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Original Article

Effect of EBUS-TBNA on diagnosis of recurrence in post-surgery patients with lung cancer

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Abstract: The endobronchial ultrasound guided tranbronchial needle aspiration (EBUS-TBNA) is commonly used in the diagnosis and staging of lymphatic metastasis of lung cancer. However, its reliability on the diagnosis of recurrence is still unclear. This study was aimed to evaluate the effect of EBUS-TBNA on the diagnosis of recurrence in post-surgery patients with lung cancer. 40 post surgery patients with lung cancer who were suspected of recurrence, and received EBUS-TBNA from Jun. 1, 2014 to Jul. 31, 2015 in Shanghai Chest Hospital were included in the retrospective study. EBUS-TBNA negative patients were further examined by means of mediastinoscopy or CT/PET-CT after 6 months follow up. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated according to standard definitions. Among 40 patients, there were, by EBUS-TBNA diagnosis, 32 recurrence cases (80%) and 8 non-recurrence cases (8%). While after mediastinoscopy examination or CT/PET-CT examination after 6 months follow-up, out of the 8 cases, there were 2 recurrence cases and 6 non-recurrence cases. For EBUS-TBNA diagnosis on recurrence, the sensitivity was 94.1%, the specificity was 100%, the positive predictive value was 100%, the negative predictive value was 75% and the accuracy rate was 95%. No serious complications related to the procedures were observed. EBUS-TBNA could be considered as a feasible, safe and promising procedure to diagnose recurrence in post-surgery patients with lung cancer.

Keywords: EBUS-TBNA, mediastinum, lung cancer, recurrence, surgery

Introduction

As the most commonly diagnosed cancer and the leading cause of cancer-related death, lung cancer leads to the great cancer burden worldwide [1]. Lung cancer patients in early stage could be treated by surgical procedure, but part of post-surgery patients may have lumps and/or enlargement of mediastinum and hilar lymph nodes, and the determination of their characteristics is of vital importance for the treatment of the disease. At present, there are many diagnostic methods for mediastinal lesions, including CT, PET-CT, thoracoscopy and mediastinoscopy, etc. Among them, the mediastinoscopy is recognized as the golden standard [2]. However, there are many limitations of mediastinoscopy examination, such as the high demand on surgical techniques, causing surgical trauma and difficulty in re-examination, etc. Especially, it's much more difficult in second examination than the first procedure of mediastinoscopy, and the lesions between lobes as well as in hilar lymph nodes and inner lung around the bronchus are always unreachable [3, 4].

The endobronchial ultrasound guided tranbronchial needle aspiration (EBUS-TBNA), Since its application in clinical practice, has been widely recognized and recommended for its high accuracy, high repeatability, simple operation and less resultant trauma [5, 6]. EBUS-TBNA has presented excellent diagnostic performance, and it is able to reach the mediastinum and inter-lobe lymph nodes that are unreachable by mediastinoscopy [7, 8]. However, the effect of EBUS-TBNA on diagnosis of recurrence in lung cancer patients was unclear. This study was aimed to investigate the application value of EBUS-TBNA in the diagnosis of recurrence in post-surgery patients with lung cancer.

Table 1. Demographic, clinical and pathological characteristics of post-surgery patients with lung cancer

Clinical characteristics	Median or percentage (%)
Sex	
Male	30 (75)
Female	10 (25)
Age	58.5 (37-78)
Pathological characteristics of primary tumor tissues	
Adenocarcinoma	22 (55)
Squamous carcinoma	12 (30)
Poorly differentiated carcinoma	1 (2.5)
Small cell carcinoma	3 (7.5)
Adenosquamous carcinoma	1 (2.5)
Lymphoepithelioma like carcinoma	1 (2.5)
Pathological staging by preliminary prognosis	
Ia	11 (27.5)
Ib	8 (20)
IIa	7 (17.5)
IIb	2 (5)
IIIa	12 (30)
Treatment following preliminary diagnosis	
Surgical excision	40 (100)
Surgery following radiochemotherapy	3 (7.5)
Radiochemotherapy following surgery	27 (67.5)
Surgical method	
Wedge-shaped excision	2 (5)
Lobe excision	38 (95)
Mediastinal lymph node dissection	32 (80)
Preliminary diagnosis by mediastinoscopy	5 (12.5)
Preliminary diagnosis by EBUS-TBNA	2 (5)

Data were presented as median and 25^{th}-75^{th} or count and percentage.

Methods

Participants

40 post surgery patients with lung cancer who were suspected of recurrence, and received EBUS-TBNA from Jun. 1, 2014 to Jul. 31, 2015 in Shanghai Chest Hospital were included in the retrospective study. Inclusion criteria: History of lung cancer surgery, agreed with regularly follow-up visits, enlargement of mediastinum and hilar lymph nodes (≥1 cm) and/or have inner lung lumps around the trachea or the bronchus were found by CT, received EBUS-TBNA examination, while patients with related surgical contraindications were excluded. This Study was approved by the Ethics Committee of Shanghai Chest Hospital, and all the participants signed the written consent.

EBUS-TBNA procedure

Before the procedure, the patient had fasting and did not drink water for at least 6 hours. Before the procedure, venous access was established, pethidine (25-50 mg, i.m.), midazolam (2-5 mg, i.v.), 2% lidocaine (intra-oral drip) were given, and 7% Lidocaine spray (pharyngolaryneal spray for 3-5 times) was added. Normal bronchoscopy examination was performed via oral route, and then the ultrasonic bronchoscope UC260F carrying electronic convex array scanning (Japanese Olympus Company) was used to examine the target lymph nodes and surrounding vessels according to international lymph node grouping standard. A water bag was placed on top of ultrasonic device (scanning frequency of 7.5 MHz), and the ultrasonic imaging was collected and processed by EU-C60 ultrasonic imaging processing device (Japanese Olympus company). The ultrasonic imaging was frozen to record the diameter of target lymph node, and a No. 22 puncture aspiration needle (NA-201SX-4022, Japanese Olympus company) was used for puncture aspiration guided by the real-time ultrasonic device, and after the needle was confirmed to have entered the target area, and needle was moved forward and backward for aspiration. Before puncture, Doppler functions were activated to prevent puncture into vessels. It was recommended to perform puncture on target lymph nodes and lump for 3 times, and 2 times were enough if sufficient tissue samples had been acquired. The cell smears were interpreted by a specialized physician with rich pathological experiences. The tissue samples acquired were fixed with methanal, and sliced after paraffin embedding, and then histological examination was performed on the samples.

EBUS-TBNA outcome definitions

When multiple lymphocyte masses were observed in the smears, it was considered that the puncture was as deep as in lymph nodes; when there was no lymphocyte observed, it

Table 2. Characteristics of punctured stations of EBUS-TBNA

EBUS-TBNA characteristics	Median value or percentage (%)
Number of lesions examined for each patient	2 (1-3)
Times of puncturing for each focus	3.5 (1-6)
Punctured lymph nodes (N = 45)	
Lymph nodes around upper trachea (#2)	2R:1 (2.2)
Lymph nodes around lower trachea (#2)	4R:14 (31.1)
	4L:3 (6.7)
Subcarinal lymph nodes (#7)	17 (37.8)
Hilar lymph nodes (#10)	10L:1 (2.2)
Inter-lobe lymph nodes (#11)	11Rs:7 (15.6)
	11L:2 (4.4)
Punctured inner lung lump (N = 8)	
Right upper lobe	2 (25)
Right middle lobe	1 (12.5)
Right lower lobe	1 (12.5)
Left lower lobe	1 (12.5)
Right middle branch	2 (25)
Subcarinal	1 (12.5)
Size of lymph nodes measured by ultrasound, mm, (N = 45)	
Short diameter	143 (51-215)
Long diameter	161 (87-339)
Size of lymph nodes measured by CT, mm (N = 45)	
Short diameter	121.7 (66.8-251.6)
Long diameter	188.1 (70-298)
Size of lump punctured, mm, (N = 8)	
Short diameter	210 (160-258)
Long diameter	303.5 (197-322)

was regarded that the puncture was in the tumor; when large amount of red blood cells or small amount of karyocytes were observed, the puncture was considered as failure; when there were clear malignant tumor cells observed in the smears, the result was considered as positive even if the type and differentiation degree cannot be identified for the time being; when highly suspected malignant tumor cells were observed in the smears, the clinical manifestations of the patient should be taken into consideration, and if it was highly suspected as lung cancer or other histological examination indicated lung cancer, it was considered as positive TBNA results, otherwise the result was negative. If the TBNA result determined for any part of the same patient was a positive result, the final TBNA result was considered as positive; when the TBNA results of all parts were negative, the final TBNA result was considered as negative. EBUS-TBNA negative patients were further examined by means of mediastinoscopy or CT/PET-CT after 6 months follow-up to check the diagnosis.

Statistics

Data analysis were performed using SPSS 22.0 statistic software, and the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated according to standard definitions.

Results

Demographic, clinical and pathological characteristics of participants

Demographic, clinical and pathological characteristics of the enrolled post-surgery patients with lung cancer were presented in **Table 1**. Among the 40 patients, there were 30 males (75%) and 10 females (25%), with median age of 58.5 (37-78) years. According to histopathology examination, there were 22 cases of adenocarcinoma (55%), 12 cases of squamous cell carcinoma (30%), 1 case of poorly differentiated carcinoma (2.5%), 3 cases of small cell carcinoma (7.5%), 1 case of adenosquamous carcinoma (2.5%) and 1 case of lymphoepithelioma like carcinoma (2.5%). At the same time, lymph node dissection had been performed for 32 cases of surgeries (80%).

Characteristics of punctured stations of EBUS-TBNA

Characteristics of punctured stations of EBUS-TBNA were presented in **Table 2**. In this study, from 40 patients, 45 stations of enlarged hilar and/or mediastinal lymph nodes were punctured: 1 for 2R group, 14 for 4R group, 3 for 4L group, 17 for 7th group, 1 for 10L group, 2 for 11L group, 7 for 11Rs group. And 8 stations of

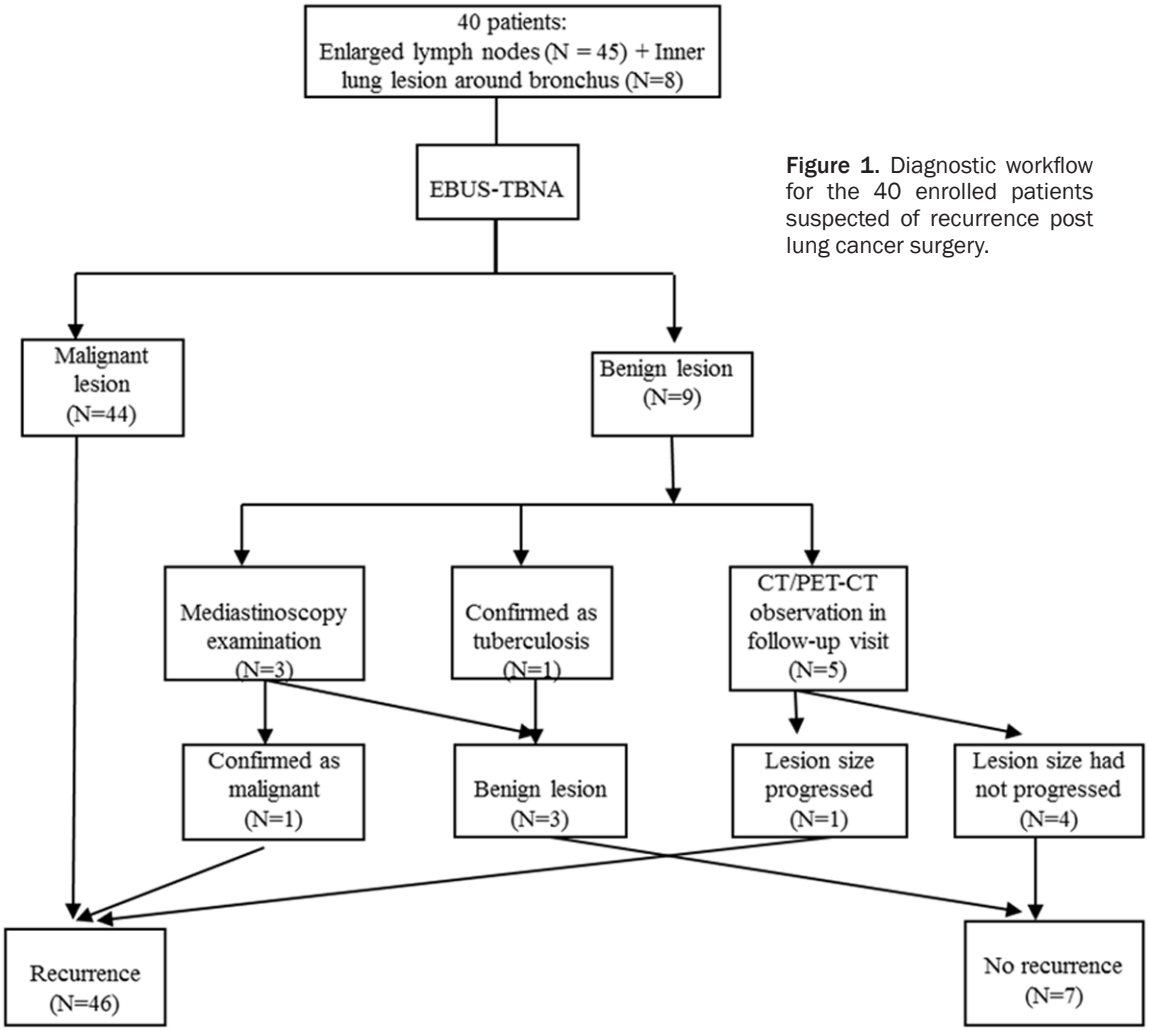

Figure 1. Diagnostic workflow for the 40 enrolled patients suspected of recurrence post lung cancer surgery.

inner lung lump were punctured as well: 2 in right upper lung, 1 in right middle lobe, 1 in right lower lobe, 1 in left lower lobe, 2 in right middle branch and 1 in subcarinal lump. The median value of puncture times for each focus was 3.5. The median value of sizes of all lymph nodes punctured was 143 × 161 mm, and the median value of punctured lump sizes was 210 × 303.5 mm.

Outcomes of EBUS-TBNA for diagnosis of recurrence

Diagnostic workflow for the 40 patients suspected with recurrence post lung cancer surgery was shown in **Figure 1**. Example of detailed diagnosis process of individual patient was presented by **Figure 2**.

Out of the 45 stations of enlarged lymph nodes and 8 stations of inner lung lumps (53 stations in total), EBUS-TBNA indicated 44 sets (83%) of recurrence of malignant lesions, 9 sets (17%) of non-malignant lesions. After mediastinoscopy examination or CT/PET-CT after 6 months follow up, out of the 9 sets, 2 were identified as recurrent and 7 were non-recurrent (**Figure 1**; **Table 3**).

For the diagnosis of recurrence post lung cancer surgery by EBUS-TBNA, as individual lesions (53 puncture stations), the sensitivity was 95.7%, the specificity was 100%, the positive predictive value was 100%, the negative predictive value was 77.8% and the diagnostic accuracy was 96.2% (**Table 4**).

Out the 40 patients, there were, by EBUS-TBNA diagnosis, 32 recurrent cases (80%) and 8 non-recurrent cases (8%), and After mediastinoscopy examination or CT/PET-CT after 6 months follow up, out of the 8 cases, there

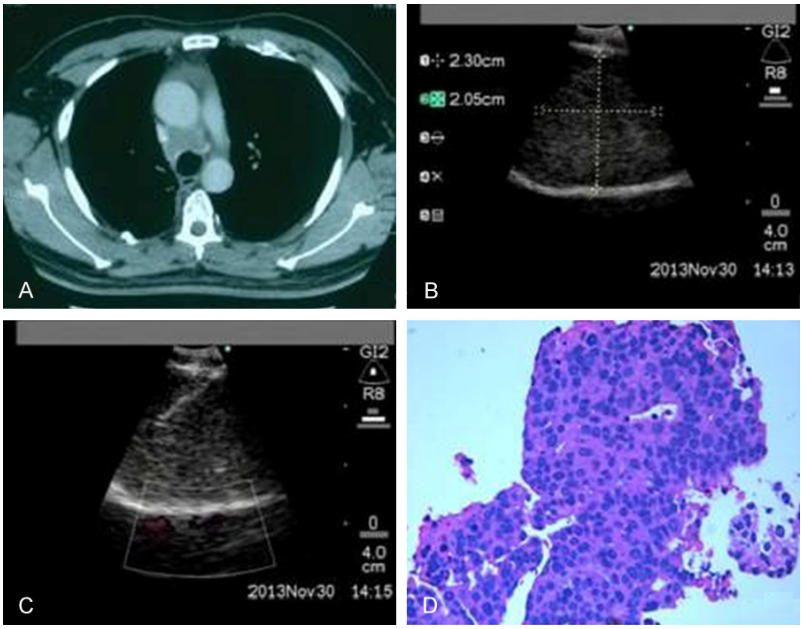

Figure 2. Example of detailed diagnosis process of individual patient. A. The patient, male, 64 years old, had enlargement of 4R lymph node indicated by chest CT. B. The position and diameter of 4R lymph nodes were measured by ultrasonic bronchoscope. C. Guided by bronchoscope, the TBNA imaging indicated the puncture needle had entered the 4R lymph nodes. D. The biopsy tissue was confirmed as adenocarcinoma cells by pathological examination.

were 2 recurrent cases and 6 non-recurrent cases. Out of the 34 patients confirmed as recurrent cases by final determination, there were 30 cases of non-small cell lung carcinoma (6 cases of poorly differentiated carcinoma, 10 cases of squamous carcinoma, 13 cases of adenocarcinoma and 1 case of unclassified lung cancer) and 4 cases of small cell carcinoma. Out of the 6 non-recurrent patients, there was 1 case of tuberculosis, 1 case of inflammation, 3 cases of reactive hyperplasia and 1 case of nodule-like reactions.

For the diagnosis of recurrence post lung cancer surgery by EBUS-TBNA, as individual patient, the sensitivity was 94.1%, the specificity was 100%, the positive predictive value was 100%, the negative predictive value was 75% and the diagnostic accuracy was 95% (**Table 4**).

Safety of EBUS-TBNA

All examined patients were able to well tolerate with EBUS-TBNA procedure, except for one patient who failed to receive sufficient examination due to violent coughing during the procedure. During the examination, except of small amount of hemorrhage observed in puncture points under endoscope, there were no severe complications identified, such as pneumothorax, mediastinal emphysema and mediastinal great vessel rupture hemorrhage.

Effect of EBUS-TBNA on subsequent post-surgery treatment decisions of lung cancer

In this study, out of the 40 patients, 37 patients (92.5%) had subsequent treatment regimen made based on EBUS-TBNA diagnostic results (**Table 5**). Among them, 9 patients received concurrent radiochemotherapy, 6 patients received radiotherapy, 7 patients received chemotherapy, 1 patient who had positive result in EGFR test received EGFR-TKI targeted therapy, 4 patients received a second surgical procedure, 1 patient had conditions improved after anti-inflammation treatment, 1 patient who was confirmed as tuberculosis by culture received anti-tuberculosis treatment.

Conclusion

Lung cancer, with 5-year survival rate less than 15%, is one of the malignant tumors with highest morbidity. Even for the patients with stage I NSCLC, there are still about 1/3 patients with poor prognosis after receiving radical surgical excision. The recurrence rate post lung cancer surgery is related to tumor staging, and several studies indicates the recurrence rate post radical surgery of lung cancer is as high as 30-75% [9-11]. It is of vital importance for the post-surgery patients with lung cancer to determine, as early as possible, the clinical and pathological features of inner lung lump and enlarged hilar mediastinal lymph nodes with no obvious cause [12].

Mediastinoscopy examination is the “golden standard” for conventional evaluation of mediastinal lymph nodes [13]. However, as a sur-

Table 3. Clinicopathologic features of 53 lesions (45 stations of enlarged lymph nodes and 8 stations of inner lung lumps)

	Median value or percentage (%)
EBUS-TBNA Cytology	
Adenocarcinoma	14 (26.4)
Squamous cell carcinoma	9 (17)
Large cell carcinoma	0 (0)
NSCLC (Indeterminate)	4 (7.5)
Atypical cellular hyperplasia	7 (13.2)
With no malignant evidence	18 (34)
Sample insufficient	1 (1.9)
EBUS-TBNA histopathology	
Adenocarcinoma	15 (28.3)
Squamous cell carcinoma	13 (24.5)
Large cell carcinoma	1 (1.9)
Adenosquamous carcinoma	0 (0)
NSCLC (Indeterminate)	4 (7.5)
With no malignant evidence	20 (37.8)
Sample sufficient	52 (98.1)
Malignancy indicated by EBUS-TBNA	44 (83)
Benign indicated by EBUS-TBNA	9 (17)
Malignancy confirmed by mediastinoscopy	1 (1.9)
Benign confirmed by mediastinoscopy	2 (3.8)
Tuberculosis confirmed by culture	1 (1.9)
Resting nodule indicated by subsequent clinical follow-ups	4 (7.5)
Progress nodule indicated by subsequent clinical follow-ups	
Time of clinical follow-ups, days (N = 5)	1 (1.9)
	232 (196-270)

Table 4. Diagnostic value of EBUS-TBNA on recurrence in post-surgery patients with lung cancer

	Unit focus (%)	Unit patient (%)
Sensitivity	95.7	94.1
Specificity	100	100
Positive predictive value	100	100
Negative predictive value	77.8	75
Diagnostic accuracy	96.2	95

gery, it is expensive and needs general anesthesia and hospitalized treatment, as well as related complications and relatively high mortality. According to related reports in literature, the morbidity of complications of mediastinoscopy examination is 0.6-3%, the risk of hemorrhage is about 0.1-0.6% and the mortality is about 0-0.3% [14-18]. Furthermore, as for hilar and inter-lobe enlarged lymph nodes and lumps around bronchus, it is difficult for the mediastinoscopy to access tissue samples [19]. Additionally, the operation becomes more difficult for a second mediastinoscopy examination, and the sensitivity and accuracy rate of the diagnosis also decreases as compared with the first examination [20].

EBUS-TBNA is one of the new techniques applied in clinical practice recently. Compared with conventional tranbronchial needle aspiration (TBNA, non-ultrasound guided blind puncture), EBUS-TBNA carried on the advantages of TBNA technique such as simple operation, minimal invasion, covering wide range of mediastinal lymph nodes and high repeatability. Meanwhile, the real-time ultrasonic imaging display function enables more accurate puncture locating of the technique, which significantly increases the puncture accuracy rate and safety [21, 22]. According to recent studies, the diagnosis of mediastinal lymphatic metastasis of malignant tumor by EBUS-TBNA is characterized by high sensitivity (89.0-98.7%) and specificity (mostly 100%). Compared with mediastinoscopy, the determination of mediastinal benign lesions, such as nodular lesions by EBUS-TBNA also has relatively high accuracy and sensitivity [16, 23-26]. Additionally, EBUS-TBNA could also be used during and after the treatment of lung cancer as well as restaging after induction treatment [27-29]. However, the effect of EBUS-TBNA on diagnosis of recurrence in post-surgery patients with lung cancer is still unclear.

This study included 40 patients suspected of recurrence post lung cancer surgery, and EBUS-TBNA examination was performed on 45 stations of enlarged lymph nodes and 8 stations of inner lung limps around bronchus. The

Table 5. Effect of EBUS-TBNA on subsequent post-surgery treatment decisions of lung cancer

	Median value or percentage (%)
EBUS-TBNA had affected subsequent post-surgery treatment decisions of lung cancer	37 (92.5)
Diagnostic NSCLC	30 (75)
Concurrent Radiochemotherapy	9 (22.5)
Radiotherapy	6 (15)
Chemotherapy	7 (17.5)
EGFR-TKI	1 (2.5)
A second surgery	4 (10)
Clinical follow-ups	6 (15)
Anti-tuberculosis treatment	1 (2.5)
Anti-inflammation treatment	1 (2.5)
EBUS-TBNA had not affect subsequent post-surgery treatment decisions of lung cancer	3 (7.5)

results showed that, as for EBUS-TBNA diagnosis of recurrence post lung cancer surgery by individual lesions, the sensitivity was 95.7%, the specificity was 100%, the positive predicative value was 100%, the negative predicative value was 77.8% and the accuracy rate was 96.2%. As for EBUS-TBNA diagnosis of recurrence post lung cancer surgery by individual patient, the sensitivity was 94.1%, the specificity was 100%, the positive predicative value was 100%, the negative predicative value was 75% and the accuracy rate was 95%. The sensitivity and specificity were similar to the results in EBUS-TBNA diagnosis of first onset mediastinal lymphatic metastasis of malignant tumor [16, 24, 26, 30].

In this study, the diagnostic negative predictive value by EBUS-TBNA by individual lesions was 77.8%. Although not all EBUS-TBNA negative stations were surgically confirmed, negative patients were further examined by means of mediastinoscopy or CT/PET-CT after 6 months follow up to check the diagnosis. Negative predictive value can be affected by disease epidemiology of the test population. The high risk of recurrence of lung cancer in the test cases of this study led to relative low negative predictive value. However, the results were still similar to the negative predictive value in previous reports on diagnosis by a second mediastinoscopy (73.3-84.5%) [31-33].

In conclusion, EBUS-TBNA could be considered as a feasible, safe and promising procedure to diagnose lymph node relapse in post-surgery patients with lung cancer.

Disclosure of conflict of interest

None.

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