall and probe as the bronchoscopy end is installed with a balloon that can be dilated with saline solution. It enables a histological examination using tissues obtained from the negative aspiration via a needle, and minimizes side effects by screening vessels via Doppler functions. Furthermore, it has an advantage of examining outpatients, who can undergo bronchoscopy except for patients with coagulopathy, under local anesthesia and analgesics. Due to the aforementioned reasons, endobronchial ultrasound-guided transbronchial needle aspiration has been useful not only for the identification of casual factors of mass including the mediastinal lymph node, but also for the examination of mediastinal lymph node invasion in lung cancer¹⁴⁻¹⁶. Adams et al. conducted a meta-analysis of mediastinal lymph node data in 817 patients with lung cancer by reviewing 10 research papers, reporting that endobronchial ultrasound-guided transbronchial needle aspiration had 88% sensitivity and 100% specificity⁶. Such result was higher than 80% sensitivity of conventional mediastinoscopic biopsy⁴. The higher sensitivity of endobronchial ultrasound-guided transbronchial needle aspiration is likely to be attributable to the following reasons. As endobronchial ultrasonogram/needle aspiration can be conducted under local anesthesia, it makes the exami-

nation of mediastinal lymph node possible in patients with old age or cardiovascular diseases, who can not undergo mediastinoscopic biopsy due to risks caused by general anesthesia. In addition, the range of the lymph node that can be examined via endobronchial ultrasound-guided transbronchial needle aspiration is similar to that of the conventional mediastinoscopic biopsy. Upper paratracheal lymph node (2L, 2R) prevertebral lymph node (3P), lower paratracheal lymph node (4L, 4R), subcarinal lymph node⁷ that can be examined via mediastinoscopy can be also examined via endobronchial ultrasound-guided transbronchial needle aspiration. In particular, subcarinal lymph node⁷ metastasis was reported to be more accurately identified in endobronchial ultrasound-guided transbronchial needle aspiration¹⁷. Furthermore, endobronchial ultrasound-guided transbronchial needle aspiration has an advantage of observing the lymph node with a size of 1 cm or less through a real-time ultrasound compared to needle aspiration. In this study, endobronchial ultrasound-guided transbronchial needle aspiration was conducted on the mediastinal lymph node whose size was 5 mm or higher in chest CT.

The result of this study confirmed that endobronchial ultrasound-guided transbronchial needle aspiration was useful for the detection of mediastinal lymph node invasion. However, this study has a few limitations in that it was not directly compared with mediastinoscopic biopsy, a conventional standard method of the examination of mediastinal lymph node, and that the lymph node opposite to the primary lesion was not resected during the surgery so that it was not compared with the lymph node examined via endobronchial ultrasound-guided transbronchial needle aspiration. Despite the aforementioned limitations, disparity between conductors was avoided as only one conductor selected the lymph node and conducted endobronchial ultrasound-guided transbronchial needle aspiration.

If a needle larger than 22-gauge needle is used in endobronchial ultrasound-guided transbronchial needle aspiration, false negativity could be reduced. Furthermore, Hwangbo et al. reported that via endobronchial

ultrasound-guided transbronchial needle aspiration with esophageal ultrasonographic needle aspiration, the lymph node beneath the aorta⁵, the paraesophageal lymph node⁸, and the pulmonary ligament lymph node⁹ were examined. Therefore, as endobronchial ultrasound-guided transbronchial needle aspiration can examine most mediastinal lymph nodes, it can be used as a pre-operative examination method replacing mediastinoscopic biopsy¹⁸.

This study confirmed that endobronchial ultrasound-guided transbronchial needle aspiration was useful for the detection of mediastinal lymph node invasion in non-small cell lung cancer. When the result of examining mediastinal lymph node invasion via endobronchial ultrasound-guided transbronchial needle aspiration was compared with the result of the actual surgery, the result of endobronchial ultrasound-guided transbronchial needle aspiration showed high sensitivity and specificity.

No large-scaled comparative study reporting that endobronchial ultrasound-guided transbronchial needle aspiration completely replaced mediastinoscopic biopsy has been reported to date. However, considering the high diagnostic rate of endobronchial ultrasound-guided transbronchial needle aspiration, it can be considered effective in mediastinal staging.

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