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Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration vs Conventional Transbronchial Needle Aspiration in the Diagnosis of Sarcoidosis

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BACKGROUND: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is superior to conventional transbronchial needle aspiration (cTBNA) in the staging of lung cancer. However, its efficiency in diagnosis of sarcoidosis when combined with endobronchial biopsy (EBB) and transbronchial lung biopsy (TBLB) has not been studied. This randomized controlled trial compares diagnostic yield of EBUS-TBNA vs cTBNA in combination with EBB and TBLB.

METHODS: Patients with clinical diagnosis of sarcoidosis were randomized 1:1 to EBUS-TBNA or cTBNA. All patients underwent TBLB and EBB. The primary outcome was detection of granulomas. The secondary end points were the individual and cumulative yields of various procedures, serious adverse events, and procedure time.

RESULTS: Of the 130 patients, sarcoidosis was diagnosed in 117 (62 cTBNA, 55 EBUS-TBNA). The two groups were similar at baseline. Granulomas were demonstrated in 104 (53 cTBNA, 51 EBUS-TBNA) patients and were similar in two groups (85.5% vs 92.7%, $P = .34$). Individually, EBUS-TBNA had the highest yield (41 of 55, 74.5%), which was better than cTBNA (30 of 62, 48.4%, $P = .004$) or EBB (40 of 111, 36.3%, $P < .0001$) but not TBLB (78 of 112, 69.6%, $P = .54$). Adding EBB/TBLB to cTBNA led to an increase in granuloma detection, whereas the addition of TBLB (but not EBB) significantly enhanced the yield of EBUS-TBNA. The procedure time was significantly longer with EBUS-TBNA. No major adverse events occurred.

CONCLUSIONS: Individually, EBUS-TBNA has the highest diagnostic yield in sarcoidosis, but it should be combined with TBLB for the optimal yield. The diagnostic yield of cTBNA (plus EBB and TBLB) is similar to EBUS-TBNA plus TBLB.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01908868; URL: www.clinicaltrials.gov

CHEST 2014; 146(3):547-556

Manuscript received October 1, 2013; revision accepted January 2, 2014; originally published Online First January 30, 2014.

ABBREVIATIONS: cTBNA = conventional transbronchial needle aspiration; EBB = endobronchial biopsy; EBUS = endobronchial ultrasound; EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; RCT = randomized controlled trial; ROSE = rapid on-site evaluation; TBLB = transbronchial lung biopsy; TBNA = transbronchial needle aspiration

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FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

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DOI: 10.1378/chest.13-2339

Transbronchial needle aspiration (TBNA) is the procedure of choice for histologic confirmation of sarcoidosis, as the hilar and mediastinal lymph nodes are the most frequent involvement with the disease. Conventional TBNA (cTBNA) has been used for this purpose for > 30 years and has shown variable success.[1,2] The advent of endobronchial ultrasonography to guide TBNA in the early 1990s and availability of real-time convex probe endobronchial ultrasound (EBUS)-guided TBNA (EBUS-TBNA) have revolutionized the use of TBNA in the last decade.[3,4] The seemingly obvious advantage of EBUS-TBNA for sampling intrathoracic lymph nodes with real-time imaging confirming the needle positioned within the lymph node has generated debates on the usefulness of cTBNA in the current scenario.[5,6] The superiority of EBUS-TBNA over cTBNA in staging of lung cancer has been established.[7,8] There are, however, insufficient data to make a comparison between cTBNA and EBUS-TBNA in other conditions.[6]

EBUS-TBNA has been used for obtaining tissue confirmation in sarcoidosis.[9,10] In a meta-analysis of the use of EBUS-TBNA in sarcoidosis, the pooled sensitivity of EBUS-TBNA was 78%.[11] A subsequent large randomized trial, the Granuloma Trial, found endosonographic TBNA better than conventional biopsies in demonstration of granulomas, but it had a sensitivity of 74%, clearly implying that one in four cases

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can be potentially missed if only EBUS-TBNA were to be performed.[12] We have previously shown that bronchoscopic procedures such as cTBNA, transbronchial lung biopsy (TBLB), and endobronchial biopsy (EBB) need to be combined to optimize the yield of bronchoscopy in diagnostic workup of sarcoidosis.[13] Given the high cost and poor availability of EBUS in developing countries, it is of further interest to study the two techniques (cTBNA vs EBUS-TBNA) in a head-to-head fashion, in combination with EBB and TBLB. We hypothesized that EBUS-TBNA should be superior to cTBNA in obtaining pathologic confirmation when combined with EBB and TBLB in patients suspected to have sarcoidosis, and we compare the two TBNA modalities in a randomized controlled trial (RCT).

Materials and Methods

This was a prospective, open-label, investigator-initiated, RCT conducted between November 2011 and December 2012 at a tertiary care research institute in India. The study protocol was approved by the Ethics Review Committee (1Trg/PG-2012/12563-601), and written informed consent was obtained from all subjects.

Patient Selection

Consecutive patients presenting with clinical and radiologic features suggestive of sarcoidosis with an indication for TBNA were eligible for inclusion in the study if they met both the following criteria: (1) age > 18 years and (2) enlarged right paratracheal (station 4R) and subcarinal (station 7) lymph nodes > 10 mm (short axis) on CT scan of the chest. Patients with any of the following were excluded: (1) hypoxemia (oxygen saturation measured by pulse oximetry < 90%) on room air; (2) severely deranged lung function (ie, FVC or FEV_1 < 50% of predicted value); (3) abnormal clotting profile (prothrombin time > 3 s or activated partial thromboplastin time > 10 s above control, respectively; platelet count < 50,000/μL); (4) pregnancy; (5) treatment with systemic glucocorticoids for > 2 weeks in the preceding 3 months; (6) diagnosis of sarcoidosis possible with another minimally invasive technique, such as skin biopsy or peripheral lymph node biopsy; or (7) failure to provide informed consent.

Patients meeting the inclusion criteria were randomized 1:1 to either the EBUS-TBNA or the cTBNA group (Fig 1). The randomization sequence was computer generated, and the assignments were placed in sealed opaque envelopes, opened prior to the procedure. Blinding of procedure was not possible. In both the arms, TBNA, EBB, and TBLB were performed. For patients without a conclusive diagnosis after bronchoscopy, it was optional to perform additional tissue sampling technique (for example, EBUS-TBNA after cTBNA, image-guided lymph node biopsy, and others).

Study Procedure

Basic evaluation included clinical history, physical examination, laboratory tests (tuberculin skin test, CBC count, coagulation profile, liver and renal function tests, serum angiotensin-converting enzyme levels, and HIV serology), ultrasound of the abdomen, spirometry, chest radiography, and CT scan of the chest. Chest radiographs were used to classify the stage of sarcoidosis.[14] CT scan of the chest was used for evaluation of intrathoracic lymph node stations and size and assessment of parenchymal abnormalities.

All bronchoscopy procedures were performed by experienced faculty or by fellows under direct supervision on an outpatient basis in a dedicated bronchoscopy suite. Nebulized 4% lignocaine (2.5 mL), 0.6 mg atropine, and 25 mg promethazine IM were used as premedication. Topical 2% lignocaine jelly was applied into the nasal cavity, and 2% lignocaine was instilled over the vocal cords and the airways. No additional sedation was used in the cTBNA group; IV midazolam and pentazocine were used in the EBUS-TBNA group. Both procedures were performed without the use of endotracheal intubation or laryngeal airway.

EBUS-TBNA (at least three passes per node) was performed in the supine position transorally using the EBUS bronchoscope (BF-UC180F; Olympus Corp) and a dedicated ultrasound image processor (model EU-ME1; Olympus Corp). Lymph node sizes were recorded both in long and short axis (in millimeters). All TBNA specimens were obtained using a dedicated, disposable, 21-gauge needle (Vizishot, NA-201 SX-4021A; Olympus Corp) from the right paratracheal and subcarinal lymph nodes in all subjects. Conventional bronchoscopy was performed in the supine position by transnasal (or oral) route using a video bronchoscope (1T150; Olympus Corp). Any endobronchial mucosal changes in the bronchial tree were recorded. cTBNA (at least three passes per node) was performed using a 21-gauge needle (Smooth Shot, NA-401D 1321; Olympus Corp) from the right paratracheal and subcarinal lymph nodes. Rapid on-site evaluation (ROSE) was not used in either arm of the study.

Patients in both arms further underwent EBB and TBLB. EBB (at least four specimens) was performed with an alligator biopsy forceps (FB15C;

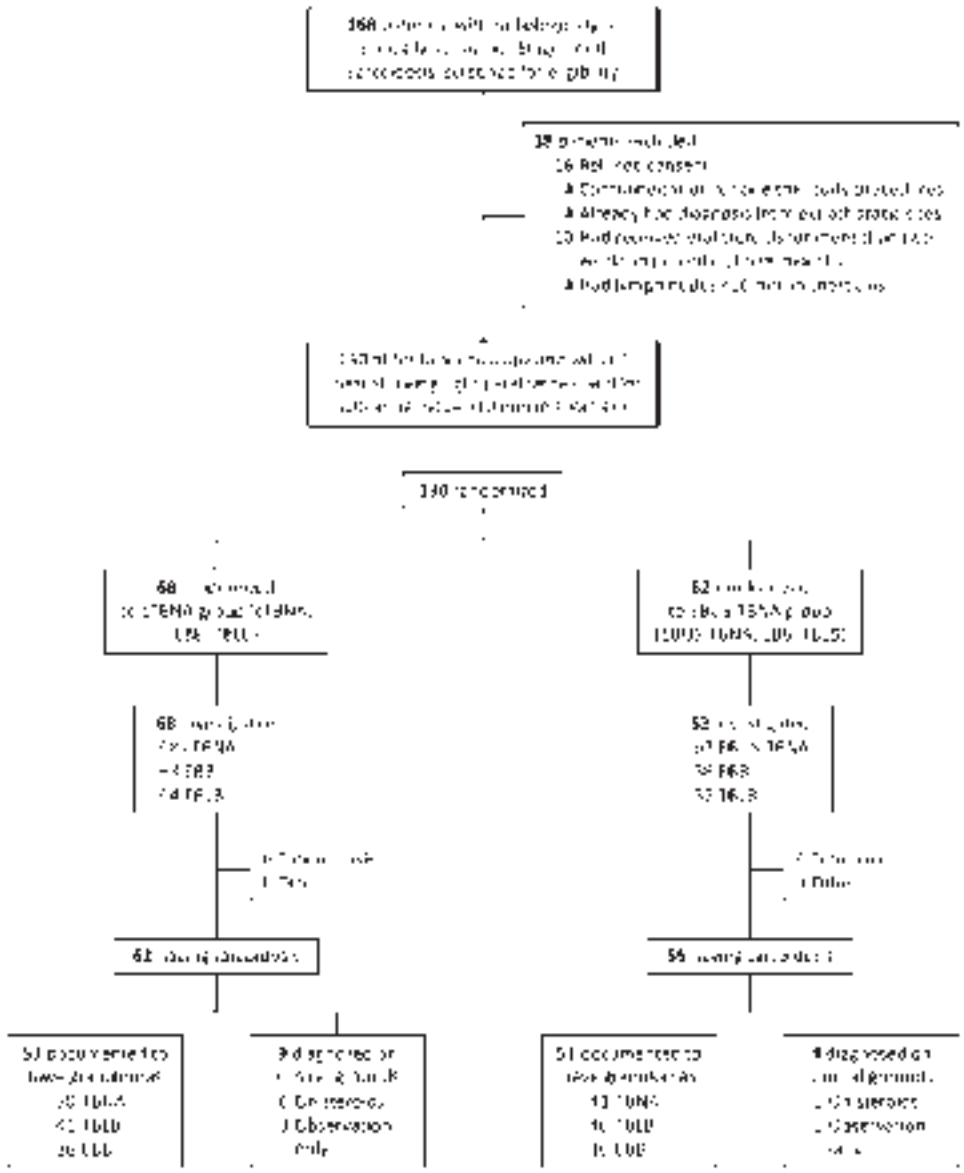

Figure 1 – *CONSORT diagram demonstrating the flow of participants in the study. cTBNA = conventional transbronchial needle aspiration; EBB = endobronchial biopsy; EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; TBLB = transbronchial lung biopsy; TBNA = transbronchial needle aspiration.*

Olympus Corp) from the abnormal-looking areas, if any, or from secondary carinal areas. TBLB (at least four specimens) were obtained with the cup biopsy forceps (FB19C; Olympus Corp) from the site of maximal involvement on CT chest scan or from the right lower lobe, if the CT chest scan was normal. No fluoroscopic guidance was used for TBLB.

Patients were observed for at least 6 hours after bronchoscopy. In all patients, a chest radiograph and ultrasound of the chest were performed to exclude pneumothorax.

Specimen Preparation

Slides were prepared from the TBNA specimen, immediately fixed in 95% alcohol, and promptly transported to the laboratory. The aspirate was also cultured for mycobacteria (mycobacterial growth indicator tube technique) and fungi. EBB and TBLB were fixed with formalin and submitted for histopathological examination. Biopsy and TBNA slides were additionally stained with Ziehl-Neelsen (for mycobacteria) and fungal stains.

Diagnosis of Sarcoidosis

The diagnosis of sarcoidosis was made using the European Respiratory Society/American Thoracic Society/World Association of Sarcoidosis and Other Granulomatous Disorders consensus statement (clinical and radiologic compatibility, presence of noncaseating granulomas, and the exclusion of similar presenting diseases). Patients were followed up clinically and radiologically for at least 6 months after randomization, and the diagnosis after 6 months was considered the final diagnosis.[15]

In the absence of demonstration of granulomas from any site, the diagnosis of sarcoidosis was made on the clinico-radiologic picture consistent with sarcoidosis and good response to empirical corticosteroid therapy or spontaneous resolution of symptoms, with no alternate diagnosis made at follow-up of at least 6 months.

End Points

The primary end point was the detection of granulomas (diagnostic yield) by any bronchoscopic procedure (TBNA, TBLB, or EBB) in

patients finally diagnosed to have sarcoidosis. The secondary end points were the diagnostic yield of individual procedures, rate of serious adverse events (pneumothorax, pulmonary hemorrhage of at least 100 mL, mediastinal infection, and death), and time taken for the procedure.

Sample Size

The sample size was calculated based on a reported yield of 95% in the EBUS-TBNA arm and a difference of 20% in the cTBNA arm (ie, 75%). With these assumptions, 59 patients would be required in each arm (confidence level [$1-\alpha$], 95%; power level [$1-\beta$], 80%) to detect the differences. Assuming 10% prevalence of other disorders, a minimum sample size of 129 was chosen.

Statistical Analysis

Data were analyzed using SPSS, version 21.0 (IBM). Statistical significance was assumed at a $P < .05$. The differences between categorical variables were analyzed using χ^2 test or Fisher exact test, and the differences between continuous variables were analyzed using the Mann-Whitney *U* test. The analysis was an intention-to-treat based on final diagnosis.

Results

Of the 168 consecutive patients with clinico-radiologic suspicion of sarcoidosis, 38 were excluded before randomization (16 refused consent, four had contraindications for the study procedure, four already had diagnosis from extrathoracic sites, 10 had received steroids for > 2 weeks in the preceding 3 months, and four had lymph node size < 10 mm on CT scan of the chest). Finally, 130 patients were randomized to either the cTBNA (68 patients) or the EBUS-TBNA group (62 patients). A final diagnosis of sarcoidosis was established in 117 patients (62 cTBNA, 55 EBUS-TBNA) groups. Of these, granulomatous inflammation could be demonstrated in 104 patients, and sarcoidosis was diagnosed in 13 (nine in cTBNA and four in EBUS-TBNA groups) on clinical grounds (eight responded to steroid treatment, and five had spontaneous resolution with no alternative diagnosis on follow-up). Disorders other than sarcoidosis were diagnosed in 13 patients (12 TB, one carcinoma) (Fig 1).

The baseline characteristics were similar in the two groups (Table 1). The mean age was 43.4 (range, 18-68) years, and 60% were women. Seven patients (5.4%) were asymptomatic, 21 (16.2%) had only pulmonary symptoms, 34 (26.2%) presented with extrapulmonary symptoms, and 68 (52.3%) had both pulmonary and extrapulmonary symptoms. Cough and dyspnea were the predominant pulmonary symptoms. Fever, weight loss, and fatigue were the most common extrapulmonary symptoms. Common extrathoracic organs involved were joints, eyes, and skin. Spirometry was available in 122 subjects and was normal in the majority (58.8%). Tuberculin skin test result was negative (< 10 mm) in 87.7% of the study subjects and was negative in 96.5% in those finally confirmed to have sarcoidosis. Radiologically, stage I disease was seen in 76.9% (75% and 79% in the cTBNA and EBUS-TBNA arms, respectively) of patients on chest radiograph, whereas 56.2% of patients (58.9% in cTBNA group and 53.2% in EBUS-TBNA group) had pulmonary infiltrates on high-resolution CT scans. The mean short-axis diameter of the paratracheal (station 4R) nodes was the same in the two groups (19.8 mm), whereas subcarinal (station 7) nodes were marginally bigger in the EBUS-TBNA group compared with the cTBNA group (20.8 ± 5.9 mm vs 19.2 ± 6.9 mm, $P = .05$).

Bronchoscopy was normal in the majority, and mucosal abnormalities (diffuse or focal granularity) were seen in 25.4% patients (27.9% in the cTBNA group and 22.6% in the EBUS-TBNA group). Besides TBNA, EBB and TBLB were performed in 121 patients. Among the patients in whom sarcoidosis was finally diagnosed (n = 117), EBB was not available in six patients (four in cTBNA and two in EBUS-TBNA arms, respectively), and TBLB was not available in five patients (two in cTBNA and three in EBUS-TBNA arms, respectively).

The primary outcome (ie, demonstration of granulomatous inflammation on any of the three sampling procedures) was achieved in 104 patients (88.9%). Diagnostic yield in the EBUS-TBNA group was numerically higher than the cTBNA group (92.7% vs 85.5%), but this difference was not significant statistically ($P = .34$). Individually, EBUS-TBNA had the highest diagnostic yield (41 of 55, 74.5%), which was significantly higher than cTBNA (30 of 62, 48.4%, $P = .004$) or EBB (40 of 111, 36.3%, $P \leq 0.0001$) but not TBLB (78 of 112, 69.6%, $P = .540$). Combining EBB or TBLB with TBNA in either group increased the diagnostic yields of TBNA to the point that the superiority of EBUS-TBNA over cTBNA was no longer significant (Table 2). In the cTBNA group, addition of any of the two biopsies led to significant increase in the granuloma detection rate of cTBNA (30 of 62) alone (vs cTBNA plus EBB: 45 of 62, $P = .006$; vs cTBNA plus TBLB: 49 of 62, $P = .0004$; vs cTBNA plus EBB and TBLB: 55 of 62, $P < .0001$). However, in the EBUS-TBNA group, the addition of TBLB alone led to significant increase in the sensitivity

TABLE 1] Baseline Characteristics of the Study Population

Characteristics	Conventional TBNA Group (n = 68)	EBUS-TBNA Group (n = 62)	Total (N = 130)	*P* Value
Age, mean (SD), y	42.9 (11.5)	44.1 (10.8)	43.4 (11.1)	.54
Male sex	27 (39.7)	26 (41.9)	53 (40.8)	.80
Symptoms				
Cough	36 (52.9)	40 (64.5)	76 (58.5)	.75
Dyspnea	26 (38.2)	23 (37.1)	49 (37.7)	.89
Fever	21 (30.9)	25 (40.3)	46 (35.4)	.26
Weight loss	18 (26.5)	24 (38.7)	42 (32.3)	.19
Anorexia	14 (20.6)	19 (30.6)	33 (25.4)	.26
Fatigue	15 (22.1)	13 (21)	28 (21.5)	.88
Arthralgia	17 (25)	10 (16.1)	27 (20.8)	.21
Red eye	11 (16.2)	5 (8.1)	16 (12.3)	.26
Chest pain	7 (10.3)	7 (11.3)	14 (10.8)	.86
Expectoration	8 (11.8)	6 (9.7)	14 (10.8)	.70
Myalgia	5 (7.4)	1 (1.6)	6 (4.6)	.92
Others	12 (17.6)	14 (22.6)	26 (20)	.48
Spirometry				
Normal	40 (58.8)	36 (58.1)	76 (58.5)	.97
Obstructive defect	16 (23.5)	14 (22.6)	30 (23.1)	…
Restrictive defect	12 (17.7)	12 (19.3)	24 (18.4)	…
Sarcoidosis stage based on chest radiograph				
Stage I	51 (75)	49 (79)	100 (76.9)	.59
Stage II	17 (25)	13 (21)	30 (23.1)	…
CT scan of chest findings				
Normal lung parenchyma	28 (41.1)	29 (46.8)	57 (43.8)	.52
Pulmonary opacities	40 (58.9)	33 (53.2)	73 (56.2)	…
Lymph node size on CT scan, short axis, mean (SD), mm				
Station 4R	19.8 (7.6)	19.8 (7.2)	19.8 (7.3)	.78
Station 7	19.2 (6.9)	20.8 (5.9)	19.9 (6.6)	.05
Elevated serum ACE levels	35 (51.5)	38 (61.3)	73 (56.2)	.26
TST negativity	61 (89.7)	53 (85.5)	114 (87.7)	.46
Abnormal mucosa on bronchoscopy	19 (27.9)	14 (22.6)	33 (25.4)	.48

All values are presented as No. (%) unless otherwise stated. ACE = angiotensin-converting enzyme; EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; TBNA = transbronchial needle aspiration; TST = tuberculin skin test.

of EBUS-TBNA (41 of 55 with EBUS alone vs 50 of 55 with EBUS plus TBLB, $P = .045$); adding EBB to EBUS-TBNA or EBUS-TBNA plus TBLB did not have significant additive effect (41 of 55 vs 45 of 55 for EBUS alone vs EBUS plus EBB, $P = .489$; 50 of 55 vs 51 of 55 for EBUS plus EBB and EBUS plus EBB and TBLB, $P > .99$). There was no difference in procedural yields in subgroups stratified by parenchymal abnormality on CT scan of the chest or visible abnormality of endobronchial mucosa on bronchoscopy (Table 3).

The procedure time was significantly longer in the EBUS-TBNA group (mean [SD], 33.5 [5.6] min vs 22.9 [3.9] min; $P = .0001$). There were no major adverse events. Three patients (2.3%) (one with cTBNA and two with EBUS-TBNA) had minor bleeding, but none of them required blood transfusion, and only one patient (0.8%)

TABLE 2] Study Outcomes

Outcome	Conventional TBNA Group (n = 62)	EBUS-TBNA Group (n = 55)	*P* Value
Primary outcome			
TBNA plus TBLB and EBB[a]	53 of 62 (85.5)	51 of 55 (92.7)	.34
Secondary outcomes			
TBNA	30 of 62 (48.4)	41 of 55 (74.5)	.004
EBB	26 of 58 (44.8)	14 of 53 (26.4)	.04
TBLB	40 of 60 (66.7)	38 of 52 (73.1)	.46
TBNA plus EBB[a]	45 of 62 (72.6)	45 of 55 (81.8)	.24
TBNA plus TBLB[a]	49 of 62 (79.0)	50 of 55 (90.9)	.16

All values are presented as n of N (%). EBB = endobronchial biopsy; TBLB = transbronchial lung biopsy. See Table 1 legend for expansion of other abbreviations.
[a]Based on intention to treat analysis.

(in the EBUS-TBNA group) developed a small pneumothorax following TBLB, which was managed with supplemental oxygen.

Discussion

This study found that EBUS-TBNA had the highest diagnostic yield compared with conventional bronchoscopic procedures like cTBNA or EBB but not TBLB. The yield of EBUS-TBNA was significantly enhanced with the addition of TBLB (but not EBB). In fact, when EBB and TBLB were combined with either EBUS-TBNA or cTBNA, the achieved diagnostic yield was similar.

In our study, 77% of the study subjects were classified as stage I on chest radiograph, whereas the prevalence of stage I was 44% if CT scan of the chest is used for staging sarcoidosis. In general, there is no indication of tissue confirmation of stage I sarcoidosis if the patient is asymptomatic with negative physical findings.[16-21] It has also been suggested that patients with erythema nodosum and uveitis and bilateral hilar adenopathy also may not need tissue confirmation.[10,16] However, in developing countries, this clinical presentation can also be encountered in TB, which makes tissue diagnosis imperative.[22,23] Even in the current study, tissue confirmation was attempted only in symptomatic patients. In the seven asymptomatic cases, tissue confirmation was attempted for specific purposes (requirement of ruling out TB for overseas immigrant visa application or as part of preemployment medical requirements). Moreover, of the 130 cases of "clinical sarcoidosis" in this study, 12 (9.2%) turned out to be TB. It would have significantly delayed establishing the correct diagnosis in

TABLE 3] Results of Various Procedures Stratified by Parenchymal Abnormalities on CT Chest Scan and Visible Endobronchial Abnormalities on Bronchoscopy

	CT Scan Evidence of Parenchymal Abnormalities		Visible Endobronchial Abnormality on Bronchoscopy		
Procedure	Absent (n = 54)	Present (n = 63)	Absent (n = 89)	Present (n = 28)	Total (N = 117)
EBB	17 (31.5)	23 (36.5)	26 (29.2)	14 (50.0)	40 (34.2)
TBLB	33 (61.1)	45 (71.4)	57 (64.0)	21 (75.0)	78 (66.7)
TBNA (either)	34 (62.9)	37 (58.7)	56 (62.9)	15 (53.6)	71 (60.7)
cTBNA	14 (25.9)	16 (25.4)	21 (23.6)	9 (32.1)	30 (25.6)
EBUS-TBNA	20 (37.0)	21 (33.3)	35 (39.3)	6 (21.5)	41 (35.1)
TBNA plus EBB	42 (77.8)	48 (76.2)	67 (75.3)	23 (82.1)	90 (82.1)
TBNA plus TBLB	44 (81.5)	55 (87.3)	74 (83.1)	25 (89.3)	99 (84.6)
EBB plus TBLB	37 (68.5)	47 (74.6)	62 (69.7)	22 (78.6)	84 (71.8)
TBNA plus EBB and TBLB	47 (87.0)	57 (90.5)	78 (87.6)	26 (92.9)	104 (88.9)

All values are presented as No. (%). There was no difference in procedural yield in subgroup stratified by parenchymal and visible abnormality on CT scan of the chest and bronchoscopy, respectively. cTBNA = conventional transbronchial needle aspiration. See Table 1 and 2 legends for expansion of other abbreviations.

these patients with a conservative approach. We do, however, believe that in the areas of the world where TB is less prevalent, a more discriminatory approach would be acceptable. Furthermore, we also are of the opinion that it is extremely rare to find lymphoma among the patients presenting with typical signs and symptoms of stage I sarcoidosis.[16,17]

EBUS-TBNA has enriched the diagnostic armamentarium by enabling sampling of mediastinal lymph nodes under direct visualization. Besides being extensively studied for lung cancer staging, its efficacy and safety in obtaining tissue diagnosis in sarcoidosis has also been reported.[7,11] However, only a few studies have compared the performance of EBUS-TBNA with other conventional bronchoscopy procedures (Table 4).[12,24-29] Most of these studies have been observational, few have analyzed cumulative yields of EBUS-TBNA with other procedures, and no study, to our knowledge, has looked at the cumulative yields of all the three procedures in a randomized fashion.

In a small prospective study, Oki et al[24] performed cTBNA from the puncture site visible after EBUS-TBNA and found similar yield (93%) with the two procedures and a cumulative yield of 100%. In another observational study in which conventional bronchoscopy was performed after EBUS-TBNA, it was shown that EBUS-TBNA had a diagnostic sensitivity of 82%, which could be increased to 93% if results of TBLB and EBB were combined with EBUS results.[25] However, cTBNA was not part of this study, and the yield of TBLB was much lower (31%) than that reported in the literature ($>60\%$).[30,31] Plit et al[28] found no difference between the diagnostic accuracy of EBUS-TBNA and TBLB (84% vs 78%, $P = .77$), and together the two procedures could diagnose disease in all the 37 patients studied retrospectively. In two separate studies, Nakajima et al[26] and Oki et al[29] performed TBLB following EBUS-TBNA in 35 and 62 patients, respectively, and found EBUS and TBLB to have a sensitivity of 63% and 31%, and 94% and 37%, respectively; however, the cumulative yield was not reported.

Two RCTs have compared EBUS-TBNA with conventional bronchoscopy. Tremblay et al[27] reported 83% yield with EBUS-TBNA compared with 54% with cTBNA. About 50% of the study population also underwent EBB or TBLB, and, interestingly, the cumulative yield of all bronchoscopic samples was 81% in cTBNA compared with 92% in EBUS-TBNA arm, which was not statistically different.[27] The study was limited by the small sample size (50 patients), and TBLB and EBB were not performed in all the subjects. Subsequently, another larger RCT (Granuloma Trial) has also shown that EBUS or endoscopic ultrasound-guided mediastinal lymph node sampling could detect granulomas in higher proportion of patients (74%) compared with conventional TBLB and EBB (48%).[12] However, the study did not combine TBLB and/or EBB to TBNA, and cTBNA was not performed in the conventional bronchoscopy arm, which should be considered a major limitation of the study.[32,33] Besides, the authors relied more on endoscopic ultrasound than EBUS: The former is seldom performed by the pulmonologists around the world.[21] We have compared EBUS-TBNA head-to-head with cTBNA using the same gauge needles (21 gauge) in both arms, and TBLB/EBB was performed in nearly all the patients. An adequate number of nodal passes and biopsies were performed. Our diagnostic yields of individual procedures (EBUS, cTBNA, TBLB, and EBB) are similar to the diagnostic yields accepted for these procedures, and the overall combined yields are also comparable to the best reported.

Prior to the availability of EBUS, cTBNA and TBLB have been the procedures of choice for diagnosis of sarcoidosis. However, they have been mired with fears of poor yield and complications.[34,35] We observed only one minor pneumothorax in 121 patients who underwent TBLB, and this has been our experience in the past also, wherein we have encountered this problem in $<1\%$ of patients,[31] even though rates up to 4% are described in the literature.[35] In a recent meta-analysis, we found acceptable diagnostic yield (62%) of conventional TBNA in sarcoidosis with practically no complications reported in >900 patients.[36] Also, the cumulative yield of TBNA and TBLB was 83%,[36] a result replicated in the present study.

Finally, our study is not without limitations. We chose only lymph nodes in the right paratracheal and subcarinal locations and only those that were >10 mm in size. This could have excluded patients with smaller nodes and difficult stations, where EBUS would presumably be better than cTBNA. However, this was a pragmatic RCT, wherein our aim was to be close to the real-world situation in sarcoidosis, where lymph nodes are bulky and most often located in these two stations. This is also supported by the fact that only four out of 168 patients (2.3%) screened were excluded due to the small size of nodes. We also did not use ROSE in our diagnostic protocol. Although ROSE does not increase

TABLE 4] Summary of Studies Comparing EBUS-TBNA With Conventional Bronchoscopy in Diagnosis of Sarcoidosis

Study/Year	Study Design	No. of Patients	Inclusion Criteria	Study Protocol	Needle Size	Lymph Node Location and Size on EBUS	Sensitivity
Oki et al[24]/2007	Prospective study	15	Stage I and II	EBUS-TBNA followed by cTBNA at same site of EBUS	EBUS: 22 cTBNA:19	12-38 mm	EBUS-TBNA: 13 of 14 (93%); cTBNA: 13 of 14 (93%); both: 14 of 14 (100)
Nakajima et al[26]/2009	Retrospective study	35	Stage I and II	Conventional bronchoscopy (BAL, TBLB) followed by EBUS-TBNA	22	4R: 14.2 (7.3-23.8). 7: 18 (10.1-30). 11: 12.3 (8-16.7). mean (range)	EBUS-TBNA: 22 of 35 (63%); TBLB: 14 of 35 (31%)
Tremblay et al[27]/2009	Prospective RCT of EBUS-TBNA vs cTBNA	50	Stage I and II	cTBNA/EBUS-TBNA: 3-5 passes/node; 4 LN groups in EBUS vs 2 in cTBNA; total No. of passes, mean 10.1 vs 8.7. EBB: 50% patients in both groups. TBLB: 38% and 40%, respectively, in cTBNA and EBUS-TBNA	EBUS: 22; cTBNA: 19	Size 17.9 (4.8) vs 16.5 (5.0); mean (SD) LN at discretion	EBUS-TBNA: 20 of 24 (83%); cTBNA: 14 of 26 (54%). Procedure time, 10 min longer. All bronchoscopy samples: 21 of 26 (81%) cTBNA vs 22 of 24 (92%) EBUS-TBNA
Navani et al[25]/2011	Prospective observational study	40	Stage I and II	4 passes EBUS-TBNA; 4-6 TBLB; 4 EBB EBUS-TBNA followed by conventional bronchoscopy	22	24 mm (10-35) median (range); 4R (n = 21) and 7 (n = 35) most common accessed followed by 10R, 4L, and 10L	EBUS-TBNA: 23 of 27 (82%); EBB: 3 of 27 (11%); TBLB: 8 of 27 (31%); EBUS plus EBB/TBLB: 25 of 27 (93%); EBB plus TBLB: 9 of 27 (35%)
Plit et al[28]/2012	Retrospective study	37	Stage I and II	Median 5 (range, 1-3) EBUS; 4-12 TBLB, 4 EBB; EBUS followed by conventional	22	16 mm (8-36), median (range), 7 most common	EBUS: 31 of 37 (84%); EBB: 10 of 37 (27%); TBB: 29 of 37 (78%); TBB + EBUS: 37 of 37 (100%); EBB + TBB + EBUS: NA
Oki et al[29]/2012	Prospective study of EBUS followed by TBLB	62	Stage I and II	EBUS-TBNA followed by TBLB; EBUS: 2 punctures, 2 lymph nodes; 5 TBLB	22	4R and 7 most common	EBUS-TBNA: 51 of 54 (94%); TBLB: 19 of 52 (37%)
von Bartheld et al[12]/2013	Prospective multicenter RCT of EBUS/EUS-TBNA vs conventional bronchoscopy (EBB + TBB)	304	Stage I and II	At least 4 nodal aspirates; at least 4 EBB and TBLB	22	Nodal status not available	Endosonography: 114 of 154 (74%); conventional: 72 of 149 (48%)

EBUS = endobronchial ultrasound; EUS-TBNA = endoscopic ultrasound-guided transbronchial needle aspiration; LN = lymph node; NA = not available; RCT = randomized controlled trial; TBB = transbronchial (lung) biopsy. See Table 1, 2, and 3 legends for expansion of other abbreviations.

the sensitivity of TBNA,[11] it does reduce the incidence of complications, since it reduces the number of passes.[22] In the specific context of our study, a positive ROSE after TBNA could have enabled us to avoid TBLB, reducing time and the related risks. Finally, although the sample size was calculated a priori, the presumed difference in the diagnostic yield of 20% between the two study arms was not seen. Therefore, the results may need to be verified in a larger, preferably multicenter trial.

What are the clinical implications of this study? EBUS-TBNA is undoubtedly the single best procedure to obtain histopathological proof in sarcoidosis, but it needs to be combined with TBLB for the best diagnostic yield. Also, if EBUS-TBNA is not available, cTBNA (with EBB and TBLB) may be used with equal efficacy. Thus, nonavailability of EBUS should not belittle the pulmonologists seeking to diagnose sarcoidosis; as aptly said by Trisolini et al,[37] "While waiting to buy a Ferrari, do not leave your current car in the garage!"

Acknowledgments

Author contributions: D. G. is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. D. G. contributed to conceiving the idea, patient management, and drafting and revising the manuscript for intellectual content; D. S. D. contributed to patient management, data collection, and drafting the manuscript; R. A. contributed to patient management and drafting and revising the manuscript; N. G. and A. B. contributed to patient management and revising the manuscript; and A. N. A. contributed to patient management, data analysis, and revising the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

References

1. Wang KP, Nelson S, Scatarige J, Siegelman S. Transbronchial needle aspiration of a mediastinal mass: therapeutic implications. *Thorax*. 1983;38(7):556-557.
2. Wang KP, Terry P, Marsh B. Bronchoscopic needle aspiration biopsy of paratracheal tumors. *Am Rev Respir Dis*. 1978;118(1):17-21.
3. Hürter T, Hanrath P. Endobronchial sonography: feasibility and preliminary results. *Thorax*. 1992;47(7):565-567.
4. Yasufuku K, Chhajed PN, Sekine Y, et al. Endobronchial ultrasound using a new convex probe: a preliminary study on surgically resected specimens. *Oncol Rep*. 2004;11(2):293-296.
5. Huang JA, Browning R, Wang KP. Counterpoint: should endobronchial ultrasound guide every transbronchial needle aspiration of lymph nodes? No. *Chest*. 2013;144(3):734-737.
6. Wahidi MM, Yasufuku K. Point: should endobronchial ultrasound guide every transbronchial needle aspiration of lymph nodes? Yes. *Chest*. 2013;144(3):732-734.
7. Adams K, Shah PL, Edmonds L, Lim E. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. *Thorax*. 2009;64(9):757-762.
8. Holty JE, Kuschner WG, Gould MK. Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis. *Thorax*. 2005;60(11):949-955.
9. Wong M, Yasufuku K, Nakajima T, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. *Eur Respir J*. 2007;29(6):1182-1186.
10. Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. *Chest*. 2007;132(4):1298-1304.
11. Agarwal R, Srinivasan A, Aggarwal AN, Gupta D. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: a systematic review and meta-analysis. *Respir Med*. 2012;106(6):883-892.
12. von Bartheld MB, Dekkers OM, Szlubowski A, et al; The GRANULOMA Randomized Clinical Trial. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. *JAMA*. 2013;309(23):2457-2464.
13. Goyal A, Gupta D, Agarwal R, et al. Value of different bronchoscopic sampling techniques in diagnosis of sarcoidosis: a prospective study of 151 patients. *J Bronchology Interv Pulmonol*. In press.
14. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. *BMJ*. 1961;2(5261):1165-1172.
15. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med*. 1999;160(2):736-755.
16. Winterbauer RH, Belic N, Moores KD. Clinical interpretation of bilateral hilar adenopathy. *Ann Intern Med*. 1973;78(1):65-71.
17. Reich JM, Brouns MC, O'Connor EA, Edwards MJ. Mediastinoscopy in patients with presumptive stage I sarcoidosis: a risk/benefit, cost/benefit analysis. *Chest*. 1998;113(1):147-153.
18. Reich JM. Tissue confirmation of presumptive stage I sarcoidosis. *J Bronchology Interv Pulmonol*. 2013;20(2):103-105.
19. Culver DA, Costabel U. EBUS-TBNA for the diagnosis of sarcoidosis: is it the only game in town? *J Bronchology Interv Pulmonol*. 2013;20(3):195-197.
20. Ribeiro Neto ML, Culver DA, Mehta AC. Sarcoidosis—no business of the bronchoscopist. *J Thorac Cardiovasc Surg*. 2012;144(5):1276-1277.
21. Narula T, Baughman RP, Mehta AC. Sarcoidosis Americana-route Europa. *J Bronchology Interv Pulmonol*. 2013;20(4):293-296.
22. Garg S, Malaviya AN, Kapoor S, Rawat R, Agarwal D, Sharma A. Acute inflammatory ankle arthritis in northern India—Löfgren's syndrome or Poncet's disease? *J Assoc Physicians India*. 2011;59:87-90.
23. Gupta A, Bansal R, Gupta V, Sharma A, Bambery P. Ocular signs predictive of tubercular uveitis. *Am J Ophthalmol*. 2010;149(4):562-570.
24. Oki M, Saka H, Kitagawa C, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. *Respirology*. 2007;12(6):863-868.
25. Navani N, Booth HL, Kocjan G, et al. Combination of endobronchial ultrasound-guided transbronchial needle aspiration with standard bronchoscopic techniques for the diagnosis of stage I and stage II pulmonary sarcoidosis. *Respirology*. 2011;16(3):467-472.
26. Nakajima T, Yasufuku K, Kurosu K, et al. The role of EBUS-TBNA for the diagnosis of sarcoidosis–comparisons with other bronchoscopic diagnostic modalities. *Respir Med*. 2009;103(12):1796-800.
27. Tremblay A, Stather DR, Maceachern P, Khalil M, Field SK. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients

with suspected sarcoidosis. *Chest*. 2009;136(2):340-346.

28. Plit M, Pearson R, Havryk A, Da Costa J, Chang C, Glanville AR. Diagnostic utility of endobronchial ultrasound-guided transbronchial needle aspiration compared with transbronchial and endobronchial biopsy for suspected sarcoidosis. *Intern Med J*. 2012;42(4):434-438.
29. Oki M, Saka H, Kitagawa C, et al. Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis. *J Thorac Cardiovasc Surg*. 2012;143(6):1324-1329.
30. Gilman MJ. Transbronchial biopsy in sarcoidosis. *Chest*. 1983;83(1):159.
31. Gupta D, Behera D, Joshi K, et al. Role of fiberoptic bronchoscopy (transbronchial lung biopsy) in diagnosis of parenchymatous lung diseases. *J Assoc Physicians India*. 1997;45(5):371-373.
32. Madan K, Guleria R. Comparison of methods to diagnose sarcoidosis. *JAMA*. 2013;310(15):1624.
33. Annema JT. Comparison of methods to diagnose sarcoidosis—reply. *JAMA*. 2013;310(15):1625-1626.
34. Dasgupta A, Mehta AC. Transbronchial needle aspiration. An underused diagnostic technique. *Clin Chest Med*. 1999;20(1):39-51.
35. Bradley B, Branley HM, Egan JJ, et al; British Thoracic Society Interstitial Lung Disease Guideline Group, British Thoracic Society Standards of Care Committee; Thoracic Society of Australia; New Zealand Thoracic Society; Irish Thoracic Society. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax*. 2008;63(suppl 5):v1-v58.
36. Agarwal R, Aggarwal AN, Gupta D. Efficacy and safety of conventional transbronchial needle aspiration in sarcoidosis: a systematic review and meta-analysis. *Respir Care*. 2013;58(4):683-693.
37. Trisolini R, Patelli M, Gasparini S. While waiting to buy a Ferrari, do not leave your current car in the garage! *Respiration*. 2010;79(6):452-453.