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ORIGINAL RESEARCH

Utility and Safety of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in the Diagnosis of Isolated Mediastinal Masses

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Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a valuable tool for diagnosing pulmonary disease due to its efficiency and safety. We retrospectively analyzed patients with mediastinal masses who underwent diagnostic EBUS-TBNA at Shanghai Chest Hospital, and evaluated the clinical accuracy of EBUS-TBNA in the diagnosis mediastinal masses.

Method: From 2009 and 2014, patients who received EBUS-TBNA to diagnose a isolated mediastinal mass were enrolled. Clinical follow-up was performed to ascertain the patient's final diagnosis.

Results: Forty-six patients were enrolled in this study. Thirty-seven were diagnosed with an oncologic disease, 3 were diagnosed with a mediastinal infection, and 2 were found to have a mediastinal goiter. The overall sensitivity, specificity, positive predictive value, negative predictive value, diagnostic yield was 63.6%, 100%, 100%, 42.9%, and 71.4%, respectively.

Conclusion: EBUS-TBNA is a safe and effective means of diagnosing mediastinal masses.

Keywords: EBUS-TBNA, mediastinum, diagnosis

Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a valuable tool for diagnosing thoracic disease due to its efficiency and safety.[1] It has excellent sensitivity and specificity, and a low incidence of complications.[2,3] The latest National Comprehensive Cancer Network (NCCN) guidelines for non-small cell lung cancer recommend EBUS-TBNA for diagnosis and staging.[4]

The mediastinum is the central compartment of the thoracic cavity. It is uncontained and surrounded by loose connective tissue that contains the heart and its vessels as well as the esophagus, trachea, phrenic and cardiac nerves, thoracic duct, thymus and lymph nodes of the central chest.[5] It is a common site for lymphoma, thymoma, germ cell tumors, neurogenic tumors, mediastinal goiters and other mass-manifesting diseases.[6,7] A precise diagnosis of mediastinal disease is necessary to direct appropriate treatment.[8–10]

Several modalities have been developed for diagnosing mediastinal masses, including mediastinoscopy and CT-guided percutaneous biopsy.[11,12] The diagnostic yield of these techniques is similar, but transthoracic needle biopsy is more attractive due to its minimally invasive nature. Also a minimally invasive biopsy technique, Endobronchial ultrasound-guided transbronchial needle aspiration

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(EBUS-TBNA), has been recently evaluated for its ability to diagnose mediastinal masses.[13–17] Yasufuku et al[14] reported a high diagnostic value of EBUS-TBNA (93.6%). However, Zhu et al[15] reported a diagnostic yield of only 62%. This difference may be the result of different patient samples, as up to 70% of the patients in Yasufuku et al's cohort had benign disease.[14] Gulla et al[17] studied the utility and safety of EBUS-TBNA in children, reporting a moderate diagnostic value. However, this work enrolled only a limited number of patients and had a short follow-up period of 2 years.

In this study we retrospectively analyzed patients with mediastinal masses who underwent EBUS-TBNA at Shanghai Chest Hospital from 2009 to 2014 and had > 5 year follow-up, and evaluated the clinical utility of EBUS-TBNA in the diagnosis of mediastinal masses.

Methods

Patient Selection

This study was performed at the clinical center for thoracic medicine at our hospital. Patients who received care from 2009 to 2014 and met our eligibility criteria (Table 1) were included in this work.

The ethics committee of Shanghai Chest Hospital approved this retrospective study (KS1970). All researchers followed the Helsinki declaration. Informed consent was obtained from all patients before they received EBUS-TBNA, and they were willing to receiving a medical following-up.

EBUS-TBNA

Food and water were forbidden for at least 6 hours before EBUS-TBNA. EBUS-TBNA was performed using an ultrasound system and a linear ultrasonic bronchoscope (BF-UC260F-OL8, Olympus Ltd, Tokyo, Japan). All patients received local anesthesia with lidocaine. EBUS-TBNA was performed by senior doctors in all cases. White light bronchoscopy was performed prior to examination of the target mass and peripheral vessels with EBUS. A 22-gauge needle was used to biopsy the target mass under real-time ultrasound guidance. Two or three aspirations were typically required in order to obtain enough histology specimens. Cytology and histology were performed by two independent pathologists. No onsite cytologic evaluation was performed.[18,19]

Table 1 Inclusion and Exclusion Criteria

Inclusion Criteria
Age >18 years old
Isolated mediastinal mass (all mediastinal stations allowed)
Underwent diagnostic EBUS-TBNA
No mass size limitation
Exclusion Criteria
Co-existent lung lesion

Pathology Evaluation

Cytology and histology specimens were sent to the pathology department at Shanghai Chest Hospital for evaluation. All specimens were examined by two senior pathologists. Hematoxylin and eosin staining were routinely performed. There are many types of mediastinal diseases so immunohistochemistry was commonly required.

Clinical Follow-Up

Clinical follow-up was pursued to understand the final diagnosis of each case. At least 5 years of follow up was performed. Other diagnostic modalities such as surgery, mediastinoscopy, and CT-guided percutaneous transthoracic biopsy were recorded. Lab and imaging data and clinical treatment records were also collected. The final diagnosis was based on the results of the EBUS-TBNA and the clinical follow-up.

Statistical Analysis

If malignant cells were found in the mediastinal mass post-resection and malignant cells were noted in the EBUS-TBNA specimen, this was defined as a true positive result. No false positives are possible due the nature of EBUS-TBNA. However, if the final mass was found to be malignant and no malignant cells were found in the EBUS-TBNA specimen, this was considered a false negative result. If the final diagnosis was benign disease and no malignant cells were found in the EBUS-TBNA specimen, this was defined as a true negative result.

The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic yield were calculated. All analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 46 patients were enrolled in this study, of whom 34 were male and the others were female. Patient age ranged from 18 to 77 years old. All patients successfully underwent EBUS-TBNA examination, defined as EBUS-TBNA obtaining enough of a sample to permit pathologic evaluation. Thirty-seven patients were diagnosed with tumors, 3 were diagnosed with a mediastinal infection,

and 2 had a mediastinal goiter No complications were observed. (Table 2).

The study flow chart is shown in Figure 1. Malignant cells were found in 21 EBUS-TBNA specimens, and 3 additional malignancies were diagnosed following additional invasive examination. The other 25 EBUS-TBNA specimens showed no evidence of malignant cells. Of the 25 patients with negative EBUS-TBNA results, 4 were censored, 3 did not undergo any additional examinations and are still alive, and 1 did not undergo any further examination and died. One patient underwent a supraclavicular lymph node biopsy and was diagnosed with squamous cell carcinoma of the lung. Two patients underwent a transthoracic biopsy and were diagnosed with sarcomatoid carcinoma and a thyroidoma, respectively. Fifteen patients received their final diagnosis based on surgical pathology. Three patients received antibiotics and their masses disappeared on subsequent imaging.

Four patients were censored in this study, so only 42 were included for future analysis. The overall sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic yield of EBUS-TBNA was 63.6%, 100%, 100%, 42.9%, and 71.4%. The diagnostic yield of EBUS-TBNA for different diseases varied. The yield of EBUS-TBNA for common tumors of the chest, such as lung or esophageal cancer, reached 100%. However, the yield fell to 0% for rare diseases such as a reproductive system or mesenchymal tumor (Table 3).

Table 2 Final Diagnosis

Oncologic Disease	
Lung cancer	
Adenocarcinoma	2
Squamous cell carcinoma	1
Small cell lung cancer	3
Not-otherwise specified	1
Esophageal squamous cell cancer	2
Thymoma	3
Thymic carcinoma	3
Hematopoiesis and lymphatic tumor	2
Thyroidoma	2
Seminoma	1
Sarcomatoid carcinoma	1
Liposarcoma	2
Fasciculated sarcoma	2
Adenoid cystic carcinoma	1
Solitary fibrous tum	1
Neurilemmoma	2
Mediastinal malignant tumor	8
Non-Oncologic Disease	
Mediastinal goiter	2
Inflammation	3

Discussion

Mediastinal diseases can originate from different tissues and therefore require different treatments. For example, thymomas are often treated with surgery, lymphoma or reproductive system tumors are always managed with chemotherapy and/or radiotherapy, and metastatic disease often requires systemic treatment.[6–10] A diagnosis is therefore required to appropriately plan treatment. Over the last few years many diagnostic methods for mediastinal masses have been used in clinical practice. One invasive examination is mediastinoscopy, but mediastinoscopy requires general anesthesia and can result in significant trauma. CT-guided percutaneous transthoracic biopsy is less invasive but exposes patients to large doses of radiation.[12,20]

EBUS-TBNA is a recently developed method for diagnosing thoracic disease. It has been widely applied in clinical practice due to its safety and high degree of accuracy. It has a lower complication rate.[21,22] EBUS-TBNA has a high sensitivity and nearly 100% specificity. It was therefore recommended by the NCCN for the diagnosis and staging of lung cancer.[4] As mediastinal disease is rare, up until now few studies have focused on the diagnostic value of EBUS-TBNA for mediastinal masses.[13,14,23] As a large center for thoracic disease we track mediastinal disease for future analysis.[24] EBUS-TBNA has been routinely performed at our center for nearly 10 years. Sun et al[25] reported that the diagnostic yield of EBUS-TBNA in lung cancer approaches 90%. The work by Yang et al[18] performed at our institution reported that EBUS-TBNA in the diagnosis of non-lymph node thoracic lesions was 95.1% accurate. With respect to benign disease, our group has reported diagnostic yields of 90% and 94.17%, in the diagnosis of intrathoracic tuberculosis and pulmonary sarcoidosis with EBUS-TBNA, respectively.[26,27] However, the clinical value of EBUS-TBNA in the diagnosis of mediastinal masses has rarely been reported.

The present work evaluated the clinical value in the diagnosis of mediastinal masses. The overall sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic yield was 63.6%, 100%, 100%, 42.9%, and 71.4%, respectively. The specificity and positive predictive value of EBUS-TBNA was 100%, as there

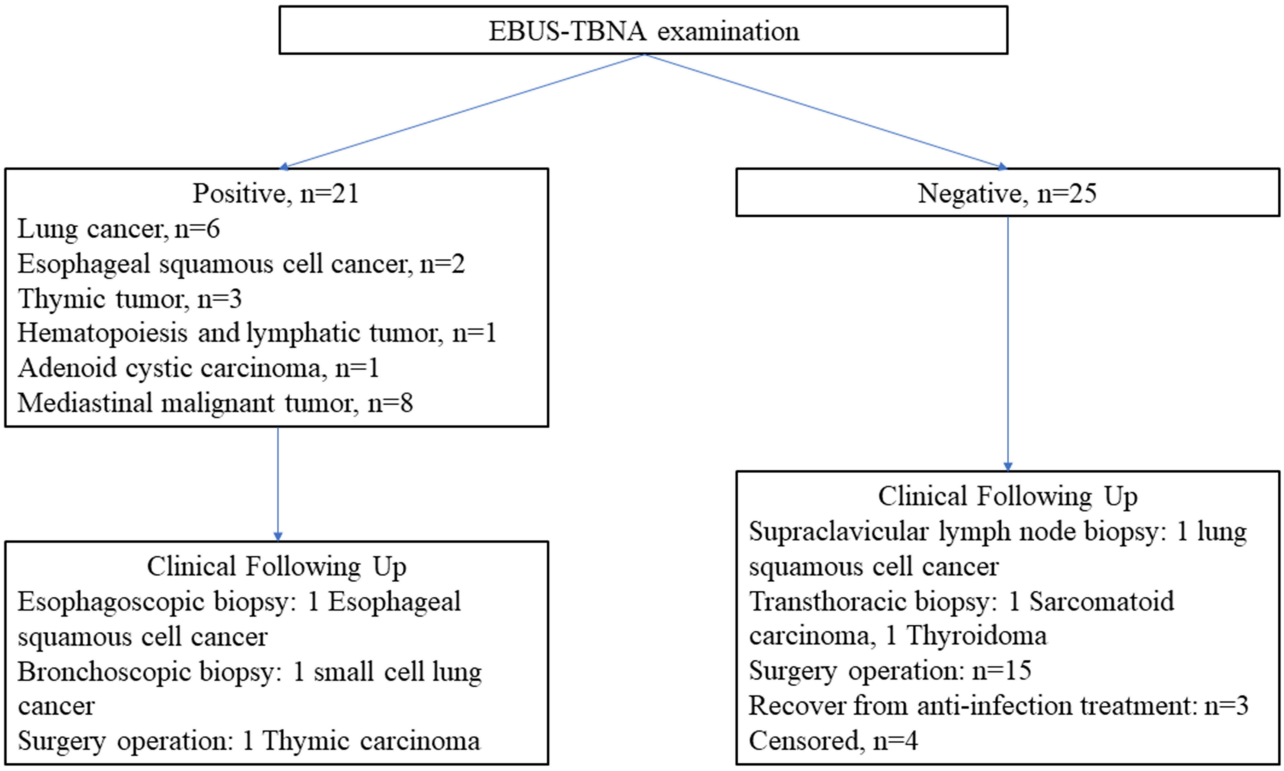

Figure 1 The flow chart of study.

were no false positive cases. The sensitivity and diagnostic yield was moderate.

The sensitivity, negative predictive value and diagnostic yield calculated in the present work are lower than those reported by other studies. To explore the reasons for this discrepancy we future divided mediastinal diseases into several groups (Table 4). With our revised classification the diagnostic value of EBUS-TBNA for esophageal tumors was 100%, but was 0% for thyroid, reproductive system, and mesenchymal tissue tumors. EBUS-TBNA had a moderate diagnostic value for thymic tumors and hematologic and lymphatic tumors. Lung, esophageal and thymic tumors are the most common diseases managed at our institution's department of thoracic surgery. We have therefore seen the highest diagnostic value of EBUS for those diseases.[28,29] One reason for this may be because lung, esophageal and thymic tumors originate from epithelial cells and are familiar to the pathologist. EBUS-TBNA yields "a long tissue core" due to acquisition of tissue with a needle. Compared with different forms of transthoracic biopsy, less lesion tissue is obtained with EBUS-TBNA. Further, less necrosis is found in lung, esophageal and thymic tumors compared with sarcoma. In our study, 2 patients were diagnosed with a hematologic and lymphatic tumor. Interestingly, one of these patients was initially diagnosed with Castleman's disease by EBUS-TBNA and

Table 3 Diagnostic Accuracy of EBUS-TBNA for Mediastinal Masses

		Final Diagnosis	
		Malignant	**Benign**
EBUS-TBNA	Malignant	21	0
	Benign	12	9

Notes: Sensitivity=63.6%. Specificity=100%. PPV=100%. NPV=42.9%. Diagnostic Yield=71.4%

Table 4 Diagnostic Yield of EBUS-TBNA for Different Diseases

Disease	**Number**	**Diagnosed by EBUS-TBNA**	**Diagnostic Yield**
Pulmonary tumor	8	8	100%
Esophageal tumor	2	2	100%
Thymic tumor	6	3	50%
Hematologic and lymphatic tumor	2	1	50%
Thyroid tumor	2	0	0
Reproductive system tumor	1	0	0
Mesenchymal tissue tumor	8	0	0

other imaging examinations. However, Reed-Sternberg cells were found in his surgery specimen, so his final diagnosis was Hodgkin's lymphoma.[30] The poor accuracy of EBUS-TBNA in the diagnosis of lymphoma has been previously reported.[31,32] In the case of seminoma, only crushed small round cells are found in the background of blood clots in the EBUS-TBNA specimen. This is consistent with the pathologic features of seminoma, which always include necrosis.[33] Of the 8 mesenchymal tumors biopsied in this work, a large amount of necrosis and blood clots was found in 6, while the other 2 specimens had bronchial mucosa epithelium, cartilage fragments and some fibrous tissue. Seven of these patients were diagnosed based on their surgical pathology, while the other was diagnosed with a transthoracic biopsy.[34,35]

Owing to the tertiary referral nature of our center, only 5 of the patients in our study were ultimately diagnosed with a non-tumor disease (88.1% malignant disease). In contrast with other studies, pulmonary, esophageal and thymic tumors were only a small part of the diseases diagnosed in this study (38%, 16/42). As this is a retrospective single center study, some bias is inevitable.

In conclusion, EBUS-TBNA is a safe and effective means for diagnosing common mediastinal masses.

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Disclosure

The authors report no conflicts of interest in this work.

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