# Prospective study of endobronchial ultrasound–guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis

Masahide Oki, MD,[a] Hideo Saka, MD,[a] Chiyoe Kitagawa, MD,[a] Yoshihito Kogure, MD,[a] Naohiko Murata, MD,[a] Shu Ichihara, MD,[b] and Suzuko Moritani, MD[b]

**Objective:** Endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) has been reported to be an accurate and safe method to confirm a pathologic diagnosis of sarcoidosis. However, only a few retrospective or small prospective studies have been published on EBUS-TBNA versus transbronchial lung biopsy (TBLB), which has been the standard method for making a pathologic diagnosis of sarcoidosis so far. The aim of this study was to compare the diagnostic yield of EBUS-TBNA and TBLB through a flexible bronchoscope in patients with stage I and II sarcoidosis.

**Methods:** A total of 62 patients with suspected stage I and II sarcoidosis were included in this prospective study. EBUS-TBNA was performed (2 lymph nodes, 2 needle passes for each lymph node), followed by TBLB (5 biopsy specimens from multiple lung segments) in the same setting. The final diagnosis of sarcoidosis was based on clinicoradiologic compatibility and pathologic findings.

**Results:** Of the 62 patients enrolled, 54 were given a final diagnosis of sarcoidosis. The diagnostic yield of EBUS-TBNA and TBLB for sarcoidois by showing noncaseating epithelioid cell granuloma was 94% (stage I, 97%; stage II, 88%) and 37% (stage I, 31%; stage II, 50%), respectively. The difference was statistically significant ($P < .001$). One case of pneumothorax and 3 cases of moderate bleeding (7%) resulted from TBLB, and 1 case of severe cough (2%) from EBUS-TBNA.

**Conclusions:** The diagnostic yield of EBUS-TBNA for stage I and II sarcoidosis is higher than for TBLB. (J Thorac Cardiovasc Surg 2012;143:1324-9)

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Although the clinical and radiologic findings are highly reliable in the diagnosis of stage I sarcoidosis (bilateral hilar and/or mediastinal lymphadenopathy) or stage II sarcoidosis (bilateral hilar and/or mediastinal lymphadenopathy and parenchymal abnormalities), proving the presence of noncaseating epithelioid cell granulomas is indispensable for its definitive diagnosis.[1] Because the lungs are involved in more than 90% of the cases, transbronchial lung biopsy (TBLB) through a flexible bronchoscope has been the standard method for making a pathologic diagnosis of sarcoidosis so far.[1] However, the diagnostic yield of TBLB, especially for stage I disease, is not sufficient.[2,3] Moreover, diseases other than sarcoidosis cannot be diagnosed or ruled out by TBLB. Such diseases involve thoracic lymph nodes but not lungs and show a similar radiographic appearance to stage I sarcoidosis, such as metastatic carcinoma, lymphoma, and various infectious diseases. The high complication rates including pneumothorax and bleeding are another problem associated with the procedure.

Transbronchial needle aspiration (TBNA) through a flexible bronchoscope has been widely established as a useful and safe clinical tool in the evaluation of hilar and/or mediastinal lymphadenopathies.[2,4] The addition of endobronchial ultrasound (EBUS) guidance (EBUS-guided TBNA; EBUS-TBNA) has greatly enhanced the diagnostic yields and safety of bronchoscopy.[5] Several investigators have reported the excellent yield and safety of EBUS-TBNA for diagnosing sarcoidosis by demonstrating noncaseating granulomas,[3,6-12] and the procedure seems to be more suitable than TBLB, which has been considered the standard technique. However, only a few retrospective[3,12] or small prospective[11] studies focused on EBUS-TBNA versus TBLB have been published. We conducted a prospective study comparing the diagnostic yield of EBUS-TBNA and TBLB in patients with stage I and II sarcoidosis.

## PATIENTS AND METHODS

Between April 2006 and December 2009, we carried out a prospective study that was approved by the institutional review board of

From the Department of Respiratory Medicine[a] and the Department of Pathology,[b] Nagoya Medical Center, Nagoya, Japan.

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Address for reprints: Masahide Oki, MD, Department of Respiratory Medicine, Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya 460-0001, Japan (E-mail: masahideo@aol.com).

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**Abbreviations and Acronyms**

| | |
|---|---|
| CT | = computed tomography |
| EBB | = endobronchial biopsy |
| EBUS | = endobronchial ultrasound |
| EBUS-TBNA | = endobronchial ultrasound–guided transbronchial needle aspiration |
| TBLB | = transbronchial lung biopsy |
| TBNA | = transbronchial needle aspiration |

Nagoya Medical Center (identifier: 2006-8) and registered with the University Hospital Medical Information Network–Clinical Trials Registry (identifier: UMIN000000507). Included in this study were 62 patients with suspected stage I or II sarcoidosis in the presence of a compatible clinical and radiologic picture with enlarged hilar and/or mediastinal lymph nodes, 10 mm or greater in the shortest diameter on chest computed tomography (CT). Patients with pathologically proven sarcoidosis were excluded. Informed consent was obtained from all patients.

The primary outcome of this study was to compare the diagnostic yield of EBUS-TBNA and TBLB for stage I and II sarcoidosis by demonstrating noncaseating epithelioid cell granulomas. Secondary outcome was to compare the complication rates of these procedures.

All bronchoscopic procedures were performed with the patient under local anesthesia using lidocaine and conscious sedation with midazolam by staff pulmonologists. An endotracheal tube was placed transorally under bronchoscopic control,[7,13] which facilitated repeated insertion and removal of the bronchoscope; bronchoscopy was then performed in the standard fashion to examine the endobronchial region. After that, EBUS-TBNA was performed, followed by TBLB in a single session. Endobronchial biopsy (EBB) was not performed except in 1 patient with an irregularity of endobronchial mucosa. Bronchoalveolar lavage was not performed in any patients.

## EBUS-TBNA Procedure

EBUS-TBNA was performed using an EBUS bronchoscope (BF-UC260F-OL8; Olympus; Tokyo, Japan) with a longitudinal convex ultrasound transducer at an ultrasonic frequency of 7.5 MHz, in combination with an ultrasound processor (EU-C2000; Olympus). The EBUS bronchoscope was passed through an endotracheal tube to the trachea, and then the ultrasound transducer covered with a saline-filled balloon was brought into contact with the airway wall and moved in all directions to identify the lesions for sampling. Once the target lesion was visualized by ultrasound imaging, needle aspiration using a 22-gauge needle (NA-201SX-4022; Olympus) was performed under real-time EBUS guidance.

The specimen collected at the lumen of the needle was pushed out by a central stylet and then blown by air from a syringe onto a glass slide. The visible tissue fragment on the glass slide was then collected and transferred into separate containers filled with formalin for histologic examination, and the remaining specimen on the glass slide was immediately smeared and fixed in 95% alcohol for cytologic examination. The residual specimen stored at the lumen of the needle and catheter was then washed and flushed into saline for culture for microbiologic analysis. The pathologic specimens obtained by EBUS-TBNA in their containers labeled with the lymph node station[14] were then submitted to the pathologist for interpretation. Rapid on-site cytologic evaluation was not performed. EBUS-TBNA was performed for 2 easily accessible, suspicious, large lymph nodes with 2 punctures at each location.

## TBLB Procedure

After EBUS-TBNA was performed, the EBUS bronchoscope was removed and a standard bronchoscope (BF-1T260; Olympus) was inserted into the trachea. TBLB using a standard-sized biopsy forceps (FB-231D; Olympus) was performed under fluoroscopic guidance. Five visible fragments were obtained from multiple lung segments, typically from both middle and lower lobes in stage I disease and visible parenchymal lesions in stage II disease in a manner similar to that previously described.[4] The pathologic specimens transferred into separate containers filled with formalin were then sent to the pathologist for examination. A chest radiograph was obtained routinely to identify pneumothorax 2 hours after the procedures.

## Diagnosis

Each histologic and cytologic specimen was interpreted separately as "positive," "suspicious," or "negative" for sarcoidosis with noncaseating epithelioid cell granulomas by an experienced pathologist. "Suspicious" findings were regarded as negative in our analysis. The final diagnosis of sarcoidosis was based on the clinicoradiologic compatibility at the time of the procedures, during the clinical follow-up period, as well as the pathological findings of noncaseating granulomas and with the exclusion of other causes of granulomas.

The chest radiographic stage was based on the findings of a posteroanterior chest radiograph or chest CT in patients with obscure radiographic findings for staging. Stage I was defined as hilar and/or mediastinal adenopathy without pulmonary infiltrates and stage II as hilar and/or mediastinal adenopathy with pulmonary infiltrates.

## Data Analysis

Statistical analyses were performed using a statistical software program (PASW Statistics 18; SPSS, Inc, Chicago, Ill). Means and percentages were presented as appropriate. Diagnostic yields or complication rates of both modalities were compared using Fisher's exact test.

# RESULTS

## Patients

A total of 62 patients were enrolled in this study. Characteristics of patients and a diagnostic flow chart were summarized in Table 1 and Figure 1, respectively. Among the 62 patients, 44 (71%) had suspected stage I sarcoidosis and 18 (29%) had suspected stage II sarcoidosis. Both EBUS-TBNA and TBLB were completed in 60 patients, but the procedures were terminated half way in 2 residual patients owing to a severe cough after examining the first lymph node with EBUS-TBNA and moderate bleeding at the initial use of TBLB. EBUS-TBNA and/or TBLB showed noncaseating epithelioid cell granulomas in 51 patients, all of whom were judged to have sarcoidosis from the clinicoradiologic compatibility. The procedures provided a diagnosis of tuberculosis in another 2 patients. Of the remaining 9 patients without definitive pathologic findings, 3 patients with suspected pathologic findings for sarcoidosis or suggestive of ocular sarcoidosis were judged to have sarcoidosis, and 6 patients had other diseases (1 lymphoma, 1 immunoglobulin $G_4$–related lymphadenopathy, 4 nonspecific lymphadenitis). Of the 4 patients given a diagnosis of nonspecific lymphadenitis, 2 patients previously underwent nondiagnostic bronchoscopy and 1 patient underwent

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**TABLE 1. Patient characteristics**

| Characteristics | Data |
|---|---|
| No. of patients | 62; all Japanese |
| Mean age, y (range) | 49.4 ± 15.6 (18-74) |
| Gender (male/female) | 26/36 |
| Smoking history | |
| Never-/ex-/current-smoker | 27/15/20 |
| Main reason for consultation | |
| Chest radiographic abnormalities | 35 |
| Clinical symptoms | 27 |
| (Respiratory/ocular/arrythmia/nonspecific) | (13/10/2/2) |
| Chest radiographic staging | |
| Stage I/II | 44/18 |
| Serum angiotensin-converting enzyme | |
| Elevation/nonelevation | 25/37 |
| Bronchoscopy | |
| Initial bronchoscopy/previous nondiagnostic bronchoscopy | 52/10 |
| Median follow-up duration, mo (range) | 21.5 (1-48) |

Data are presented as number or mean ± standard deviation unless otherwise stated.

nondiagnostic EBUS-TBNA again shortly afterward. All 4 patients showed no clinical or radiologic deterioration during the follow-up period (range, 13-42 months). Thus, a total of 54 patients were given a final diagnosis of sarcoidosis. Median follow-up duration was 21.5 months.

### Diagnostic Yield

A total of 123 lymph nodes with a mean shortest diameter of 16.2 mm (range, 10-33 mm) were examined by EBUS-TBNA. The lymph node locations examined were as follows: station 2R (n = 4), 3p (n = 1), 4R (n = 42), 4L (n = 2), 7 (n = 39), 10R (n = 3), 11R (n = 28), and 11L (n = 4).

EBUS-TBNA confirmed a diagnosis of sarcoidosis by identifying noncaseating epithelioid cell granulomas in 37 (97%) of 38 patients with stage I disease, 14 (88%) of 16 patients with stage II disease, and overall 51 (94%) of 54 patients (Table 2). The sensitivity, specificity, and accuracy of EBUS-TBNA for pathologic diagnosis of sarcoidosis were 94%, 100%, and 95%, respectively. Cytologic specimens contained diagnostic material in 41 (76%) of 54 patients (Figure 2, *A*) and histologic specimens in 42 (78%) of 54 patients (Figure 2, *B*). Among 107 nodal lesions examined in the 54 patients with a final diagnosis of sarcoidosis, noncaseating epithelioid cell granulomas were demonstrated in 91 lesions (85%).

TBLB allowed a pathologic diagnosis of sarcoidosis in 11 (31%) of 36 patients with stage I disease, 8 (50%) of 16 patients with stage II disease, and overall 19 (37%) of 52 patients (Table 2). In stage II disease, TBLB provided diagnostic material in 7 (58%) of 12 patients with bilateral lung lesions and 1 (25%) of 4 with unilateral lung lesions. The sensitivity, specificity, and accuracy of TBLB for pathologic diagnosis of sarcoidosis were 37%, 100%, and 45%, respectively. All 19 patients who were provided diagnostic material from TBLB were also provided diagnostic material from EBUS-TBNA. The diagnostic yield of EBUS-TBNA was significantly higher than that of TBLB in stage I or II sarcoidosis (stage I, $P < .001$; stage II, $P = .027$; overall, $P < .001$).

### Safety

One case of pneumothorax and 3 of moderate bleeding (4/61 patients; 7%) resulted from TBLB; in another case (1/62 patients; 2%) a severe cough during EBUS-TBNA prevented continuation of the bronchoscopy ($P = .21$).

## DISCUSSION

Our study demonstrated that the diagnostic yield of EBUS-TBNA for patients with stage I or II sarcoidosis was significantly higher than that of TBLB. TBLB alone did not provide any information for diagnosis in addition to the results of EBUS-TBNA in our population. Although a few retrospective[3,12] or small prospective[11] studies have been published so far, to the best of our knowledge, this study, which was conducted after our preliminary study[7] and registered with a clinical trials registry in 2006, is quite original in comparing the diagnostic yield of EBUS-TBNA and TBLB by showing noncaseating granulomas for stage I and II sarcoidosis.

Since the development of flexible bronchoscopes in the late 1960s, bronchoscopy including TBLB, EBB, or TBNA has been a conventional technique for the pathologic diagnosis of sarcoidosis.[2,4,15,16] However, despite the widespread use of these conventional procedures, the results are often unsatisfactory. A recent multicenter prospective trial in 2010 with 15 participating institutions demonstrated that the diagnostic yield of bronchoscopy with flexible scopes for sarcoidosis was 45%, even though 40% of patients had stage II-IV disease.[10] The diagnostic yield of TBLB depends on the bronchoscopist's skill, the number of sampled specimens, and the chest radiographic staging. The diagnostic yield of TBLB for stage I sarcoidosis is far from satisfactory. Although the reported yield seems to be acceptable, several investigators commented that the high diagnostic yield of conventional bronchoscopy in patients with suspected sarcoidosis reported in early studies cannot be realized in current daily practice.[6,17] In fact, recent studies[2,3,11,18] have demonstrated that the lower diagnostic yield of TBLB ranged from 12% to 43% for stage I sarcoidosis against a diagnostic yield of more than 70% in early studies.[15,16] Additionally, a recent study suggested the diagnostic yields of TBLB were not different between patients with parenchymal disease (stage 0/I sarcoidosis) and those without it (stage II/III/IV sarcoidosis).[18] The diagnostic yield of TBLB reported in recent publications seems to be lower, and likewise the yield in the present study was lower than in

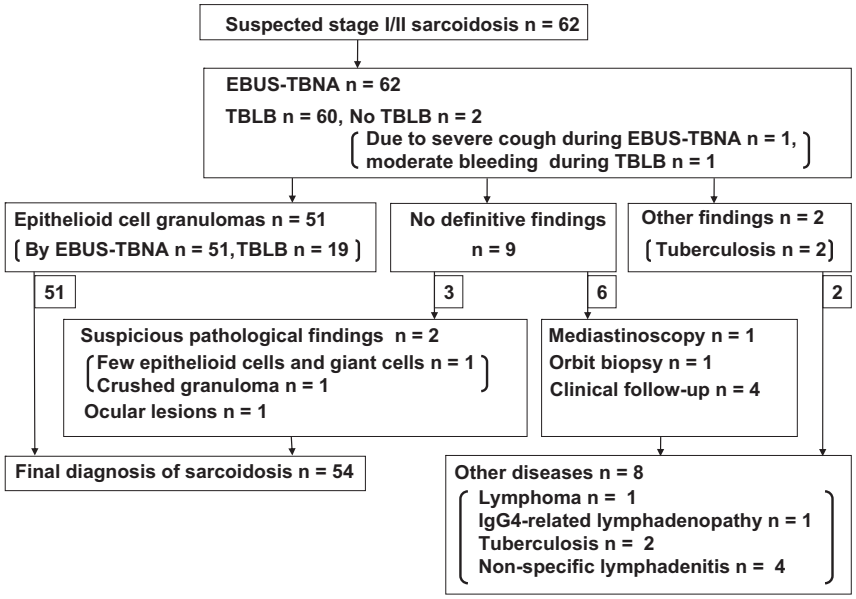


**FIGURE 1.** Diagnostic flow chart. *EBUS-TBNA,* Endobronchial ultrasound–guided transbronchial needle aspiration; *TBLB,* transbronchial lung biopsy; *IgG,* immunoglobulin G.

early studies. The reasons are unclear but may relate to the recent advances in imaging technologies, especially CT technologies. High-resolution CT provides clear thoracic images that serve to identify small, early-stage lesions. Consequently, the opportunities to encounter patients with suspected sarcoidosis, especially early-stage sarcoidosis, seem to be increasing. Although chest CT is considered unnecessary for diagnosis of most patients with sarcoidosis,[1] preprocedural chest CT was obtained in almost all patients enrolled in recent trials, including ours, focusing on bronchoscopic diagnosis of sarcoidosis. The staging of sarcoidosis should be based on the posteroanterior chest radiograph, and the obscure findings of chest radiographs can be clarified by chest CT. Consequently, even in the same stage, recent studies may include more patients with mild abnormalities than earlier ones.

The development of the echo-endoscopes has dramatically changed the way of evaluating mediastinal lesions. The accuracy of transesophageal endoscopic ultrasound–guided fine needle aspiration or EBUS-TBNA for mediastinal lesion has been reported to be extremely high.[5,19-24] In the mediastinal nodal staging in lung cancer, several authors have reported that the sensitivity of either or a combination of these modalities surpasses that of mediastinoscopy, which has been thought to be the "gold standard" for mediastinal exploration.[20,21] These needle aspiration procedures are useful for diagnosing not only malignant disease but also benign disease including sarcoidosis. The sensitivity of endoscopic ultrasound–guided fine needle aspiration and EBUS-TBNA for sarcoidosis has been reported to range from 82% to 100%[10,17,25-27] and 71% to 93%,[3,6-12] respectively. In our study, the diagnostic yield of EBUS-TBNA was 94%, which was consistent with the result of 93% in our preliminary study.[7] Our diagnostic yields are at the higher end of what has been reported before, but they seem not surprisingly high. The reason for our high diagnostic yields may relate to the number of lesions punctured. The diagnostic yield per patient resulted from EBUS-TBNA for 2 lymph nodes, although the diagnostic yield per lesion was 85%. In the study of Wong and associates,[6] the comparable diagnostic yield of 92% in relation to our yield was obtained by EBUS-TBNA for the mean number of 1.2 lymph nodes per patient. Similarly, Nakajima and colleagues[3] demonstrated that the diagnostic yield of 91% resulted from EBUS-TBNA for the mean number of 1.3 lymph nodes per patient. EBUS-TBNA, which is a highly accurate and less invasive method, will surely decrease the need for second diagnostic

**TABLE 2. Diagnostic yield of EBUS-TBNA versus TBLB for sarcoidosis**

| | EBUS-TBNA | | TBLB | | |
|---|---|---|---|---|---|
| **Chest radiographic staging** | **Patients diagnosed/examined (%)** | | **Patients diagnosed/examined (%)** | | ***P* value** |
| Stage I | 37/38 | (97) | 11/36 | (31) | <.001 |
| Stage II | 14/16 | (88) | 8/16 | (50) | .027 |
| Total | 51/54 | (94) | 19/52 | (37) | <.001 |

*EBUS-TBNA,* Endobronchial ultrasound-guided transbronchial needle aspiration; *TBLB,* transbronchial lung biopsy.

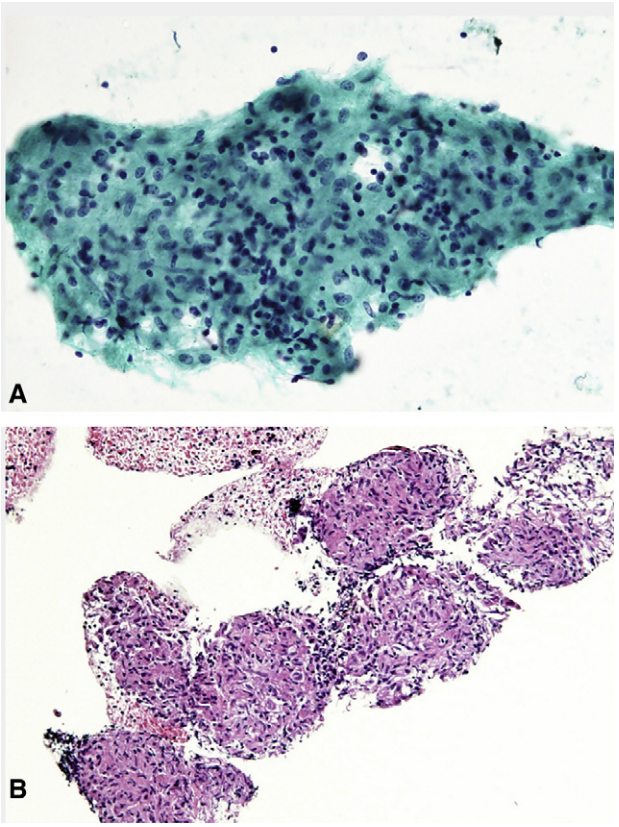


**FIGURE 2.** Specimens obtained by endobronchial ultrasound–guided transbronchial needle aspiration in patients with sarcoidosis. A, Cytologic specimen showing nonnecrotizing epithelioid cell granuloma. (Papanicolaou stain, original magnification ×200.) B, Histologic specimen containing noncaseating epithelioid cell granulomas (hematoxylin and eosin stain, original magnification ×100).

procedures including mediastinoscopy in patients with suspected sarcoidosis. The requirement of a second procedure for patients with a nondiagnostic EBUS-TBNA result depends on the probability of alternative disease. For nonsymptomatic patients with typical clinicoradiologic features of sarcoidosis, close clinical observation may be sufficient,[28] whereas the accuracy of EBUS-TBNA to establish an alternative diagnosis of malignant lymphoma may be insufficient.[29] In our study, 1 patient with negative EBUS-TBNA results underwent mediastinoscopy, which established the diagnosis of lymphoma. In patients with presumptive malignancy as alternative diseases, mediastinoscopy still plays an important role.

To date, a few studies have compared the diagnostic yield of EBUS-TBNA with other bronchoscopic modalities for sarcoidosis.[3,9,11,12] In the study of Tremblay and associates,[9] a total of 50 patients with suspected stage I or II sarcoidosis were randomized to undergo EBUS-TBNA and conventional TBNA using a 19-gauge needle. The diagnostic yield of EBUS-TBNA was significantly higher than that of conventional TBNA (83% vs 54%). In the study of Nakajima and colleagues,[3] the diagnostic yield of EBUS-TBNA, TBLB, and bronchoalveolar lavage for 38 patients with suspected stage I and II sarcoidosis was retrospectively analyzed. They demonstrated that the diagnostic yield of EBUS-TBNA for sarcoidosis was significantly higher than that of TBLB (91% vs 40%). The results of the present study were comparable with those of their retrospective study.

Although our results could not show statistically significant differences owing to the small sample size, EBUS-TBNA appears to have the advantage of a lower complication rate compared with TBLB from previous reports. Pneumothorax and bleeding are widely known complications associated with TBLB with an occurrence rate of 1% to 5% and 9%, respectively.[30] On the other hand, the safety of EBUS-TBNA is widely established. One article reviewing 20 publications on EBUS-TBNA demonstrated no serious complications had occurred.[5] The fact that EBUS-TBNA does not require fluoroscopy may also be a potential advantage over TBLB, which is often performed under fluoroscopy in terms of radiation exposure for both examiner and patients.

The major limitation of our study is the nonrandomized design. In our study, EBUS-TBNA was performed followed by TBLB in a single session in each patient. The order of the procedures might affect the results of the study. Another potential limitation is that we did not perform EBB, which has been reported to play a complementary role to TBLB in terms of diagnostic yield in US studies.[31] TBLB is the standard method for pathologic diagnosis of sarcoidosis in Japan, whereas EBB is somewhat underused because of the limited role for detecting sarcoidosis in Japanese patients.[32] To elucidate in more detail, randomized studies comparing EBUS-TBNA with other biopsy modalities may be required.

In conclusion, the diagnostic yield of EBUS-TBNA for stage I and II sarcoidosis is clearly higher than for TBLB. Although this procedure is available in only a limited number of institutions at the present time, the accumulation of study results on the usefulness of this procedure will lead to its greater availability in the near future. If so, we recommend EBUS-TBNA rather than TBLB for patients in whom stage I or II sarcoidosis is suspected.

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