Original Article

Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of non-lymph node thoracic lesions

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Abstract:

AIMS: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has shown excellent diagnostic capabilities for mediastinal and hilar lymphadenopathy. However, its value in thoracic non-lymph node lesions is less clear. This study was designed to assess the value of EBUS-TBNA in distinguishing malignant from benign thoracic non-lymph node lesions.

METHODS: From October 2009 to August 2011, 552 patients underwent EBUS-TBNA under local anesthesia and with conscious sedation. We retrospectively reviewed 81 of these patients who had tracheobronchial wall-adjacent intrapulmonary or isolated mediastinal non-lymph node lesions. On-site cytological evaluation was not used. Immunohistochemistry (IHC) was performed to distinguish the origin or type of malignancy when necessary.

RESULTS: EBUS-TBNA was performed in 68 tracheobronchial wall-adjacent intrapulmonary and 13 isolated mediastinal non-lymph node lesions. Of the 81 patients, 77 (95.1%, 60 malignancies and 17 benignancies) were diagnosed through EBUS-TBNA, including 57 primary lung cancers, 2 mediastinal tumors, 1 pulmonary metastatic adenocarcinoma, 7 inflammation, 5 tuberculosis, 3 mediastinal cysts, 1 esophageal schwannoma, and 1 focal fibrosis. There were four false-negative cases (4.9%). Of the 60 malignancies, there were 9 (15.0%) which originally had no definite histologic origin or type. Thus, IHC was performed, with 7 (77.8%) being subsequently confirmed. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EBUS-TBNA in distinguishing malignant from benign lesions were 93.4% (60/64), 100% (17/17), 100% (60/60), 81.0% (17/21), and 95.1% (77/81), respectively.

CONCLUSION: EBUS-TBNA is a safe procedure with a high sensitivity for distinguishing malignant from benign thoracic non-lymph node lesions within the reach of EBUS-TBNA, with IHC usually providing a more definitive diagnosis.

Key words:

Endobronchial ultrasound, immunohistochemistry, lung cancer, thoracic lesion, transbronchial needle aspiration

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Convex probe endobronchial ultrasound (CP-EBUS), with the ability to perform real-time EBUS-guided transbronchial needle aspiration (EBUS-TBNA), has increased the diagnostic possibilities for mediastinal and hilar lymphadenopathy, including lymph nodes metastasis of lung cancer, sarcoidosis, tuberculous lymphadenopathy, and lymphoma.[1-8] However, there are few studies on usefulness of EBUS-TBNA in the diagnosis of thoracic non-lymph node lesions.[9-11] Studies have shown that immunohistochemistry (IHC) can further refine the diagnoses of malignancies, even with small biopsies or cytology specimens lacking definite classification, especially for the non-small cell lung cancer (NSCLC)-not otherwise specified (NOS) type.[11-13]

In order to evaluate the efficiency of EBUS-TBNA in distinguishing malignant from benign thoracic non-lymph node lesions and to better define the diagnoses of malignant and benign diseases, data from 81 patients were retrospectively analyzed.

Methods

Patients

We retrospectively reviewed the records of 552 patients who underwent EBUS-TBNA in the Pulmonary Department, Shanghai Chest Hospital, from October 2009 to August 2011. Eighty-one patients were included according to the following guidelines: (i) presence of tracheobronchial wall-adjacent intrapulmonary or isolated mediastinal non-lymph node lesions within the reach of EBUS-TBNA based on computerized tomography (CT); (ii) informed consent signed for an EBUS-TBNA examination; and (iii) no contraindication to the procedure. The protocol was approved by the Ethics Committee of Shanghai Chest Hospital. Five lung cancer cases have been previously reported.[14]

Endobronchial ultrasound-guided transbronchial needle aspiration procedures

The same bronchoscopist (SJ) performed all EBUS-TBNA procedures upon completion of the first 30 procedures, comprising the learning curve training.[15] EBUS-TBNA was performed as we described previously.[14,15] Patients abstained from solid food and liquids for at least 4 h before the procedure. After achieving vascular access for intravenous infusions, local anesthesia was achieved with 2 ml 2% lidocaine solution, orally, plus 3-5 sprays of 7% lidocaine solution to the pharynx. Conscious sedation was administered with intramuscular pethidine (25-50 mg) and intravenous midazolam (1-5 mg) injection before the procedure.

After oral bronchoscopy, target lesions and peripheral vessels were examined by EBUS, using a linear array ultrasonic bronchoscope (BF-UC 260F-OL8; Olympus Ltd, Tokyo, Japan). Scanning was performed at a frequency of 7.5 MHz and images were processed by an Olympus ultrasound processor (EU-C2000; Olympus Ltd). Target lesion diameter was measured and recorded under frozen ultrasound image. A dedicated 22-gauge needle was used for aspiration (NA-201SX-4022; Olympus Ltd). Three needle aspirations were performed for each target mass. However, if an obvious histology specimen was obtained, two aspirations were acceptable. On-site cytological evaluation was not performed. Cytological smears were stained with hematoxylin and eosin by two cytopathologists blinded to subject details. Aspirated histologic material was formalin-fixed and paraffin-embedded before being examined by another two pathologists under light microscopy. Microbiological tests were performed as deemed appropriate.

Data collection and outcome

Data collected included target location and diameter, aspiration times/lesion and complications. Pathologic diagnoses by EBUS-TBNA and the final diagnoses were also reviewed. Isolated mediastinal lesions revealed by CT and eventually diagnosed pathologically as lung cancer by EBUS-TBNA were categorized as primary lung cancers rather than primary mediastinal tumors.

To evaluate the reasons for selecting EBUS-TBNA, white light bronchoscopic findings were divided into four categories: (i) no endobronchial lesions; (ii) extrinsic compression without mucosal change; (iii) submucosal lesions (erythema, edema, mucosal thickening, bronchial narrowing, disappearance of mucosal signs, and/or marked vascular structures) without definite mucosal tumor invasion; and (iv) definite mucosal tumor invasion.[16,17]

EBUS-TBNA specimens were classified as "positive" if malignant cells were found and "negative" if none was found. Negative results were further categorized as definitely benign or no specific pathology. Specimens were categorized as positive if there were unambiguous tumor cells, even if the histologic subtype was unclear.

EBUS-TBNA diagnosis was subsequently confirmed by results of another pathological examination involving thoracotomy, mediastinoscopy, thoracoscopy, or CT-guided transthoracic needle aspiration (CT-TTNA), or by clinical follow-up.

Statistical analysis

Pathology of the EBUS-TBNA specimens providing a definite diagnosis of lung cancer or other malignancies was judged to be true positive. Pathology providing evidence of malignancies not confirmed by further tests was judged to be false positive. Pathology providing no lung cancer or other malignancies, and being confirmed benignancy by other pathologic results or clinical follow-up was judged to be true negative. Finally, pathology providing no evidence for malignancy but found to show malignancy by further tests was defined as false negative.

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated according to the standard definitions of the diagnosis of lung cancer and malignancy by using the software package SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics, target lesions, bronchoscopic findings, and Endobronchial ultrasound-guided transbronchial needle aspiration procedures

Of the 81 patients, 52 were males and 29 females, with a mean age of 56.6 (28–80) years. Sixty-eight patients with tracheobronchial wall-adjacent intrapulmonary non-lymph node lesions and 13 with isolated mediastinal non-lymph node lesions were evaluated [Figure 1]. White light bronchoscopic findings, locations, diameters of target lesions, and average aspiration times per target lesion are shown in Table 1. Six (7.4%) cases had definite, visible neoplasms, but EBUS-TBNA was performed due to expected low diagnostic yield or bleeding complication; five had necrotic tumors, of which two also had prior negative endobronchial biopsies; and one had active bleeding tumor.

Endobronchial ultrasound-guided transbronchial needle aspiration results

Among the 81 subjects, 64 malignancies (60 primary lung cancer, 1 primary mediastinal seminoma, 1 thymoma, 1 pulmonary metastatic adenocarcinoma, and 1 pulmonary nodular sclerosis Hodgkin lymphoma) and 17 benign diseases (7 inflammation, 5 tuberculosis, 3 mediastinal cyst, 1 fibrosis, and 1 esophageal schwannoma) were eventually diagnosed. Of the 64 malignant tumors, 60 cases were diagnosed by EBUS-TBNA and IHC was performed in 9 (15.0%) cases which originally had an uncertain origin, and 7 (77.8%) malignant tumors (3 primary SCLC, 2 primary pulmonary adenocarcinoma, 1 pulmonary metastatic adenocarcinoma, and 1 seminoma) were further confirmed. Representative cases diagnosed as lung cancer, inflammation, and tuberculosis are shown in Figure 2. EBUS-TBNA specimens showed malignancies in 60 (74.1%) cases, specific benign disease in 11 (13.6%) cases, and non-specific benign evidence in 6 (7.4%) cases. Regarding the 60 malignancies, in 3 (5.0%) the diagnosis was made by cytology, in 6 (10.0%) by histology, and in 51 (85.0%) by both cytology and histology [Table 2]. There were 55 of 75 (73.3%) cases where bronchoscopy showed no definite endobronchial neoplasms lesions, which were diagnosed as malignancy by EBUS-TBNA. Diagnoses of 14 cases were subsequently confirmed by thoracotomy, 3 by CT-TTNA, 2 by mediastinoscopy, and 2 by thoracoscopy.

Of the 60 primary lung cancers, 57 (including 6 mediastinal lesions diagnosed as lung cancer) were thus diagnosed through EBUS-TBNA (representative cases shown in Figure 2a-c). Initially, seven cases were diagnosed only as poorly differentiated carcinoma. However, IHC demonstrated that two cases had a positive thyroid transcription factor-1 (TTF-1) and cytokeratin 7 (CK 7) and negative P63, thus making the diagnosis as adenocarcinoma. Two cases remained NSCLC-NOS following IHC and three had inadequate tissue to perform IHC. Three SCLC were distinguished from mediastinal tumors by IHC (representative cases shown in Figure 3). One poorly differentiated carcinoma and two sarcomatoid carcinomas which were undiagnosed by EBUS-TBNA were considered false negative, being finally diagnosed by EBUS-TBNA pathology of lymph node, thoracoscopy, and thoracotomy, respectively. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EBUS-TBNA in the diagnosis of lung cancer were 95.0%, 100%, 100%, 87.5%, and 96.3%, respectively [Table 3].

Table 1: Patient characteristics, target lesions, bronchoscopic findings, and EBUS-TBNA procedures

Characteristic	Data
Number of patients (*n*)	81
Average age, years (range)	56.6 (28-80)
Gender, *n* (%)	
Male	52 (64.2)
Female	29 (35.8)
Location of the mass, *n* (%)	
Right upper lobe	37 (45.7)
Right middle lobe	3 (3.7)
Right lower lobe	14 (17.3)
Left upper lobe	7 (8.6)
Left lower lobe	6 (7.4)
Paratrachea	1 (1.2)
Mediastinum	13 (16.1)
White light bronchoscopic findings, *n (%)*	
No endobronchial lesions	19 (23.5)
Extrinsic compression	18 (22.2)
Submucosal lesions	38 (46.9)
Definite neoplasm	6 (7.4)
Size by EBUS (range), mm	
Long axis	25.8 (12.6-38.8)
Short axis	19.2 (8.0-26.4)
Aspiration times per lesion (range), time	3.6 (1-8)

EBUS = Endobronchial ultrasound; EBUS-TBNA = Guided transbronchial needle aspiration

Both 2 primary mediastinal tumors were proven to be malignant by EBUS-TBNA–obtained pathology. However, only one had a specific tumor type identified. That tumor was CD117+ and expressed placental alkaline phosphatase, thus diagnosed as seminoma, and further confirmed by mediastinoscopy. The other case had a definitive diagnosis of one thymoma made by the presence of clustered epithelioid cells with cellular atypia, combined with clinical observations.

One case with a thyroid carcinoma history was diagnosed as pulmonary metastatic adenocarcinoma, with specimens showing adenocarcinoma and IHC confirming the thyroid origin [Figure 3].

One right upper lobe lung lesion (41.7 × 33.7 mm in diameter by CT), EBUS-TBNA-negative, being further confirmed as nodular sclerosis Hodgkin lymphoma (NSHL) by thoracotomy subsequently, was classified as false negative.

All 17 benign diseases (7 inflammation, 5 tuberculosis, 3 mediastinal cysts, 1 fibrosis, and 1 esophageal schwannoma) were diagnosed by EBUS-TBNA specimens showing no malignant cells, of which 11 had a specific pathologic evidence. Of the seven inflammation cases, an inflammatory exudate, necrosis, or fibrous tissue were found in five, with four cases having a negative microbiological examination. In two of these seven cases, no specific diagnosis could be made, the final diagnosis of inflammation being made clinically. All seven inflammation patients received anti-inflammatory therapy, with the final diagnosis being confirmed by clinical

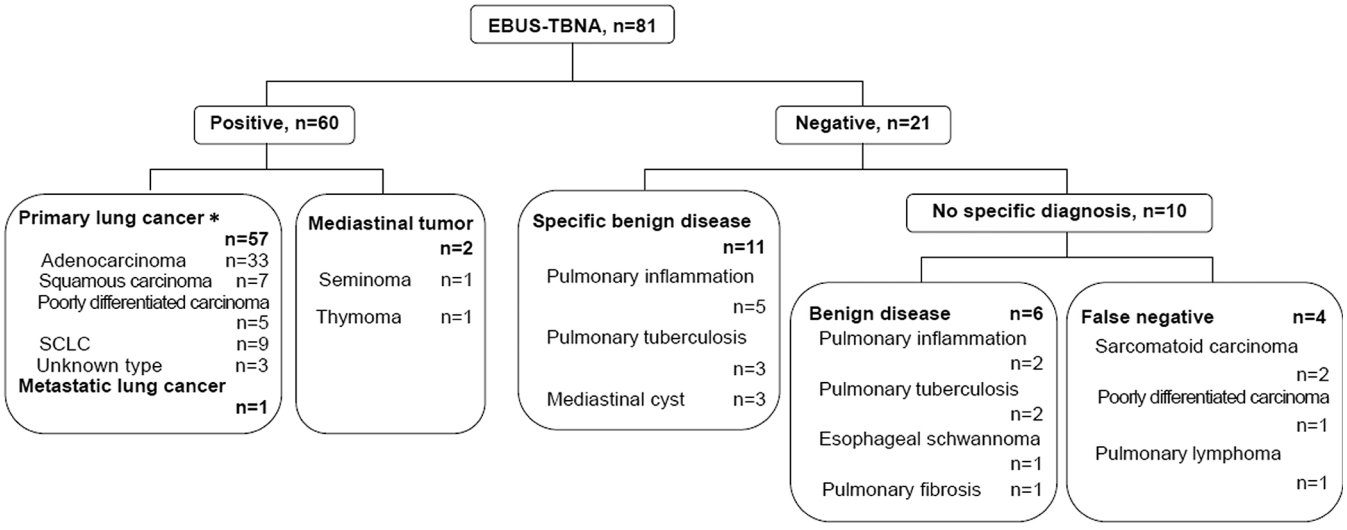

Figure 1: Clinical courses and final diagnoses of patients. *57 lung cancers, including 6 isolated mediastinal lesions diagnosed as lung cancer. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; NSCLC-NOS = non-small cell lung cancer-not otherwise specified

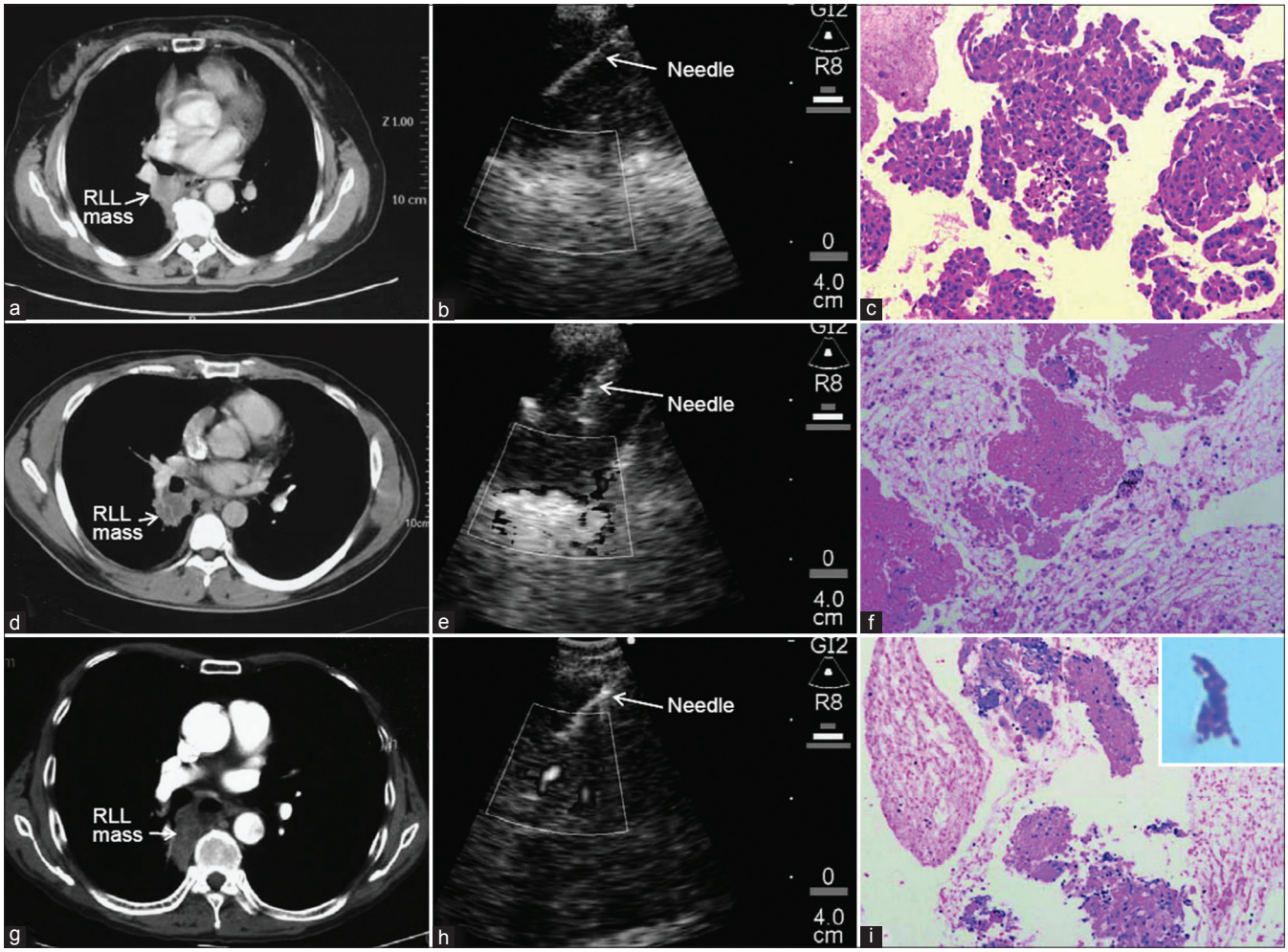

Figure 2: Representative cases of EBUS-TBNA in distinguishing malignant from benign lesions. Chest CT demonstrates RLL masses diagnosed as lung adenocarcinoma (a), inflammation (d), tuberculosis (g). EBUS images of targets (b, e, h, respectively). TBNA tissue specimen revealed lung adenocarcinoma (c, ×20). Necrosis with inflammatory exudation (f, ×20) found in TBNA tissue. epithelioid granuloma with caseous necrosis (i, ×20) together with positive acid-fast staining found in TBNA tissue. RLL, right lower lobe

Table 2: Results of real-time EBUS-TBNA in 60 patients with malignant thoracic non-lymph node lesion by location

	Malignant masses (*n*)	Cytology positive (*n*)	Histologypositive (*n*)	Cytology and histology positive (*n*)	Total positive (*n*)	Lesions diagnosed (%)
RUL	30	24	26	22	28	93.3
RML	3	3	2	2	3	100
RLL	10	9	9	9	9	90
LUL	7	6	7	6	7	100
LLL	5	5	5	5	5	100
Mediastinum	9	7	8	7	8	88.9
Total	64	54	57	51	60	93.8

RUL = Right upper lobe; RML = Right middle lobe; RLL = Right lower lobe; LUL = Left upper lobe; LLL = Left lower lobe; EBUS-TBNA = Endobronchial ultrasound-guided transbronchial needle aspiration

Table 3: Diagnostic value of EBUS-TBNA in lung cancer or malignancy diagnoses

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Lung cancer	95.0 (57/60)	100 (21/21)	100 (57/57)	87.5 (21/24)	96.3 (78/81)
Malignancy	93.4 (60/64)	100 (17/17)	100 (60/60)	81 (17/21)	95.1 (77/81)

EBUS-TBNA = Endobronchial ultrasound-guided transbronchial needle aspiration; PPV = Positive predictive value; NPV = Negative predictive value

improvement. A representative case diagnosed as inflammation is shown in Figure 2d-f.

Of the five tuberculosis cases, epithelioid granulomas and/or caseous necrosis were found in three, two of which had positive mycobacterium cultures. Of the two other cases with no pathologic or microbiologic evidence of tuberculosis, one subsequently had pathologic evidence of tuberculosis through CT-TTNA, while the other was diagnosed by positive acid-fast staining of sputum smear. All five received anti-tuberculosis therapy, with follow-up showing that these patients responded well. A representative case diagnosed as tuberculosis is shown in Figure 2g-i.

Of the three mediastinal cyst cases, cystic fluid was aspirated during EBUS-TBNA, with cytology showing only histiocytes. All three were subsequently confirmed at thoracotomy.

There was one case with pulmonary fibrosis and one of an esophageal schwannoma, felt to be benign disease by negative TBNA and clinical manifestations, with both cases being confirmed by thoracotomy.

Overall, 77 of 81 (95.1%) were diagnosed by EBUS-TBNA, with four false-negative (4.9%) and no false-positive cases [Table 3]. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EBUS-TBNA in distinguishing malignant and benign lesions were 93.4%, 100%, 100%, 81.0%, and 95.1%, respectively [Table 3].

Complications

With conscious sedation, all subjects tolerated the procedure well, except for insufficient examination caused by coughing in two cases and transient lower oxygen saturation in two cases.

No major complication, such as pneumothorax, mediastinal emphysema, or bleeding from ruptured major mediastinal vessels, was observed. However, there was moderate puncture site bleeding during needle aspiration noted in one hypercoagulable subject (fibrinogen 4.9 g/L, normal range is 2-4 g/L) diagnosed as lung adenocarcinoma by EBUS-TBNA. That patient had central airway obstruction caused by clots, resulting in oxygen saturation dropping dramatically. The clots were cleared after common bronchoscope-guided tracheal intubation, with vital signs quickly returning to normal.

Discussion

Radiologically suspicious chest lesions may represent malignancy, warranting further workup. Conventional bronchoscopy and/or TBNA and CT-TTNA are commonly the first choice. However, these methods are not widely practiced, often because of a perceived low diagnostic yield or risk of pneumothorax or hemoptysis.[18-21] More invasive tools such as surgical mediastinoscopy or thoracoscopy may pose significant risk, as well as cost, to the patient, requiring general anesthesia and operating room use.[22]

In our study, of 75 of 81 EBUS-TBNA cases (92.6%) in which the bronchoscopy showed no definite endobronchial neoplasms, EBUS-TBNA was able to diagnose malignancy in 55 of the 75 (73.3%) and in 55 of the total 81 cases (67.9%). Similar to other studies,[9,10] we found EBUS-TBNA to be safe and having

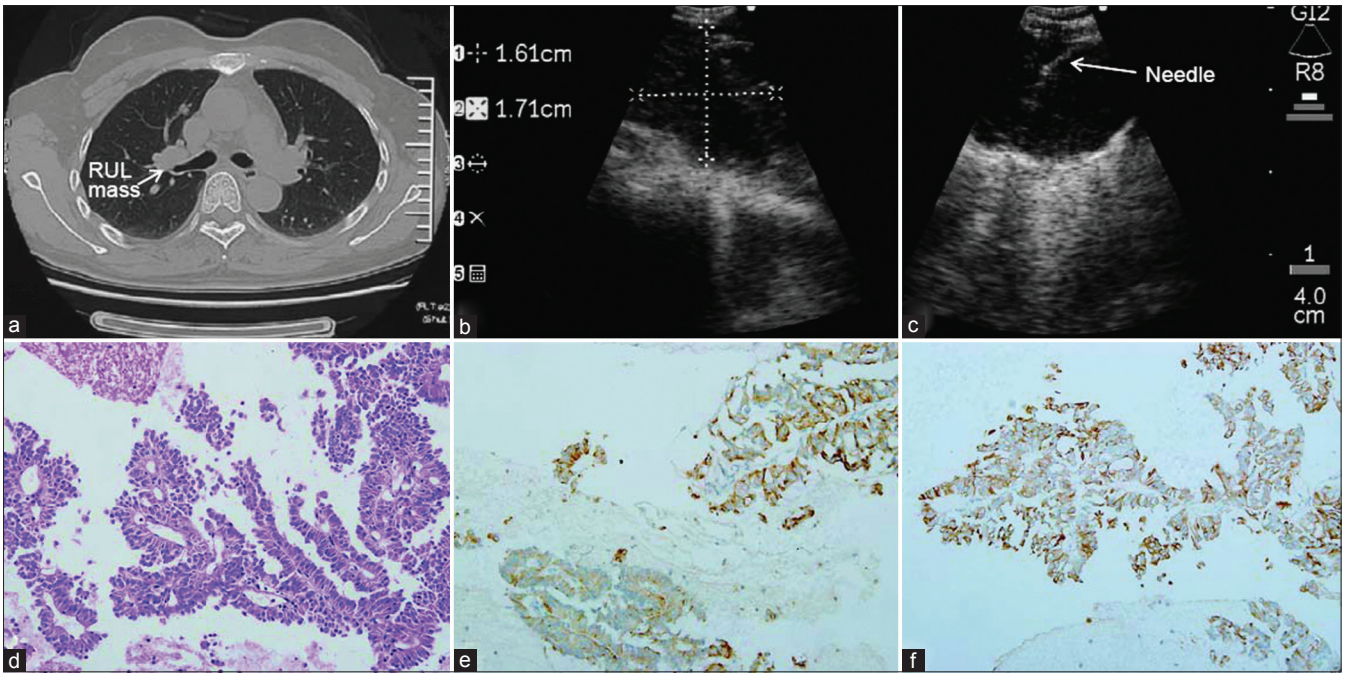

Figure 3: Representative case of EBUS-TBNA in diagnosis of metastatic lung cancer. 54-year-old female presented with RUL mass (a) and a history of thyroid cancer ten years previously. EBUS images of measurement (b) and real-time aspiration with needle within target lesion (c). Metastatic lung adenocarcinoma from thyroid carcinoma was diagnosed by H and E (d, ×20) and IHC demonstrating positive Cytokeratin 7 (e, ×20) and Thyroglobulin (f, ×20), and negative Villin, Napsin A, Cytokeratin 20, Signal-induced- proliferation-associated protein (figures not shown). RUL, right upper lobe

a high diagnostic sensitivity (93.4%) and accuracy (95.1%) for distinguishing malignant from benign thoracic non-lymph node lesions.

IHC plays an important role in the classification of NSCLC-NOS and mediastinal malignant tumors.[11-13,23] In our study, IHC was performed in nine malignancies lacking definitive diagnoses, with three primary SCLC, two primary pulmonary adenocarcinoma, one pulmonary metastasis of thyroid adenocarcinoma, and one primary mediastinal seminoma being further clarified. For small biopsies and cytology, we recommend a minimal panel of IHC stains to diagnose NSCLC, both adenocarcinoma and squamous cell carcinoma, because methods using large panels of IHC stains may not provide an advantage over routine light microscopy with a limited IHC investigation.[24]

There were 4 (4.9%) false-negative cases in this study. The first case, in whose TBNA specimen only inflammatory exudate with anthracotic pigment was found, was eventually diagnosed by finding poorly differentiated lung cancer cells in lymph nodes obtained by EBUS-TBNA during the same procedure. Tissue obtained from an obstructed inflammation area may be the reason. The second case was identified as NSHL only by thoracotomy. The NSHL being undiagnosed by EBUS-TBNA was probably due to this type of Hodgkin disease usually contains large amounts of fibrous tissue. For lymphomas, EBUS-TBNA, with flow cytometry and IHC analysis, is safe, minimally invasive, and highly accurate, thus decreasing the need for more invasive procedures such as mediastinoscopy.[8,25,26] Further distinguishing the subtype of lymphoma will provide evidence for specific management. Thus, sufficient tissue is needed. The diagnostic sensitivity for full evaluation of lymphoma is lower than that for lung cancer, largely because of the difficulties of confirming the lymphoma subtype from a small specimen. EBUS-TBNA may still be considered as the initial investigative technique of suspected lymphoma as it may avoid a more invasive surgical biopsy.[26] The third case was confirmed as mediastinal sarcomatoid carcinoma through thoracoscopy, with only hyaline degeneration and fibrosis being found by EBUS-TBNA. The fourth case was diagnosed as a pulmonary sarcomatoid carcinoma by thoracotomy. With EBUS-TBNA, ultrasound showed that the mass was covered by a fluid-filled cyst, and 15 ml of coffee-like fluid was aspirated. However, the needle was not deep enough into the mass due to the mass not being adjacent to the trachea. Thus, the sample was inadequate. The diagnosis of sarcomatoid carcinoma usually relies on hematoxylin–eosin-stained sections, with IHC characterization often being used to better highlight the different cell components.[27] In our study, neither pulmonary nor mediastinal sarcomatoid carcinomas were diagnosed by EBUS-TBNA, mainly because of inadequate samples.

So, how to improve the negative predictive value is a problem needing further study. Generally, intrapulmonary lesions farther from the trachea or bronchus, rich with accompanying vessels compared to lymph nodes, and moving with respiration add to the difficulty of successfully diagnosing with EBUS-TBNA. The operator should obtain as much tissue as safely possible, for pathology, IHC, and perhaps genetic analysis. In addition, on-site cytology may be of value during EBUS-TBNA, possibly reducing the frequency and duration of punctures, as well as judging specimen quality. However, there are meta-analyses showing no difference in the diagnosis of lung cancer with or without on-site cytology.[5,28]

Regarding benign diseases, various microbiologic tests should be performed, depending on the clinical situation and on-site cytology judgment. For patients with inflammation, it is more important to rule out tuberculosis by TBNA than bacterial culture because of antibiotic therapy prior to EBUS, needle contamination by oropharyngeal bacteria, and low rate of positive bacteria cultures.[29] Our study suggests that abnormalities such as inflammatory exudates or non-caseating necrosis are the signs of acute inflammation or acute exacerbation of chronic inflammation, while fibrous tissue and/or inflammatory granulomas suggest chronic inflammation.

Tissue biopsy is, of course, the most important diagnostic tool in diagnosing granulomatous disease.[30] It has been shown that EBUS biopsy is minimally invasive and has a high diagnostic yield in diagnosing tuberculous intrathoracic lymphadenopathy.[7] Similar to the diagnosis of intrathoracic lymph node tuberculosis, diagnostic criteria for pulmonary tuberculosis should include positive acid-fast staining or mycobacterium culture of aspiration specimens, or evidence of epithelioid granulomatous reaction and/or caseous necrosis, together with clinical characteristics.

Although most mediastinal cysts are asymptomatic, some may cause symptoms, infection, or even malignant degeneration,[31] so many clinicians emphasize the importance of early diagnosis, in which case surgical methods may have risks.[31,32] However, an EBUS-TBNA can lead to the cyst being drained safely with endobronchial ultrasound technology, obtaining a better understanding of the mediastinal structure.[33] We were able to drain three mediastinal cysts during EBUS-TBNA, thus providing symptomatic relief.

Major complications related to EBUS-TBNA are rare. To date, complications such as blood at the site of puncture, cough, agitation, hypoxemia, pneumothorax, infection, airway laceration, intramural hematoma of the pulmonary artery, and hemopneumomediastinum have been reported.[4,5,34-37] In our study, complications of EBUS-TBNA were mainly coughing and hypoxemia. These complications were not EBUS-TBNA-specific and might happen during ordinary bronchoscopy, while airway blockage from blood clots resulting from a hypercoagulable state is rare but potentially serious.

Our data suggest that for thoracic non-lymph node lesions found by CT, EBUS-TBNA can be a useful diagnostic method in distinguishing usually specific malignant from benign conditions, as long as lesions are within puncture range of the endobronchoscope. This is a minimally invasive, effective, and rapid real-time procedure that can be safely performed under moderate sedation in the outpatient setting.

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