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A randomized controlled study of conventional TBNA versus EBUS-TBNA for diagnosis of suspected stage I and II sarcoidosis

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Abstract. *Objectives:* The aim of this study was to compare the diagnostic yield of TBNA and EBUS-TBNA in the patients with suspected stage I and II sarcoidosis in the case of the same number of needle aspiration lymph nodes and the same lymph nodes needle aspiration times. *Methods:* A total of 62 patients with suspected stage I and II sarcoidosis were randomly divided into TBNA group and EBUS-TBNA group, based on the clinical and radiologic manifestations. Biopsy specimens of each patient in both groups were taken from two lymph nodes with two needle passes per lymph node. The diagnostic yields of subgroup were separately calculated including the 4th and 7th lymph nodes (referred to as group A), in other stations (group B), greater than 15 mm and less than 15 mm in the shortest diameter. *Results:* The diagnostic yield of TBNA and EBUS-TBNA for sarcoidosis was 64% and 93%, respectively ($\chi 2=7.12$, $P<0.05$). Subgroup analysis showed that the percentages of positive pathological diagnosis in group A for TBNA and EBUS-TBNA were 79% and 95% ($\chi 2=3.47$, $P>0.05$). The percentages of positive pathological diagnosis greater than 15 mm in the shortest diameter were 78% and 94% ($\chi 2=2.29$, $P>0.05$). *Conclusion:* The overall diagnostic yield of EBUS-TBNA for stage I and II sarcoidosis was higher than TBNA. However, Conventional TBNA has very high diagnostic yield similar to EBUS-TBNA, if the lymph nodes located on the 4th and 7th group or the shortest diameter was greater than 15 mm. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 211-218)*

Key words: Sarcoidosis, diagnosis, endobronchial ultrasound-guided transbronchial needle aspiration, transbronchial needle aspiration

Introduction

Sarcoidosis is termed as a systemic granulomatous disease characterised by affecting several organs and tissues. The etiology and pathogenesis are not yet entirely clarified (1). The most easily affected organs are lung and lymph nodes. The chest radiography showed hilar or mediastinal lymph nodes enlargement in nearly 90% of the patients (2). In accordance with the guidelines, the diagnosis of sarcoidosis should be established in presence of compatible clinicoradiographic findings and histologic evidence of noncaseating epithelioid cell granulomas after exclusion of other known causes for granulomatous inflammation (3). For patients with suspected sarcoidosis and especially for patients considering systemic steroids therapy, it is necessary to obtain pathological diagnosis in order to exclude the malignant tumor and tuberculosis. Biopsy specimens should be obtained from the most readily accessible organ using the least invasive method. (2). Because lung and mediastinal lymph nodes are the most easily affected organs, bronchoscopic techniques are often used to confirm the presence of non-caseous granulomas. Currently, the bronchoscopic techniques used for obtaining pathologic sarcoidosis specimens include transbronchial lung biopsy

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(TBLB), bronchial biopsy, transbronchial needle aspiration (TBNA), and ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

TBLB has been the standard method recommended by guidelines for the diagnosis of sarcoidosis (3). However, the literature reported that the diagnostic yield was about 40%, and there were risks of pneumothorax, hemoptysis, and other complications (4-6). Bronchial biopsy for the diagnosis of sarcoidosis remained controversial and the diagnosis yield reported in different literature varied greatly (7, 8). TBNA and EBUS-TBNA have been reported to be an effective method for diagnosis of stage I and II sarcoidosis with less trauma, fewer complications, and higher diagnostic yield. Recently, meta-analysis showed that the diagnostic yield of TBNA was 62% for sarcoidosis (9). The diagnostic yield of EBUS-TBNA for sarcoidosis has been reported to be about 90% (4,5,10-12). One recent study (13) showed that endosonographic (esophageal or endobronchial ultrasonography) nodal aspiration compared with conventional bronchoscopy biopsy(transbronchial and endobronchial lung biopsy) resulted in greater diagnostic yield. However, few randomized controlled studies were performed to directly compare TBNA and EBUS-TBNA. Tremblay compared the diagnostic yield between TBNA and EBUS-TBNA (12), and revealed EBUS-TBNA was superior to TBNA using a standard 19-gauge needle in patients suspected stage I and II sarcoidosis. However, there were differences of the number of the lymph nodes aspirated and needle aspiration times per lymph node between TBNA and EBUS-TBNA group. Whether the superiority of EBUS-TBNA is resulted from the greater average number of lymph node stations sampled? Biopsy specimens were taken from the two lymph nodes in each patient in TBNA and EBUS-TBNA group with two needle passed per lymph node in our hospital and we achieved satisfactory results. In this randomized controlled study, we compared the diagnostic yield between TBNA and EBUS-TBNA for sarcoidosis by puncturing two lymph nodes per patient and two needle passes for each lymph node, wishing to reach a more objective conclusion. We wish our study could contribute to the standardization of TBNA and EBUS-TBNA in the diagnosis of sarcoidosis.

Materials and Methods

Study design

This study was a single-center, randomized, controlled trial. Block randomization was performed, stratifying for stage I vs II. A computer-generated random number list was used. For all patients, the random-sequence allocation remained concealed until prior to the start of the procedure.

Patients

This study was a prospective study (Number 2009GG10002061) with the protocol approved by Shandong Provincial Hospital Ethics Committee. The written informed consent was obtained from each patient included in this study. A sample size of 31 patients per group was calculated based on the diagnostic yield which was 62% and 92% for TBNA and EBUS-TBNA respectively(the diagnostic yield of EBUS-TBNA was derived from the medial diagnostic yield of literature 4,5,10,11and 12), with a power of 0.8 and of 0.05. Between October 2009 and December 2012, a total of 62 patients were enrolled in this study in respiratory clinic of Shandong Provincial Hospital, diagnosed with sarcoidosis on the basis of the clinical details and radiological findings. Chest CT showed hilar or mediastinal lymph nodes enlargement in these patients.

Inclusion criteria:

Patients were eligible for this study if they signed the informed consent forms, were >18 years of age, had at least two groups of enlarged hilar or mediastinal lymph nodes (the shortest diameter >10 mm) confirmed on the enhanced chest CT scan, were considered to have a likely diagnosis of sarcoidosis based on clinical and radiologic assessment, or if they requested for pathological diagnosis.

Exclusion criteria

The exclusion criteria included: intolerance to endoscopic or surgical intervention; uncontrollable coagulation disorders (PLT<100*10^9/L, INR>1.3, applying clopidogrel in 7 days); receiving systematic steroids more than 30 days prior to the bronchoscopy (12); patients with Lofgren's syndrome; suspected or diag-

nosed malignant tumors or a previous diagnosis of sarcoidosis; confirmed extrapulmonary sarcoidosis through a simple diagnostic techniques (14).

Checking sequence

A total of 72 patients were screened, of which 62 patients met the inclusion criteria. The patients were randomly divided into two groups labeled as TBNA and EBUS-TBNA group. Patients were given 5 ml of 2% lidocaine by aerosol inhalation before the produre. At insertion of the standard bronchoscope, an additional 2 ml of 2% lidocaine was applied to the vocal cords and bronchial tree if patients underwent severe coughing. Furtherore, 2.5-5 mg midazolam and 75 ug fentanyl were intraoperatively given to keep conscious sedation, monitoring ECG, blood pressure, and the mean pulse oxygen. The same operator punctured the easily accessible lymph nodes for the both groups. Station 7 and 4 were preferred if patient had more than 2 enlarged nodes, otherwise the largest 2 was the preference. Rapid on-site cytologic evaluation(ROSE) was not performed. All procedures were conducted without an anaesthetist being present.

TBNA procedure

The punctured lymph nodes were classified according to the 7th edtion of theTNM system for lung cancer staging (15). According to the method described in the literature (16), TBNA was performed using a standard bendable bronchoscope (BF-260, Olympus; Tokyo, Japan) and Wang 319-pin (Conmed Corprotion, USA) in two lymph nodes with two needle passes for each lymph node. The decion as to whether or not to proceed to endobronchial biopsy and TBLB was left to the discretion of the operator. When TBLB was performed, the standard biopsy forceps (FB-231, D; Olympus) was used in the absence of X-ray guidance according to the literature (4). If the operator considered it necessary to perform the bronchial biopsy, the procedure would be carried out according to the literature (7).

EBUS-TBNA procedure

EBUS-TBNA was performed using an EBUS bronchoscope (CP-EBUS; BF-UC260F-OL8; Olympus; Tokyo, Japan) with a longitudinal convex ultrasound transducer through a mouth or nose insertion. The endoscopic probe was fixed to a predetermined puncture site and the ultrasound examination was used to determine the puncture lesions, and the open of multi-Doppler blood flow was used to identify the puncture target lesion. The puncture needle (NA-201SX-4022, Olympus; Tokyo, Japan) was inserted through a conventional endoscopic needle insertion mode. The insertion depth was appropriately adjusted to observe the needle cannula tip under endoscopic vision. The ultrasound endoscope covered with a saline-filled balloon was brought into contact with the airway wall and was moved in all directions to identify the puncture pathway. The puncture was performed when the balloon snapped to the puncture site. The strong echo of the puncture needle was visible within the lesion if successfully punctured. Biopsy specimens of each patient in EBUS-TBNA group were taken from two lymph nodes with two needle passes per lymph node.

TBLB and bronchial biopsy specimens were fixed in formalin for histopathologic examination after bronchoscopy was completed. TBNA and EBUS-TBNA biopsy fragment was directly transferred onto the glass slides, air-dried, fixed in 95% alcohol for cytological examination. The visible tissue fragment on the glass slide was then collected and transferred into separate containers filled with formalin for histologic examination. The residual specimen stored at the lumen of the needle and catheter was then washed and flushed into the saline for microbiologic analysis culture including microscopic fungi, acid-fast staining, fungal culture, and mycobacterial culture. A chest radiograph was routinely obtained to identify the pneumothorax 2 hours after the procedures.

The EBUS-TBNA was performed another time if TBNA did not confirm the diagnosis. If necessary, mediastinoscopy or video-assisted thoracoscopic surgery (VATS) was performed for further diagnosis. The mediastinoscopy or VATS was considered to be the surgical pathological sampling if EBUS-TBNA did not confirm the diagnosis. All the patients were clinically radiologically followed-up for at least six months.

Diagnosis

The final diagnosis of sarcoidosis was based on the clinical and radiographic manifestation compat-

ibility, the cytologic or histologic findings of non-caseating epithelioid cell granulomas, with negative microbiology examination and no evidence of malignancy (17). If the pathological and microbiological tests were negative, it was interpreted as "indefinite" (5).

Statistical analysis

The primary endpoint was the diagnostic yields of TBNA and EBUS-TBNA for sarcoidosis, The secondary endpoint were the diagnostic yields of TBNA and EBUST-TBNA of subgroup including the 4th and 7th lymph nodes (referred to as group A), in other stations (group B), greater than 15 mm and less than 15 mm in the shortest diameter. Additional secondary outcome included the diagnostic yield of TBNA combined with TBLB, bronchial biopsy, and the incidence of complications. Statistical analyses were performed using a statistical software program (SPSS17.0, Inc, Chicago, Ill). Diagnostic yields were compared using χ^2 test.

Results

A total of 72 patients were screened, where 62 patients were randomly assigned to TBNA (31 patients) or EBUS-TBNA (31 patients) in this study, including 15 males and 47 females (Fig. 1). The average age and disease stage of patients in two groups are shown in Table 1. The lymph node distributions are shown in Table 2, according to the international staging system. The difference between the two groups was not statistically significant. The procedures in TBNA and EBUS-TBNA group were successfully completed.

From among 62 patients, 57 had sarcoidosis, three had tuberculosis, and two had lymphoma (Table 3). From among the sarcoidosis cases, 27 were diagnosed in the EBUS-TBNA group, 26 were diagnosed in TBNA group. Two and one patients were diagnosed to be tuberculosis in TBNA and EBUS-TBNA groups, respectively.

From among the cases not diagnosable by TBNA group, two were diagnosed as sarcoidosis by EBUS-TBNA. A case not diagnosable by EBUS-TBNA was confirmed to be lymphoma by mediastinoscopy.

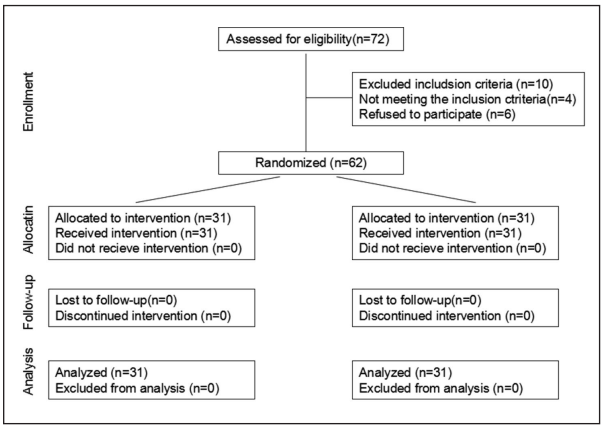

Fig. 1. Participant flow.

Table 1. Baseline Values

Variables	TBNA (n=31)	EBUS-TBNA (n=31)
Age (yr)	38.8±9.6	39.2±8.4
Male gender/Female gender	8/23	7/24
Disease stage		
Stage I	22	19
Stage II	9	12
Node size (mm)	17.9±5.7	15.4±4.5

Data are presented as number or mean ±standard deviation.

Table 2. Characteristics of lymph nodes sampled by TBNA and EBUS-TBNA.

Station	TBNA (n)	EBUS-TBNA (n)
2R	8	6
2L	6	7
4R	18	16
4L	6	5
7	14	21
10R	3	3
10L	3	2
11R	2	1
11L	2	1
Total	62	62

Data are presented as n. R: right; L: left.

A case with negative EBUS-TBNA results underwent mediastinoscopy, which established the diagnosis of lymphoma. The other two undiagnosed cases refused mediastinoscopy. However, after their families agreed with EBUS-TBNA, it was confirmed to be sarcoidosis.

Table 3. Final pathological diagnosis of the mediastinal lymph nodes in the study population.

DIAGNOSIS	TBNA group	EBUS-TBNA group
Sarcoidosis	28*	29**
Tuberculosis	2	1
Lymphoma	1	1
No definite pathological diagnosis	0	0

** Two cases were diagnosed by EBUS-TBNA ** Two cases were diagnosed by EBUS-TBNA twice*

In TBNA group, 18 cases were diagnosed with sarcoidosis by TBNA, eight cases by TBLB (8/22), and one case by bronchial biopsy (1/20). All patients were clinically followed up for at least six months and the diagnosis was not modified.

The study's primary endpoint was the diagnosis yield (Table 4). The diagnostic yields of TBNA and EBUS-TBNA were 64% (18/28) and 93% (27/29), respectively (χ^2=7.12, P<0.05). The combination of TBNA, TBLB, and bronchial biopsy for sarcoidois diagnosed a total of 26 cases. Compared with EBUS-TBNA, there was no statistically significant difference (χ^2=0.000, P>0.05).

The diagnostic yield of TBNA and EBUS-TBNA in group A was 79% (30/38) and 95% (40/42), respectively. However, the difference was not statistically significant (χ^2=3.47, P>0.05). The diagnostic yield of TBNA and EBUS-TBNA in group B was 17% (4/24) and 90% (18/20), respectively (χ^2=23.47, P<0.05).

The diagnostic yields of TBNA and EBUS-TBNA in lymph nodes greater than 15 mm were 78% (28/36) and 94% (30/32), respectively. However, the difference was not statistically significant (χ^2=2.29, P>0.05). The diagnostic yields of TBNA and EBUS-TBNA in in lymph nodes less than 15 mm were 15% (4/26) and 90% (27/30), respectively (χ^2=31.38, P<0.01).

Four cases of moderate mucosal bleeding occurred during TBNA. The bleeding was stopped by topical application of epinephrine. One case of pneumothorax resulted from TBLB. The closed thoracic drainage was not performed and the pneumothorax was ameliorated after oxygen uptake treatment. In another case, a hemoptysis of about 50 ml occurred after TBLB, which was improved after the oral Yunnanbaiyao and intravenous hemocoagulase. Two cases of moderate mucosal bleeding occurred during EBUS-TBNA, which were not handled.

Table 4. Diagnostic yields obtained wtih TBNA and EBUS-TBNA

	TBNA	EBUS-TBNA	P
Overall	64% (18/28)	93% (27/29)	<0.05
Group A*	79% (30/38)	95% (40/42)	>0.05
Group B**	17% (4/24)	90% (18/20)	<0.05
Greater than 15 mm	78% (28/36)	94% (30/32)	>0.05
Less than 15 mm	15% (4/26)	90% (27/30)	<0.05

Discussion

Our study found that the diagnostic yield of EBUS-TBNA for stage I and II sarcoidosis was higher than that of the TBNA (93% and 64%, respectively). The diagnostic yield was consistent with the previously reported results (4,5,10-12,18,19). Furthermore, the subgroup analysis showed that the diagnostic yield between them was similar when the 4th and 7th lymph nodes were enlarged or when the shortest diameter of the enlarged lymph nodes was greater than 15 mm. The randomized controlled methods were used in this study and reached these conclusions. However, because the sample size was small and the study was a single-center study, the definitive conclusions were not obtained. A large sample size along with a multi-center study will be needed to further confirm this conclusion.

No diagnosis of epithelial lung cancer was made probably because most people have received lung tumor marker examination before the trail, and the patients with significantly elevated lung tumor maker were excluded. However, as there are no specific serological or chest radiographic examinations for lymphoma and mediastinal lymphonode tuberculosis, the inclusion of mediastinal lymphonode tuberculosis (3 cases) and lymphoma (2 cases) could not completely be avoided. In addition, only 5 patients were diagnosed with diseases other than sarcoidosis, it seemed that diagnosing sarcoidosis according to clinical symptoms, laboratory examinations, and radiographic examinations could provide high accuracy, but pathological examinations could not be excluded for the fact that treatments for lymphoma and mediastinal lymphonode tuberculosis, which could be misdiagnosed as sarcoidosis, are definitely different from sarcoidosis, and treating lymphoma or mediastinal lymphonode tuberculosis with glucocorticoids could result in poor outcomes.

The factors affecting the positive diagnosis of TBNA included the operator skills (20), the location and size of lymph nodes (21-23), needle type (24), and the application of on-site cytology (25). The location and size of the lymph nodes are two important factors affecting the diagnosis positive rate. EBUS-TBNA was performed under the ultrasound guidance, which was moderately affected by the location and size of the lymph nodes. In our study, the diagnostic yield between TBNA and EBUS-TBNA was similar when the 4th and 7th lymph nodes were enlarged (79% and 95%; *P*>0.05). The diagnostic yield of TBNA performed in the 4th and 7th lymph nodes was higher, which was consistent with the results previously described in the literature (18, 26). This study found that there was no significant difference (78% and 94%; *P*>0.05) between TBNA and EBUS-TBNA when the lymph nodes' diameter were greater than 15 mm. Ten cases undiagnosed by TBNA had the enlarged lymph nodes not belonging to the 4th and 7th group, or with a diameter of less than 15 mm. Of those, two cases were diagnosed by EBUS-TBNA, suggesting a potential advantage for the EBUS-TBNA was being able to puncture the lymph nodes not belonging to the 4th and 7th group or a diameter of less than 15 mm.

In this study, we separately analyzed the diagnostic yield in the 4th and 7th group and empirically selected 15 mm as the cut-off for the subgroup analysis. Herth et al. independently analyzed the 7th lymph node (27). In our daily practice, the diagnostic yield in the 4th and 7th groups was similar and so a separate analysis was conducted in this study. Our recent study (28) found that there was no statistic significance between the diagnostic yields of TBNA and EBUS –TBNA when the diameter of lymph nodes were more than 15mm, so we selected 15mm as the cutoff. Rong's studies (29) implied that satisfactory puncture results could be obtained by either TBNA or EBUS-TBNA, and the positive diagnosis yield did not significantly differ after perfect mastering of the techniques and methods. Although these two studies were not specially designed for the sarcoidosis patients, we believed that the influence of the lymph node location and size on the needle biopsy positive rate would decrease gradually with the advances of the operator skills. Therefore, the settled cutoff would also subsequently reduce.

In the diagnosis of sarcoidosis by TBNA and EBUS-TBNA, the number of needle aspiration lymph nodes and the needle aspiration times per lymph node have been inconclusive. Tremblay's study reported that the average of 2.2 lymph nodes per patient and 4 needle passes per lymph node were reliable for TBNA, while these numbers were the average of 4 lymph nodes per patient and 2.5 needle passes per lymph node for EBUS-TBNA (12). Baram found that the first two needles could obtain the required specimens for diagnosis in most cases when performing TBNA (25). Trisolini has found that sampling of more than one nodal station during TBNA increased the diagnostic yield (30). Cetinkaya found that sampling of at least two separate lymph nodes during EBUS-TBNA increased diagnostic yield (31). Thus this study's strategy was to puncture two lymph nodes per patient and two needles per lymph nodes, which generated a similar diagnostic yield as compared to the literature (4,5) (10-12,14,18,19). This might be contributed to the endoscopists with 10 years of TBNA and three years of EBUS-TBNA operating experience. Compared with Tremblay (12), the number of needle aspiration lymph nodes and the needle aspiration times per lymph node were the same. Although the study's conclusions were consistent, our study was more objective and reliable.

In the diagnosis of suspected sarcoidosis, the combination of TBLB, bronchial biopsy, and TBNA were complementary. The diagnosis of sarcoidosis must exclude other granulomatous diseases. Therefore, the above combination made the diagnosis for exclusion of other diseases with greater accuracy. In the present study, the combination of TBLB, bronchial biopsy, and TBNA rose the diagnosis yield up to 83%, which was consistent with the results previously reported in the literature (6,18,32). There was no significant difference as compared with the EBUS-TBNA group. Due to the small sample size, whether the combination of TBLB, bronchial biopsy and TBNA could really achieve the similar performance to EBUS-TBNA need further study. The combination of TBLB, bronchial biopsy, and TBNA was an approach to improve the diagnosis yield for sarcoidosis when the EBUS-TBNA could not be performed in the hospital.

One potential limitation of our study is that rapid on-site cytologic evaluation (ROSE) was not carried out in this study. ROSE has been used in TBNA examination since 1990, which was able to

quickly determine the adequacy of the specimen and to provide the operator with a preliminary diagnosis (33). Meta-analysis indicated that there was a little impact on the diagnostic yield for EBUS-TBNA, irrespective of the use of ROSE (34). It is still controversial to perform ROSE during TBNA. Some studies (33,35,36) found that ROSE could reduce the needle aspiration times and shorten the operation time, while not reducing the diagnostic yield, which fitted the cost-effectiveness ratio. Thus the utility of ROSE were advocated when performing TBNA. However, other studies showed that the diagnostic yield was unchangeable whether ROSE was performed or not (25). Since ROSE could be impossible to be achieved in every hospital, and the application of ROSE will increase the cost and requires a high manpower (37), some experts suggested that ROSE should be selectively performed during TBNA (25). However, one recent study (38) may change this situation. This study demonstrated that a trained pulmonologist can assess the adequacy of cytological smears on site, and so training pulmonologists to have a basic knowledge of cytopathology could obviate most difficulties related to the involvement of cytopathologists in routine diagnostic activities. Maybe in the future ROSE could be a routine when performing TBNA or EBUS-TBNA. One randomized controlled study of TBNA VS EBUS-TBNA with ROSE is needed.

In short, the diagnostic yield of EBUS-TBNA for suspected stage I and II sarcoidosis was higher than that of the TBNA in this study. However, conventional TBNA of stations 7 and 4 nodes if size is greater than 15 mm has very high diagnostic yield, similar to EBUS-TBNA. It is more widely available and cheaper and hence the technique should continue to be utilized particularly where EBUS-TBNA is not available.

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