Endobronchial ultrasound increases the diagnostic yields of polymerase chain reaction and smear for pulmonary tuberculosis

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Objectives: Our objective was to determine the contribution of endobronchial ultrasound in the diagnostic yields of acid-fast bacillus smear, nucleic acid amplification tests, and culture in bronchoalveolar lavage fluid for pulmonary tuberculosis.

Methods: During a 1-year interval, 99 patients who had initial sputum-negative acid-fast bacillus smears or no sputum but were later proven to have a positive culture for *Mycobacterium tuberculosis* in their sputum or bronchoalveolar lavage fluid were retrospectively studied. Among them, 56 patients underwent bronchoscopy with endobronchial ultrasound (EBUS group) and 43 patients received conventional bronchoscopy for bronchoalveolar lavage (non-EBUS group).

Results: The diagnostic yields of the nucleic acid amplification tests (89.3%, 50/56; $P = .006$), acid-fast bacillus smear (30.4%, 17/56; $P = .013$), and *M tuberculosis* culture in bronchoalveolar lavage fluid (67.9%, 38/56; $P = .041$) were significantly higher in the EBUS group of patients. The results of those who underwent conventional bronchoscopy were 65.1% (28/43), 9.3% (4/43), and 46.5% (20/43), respectively. Combining bronchoalveolar lavage fluid smear and nucleic acid amplification tests, we made a rapid diagnosis of pulmonary tuberculosis in 51 (91.1%) of the 56 EBUS patients and 29 (67.4%; $P = .004$) of the 43 non-EBUS patients.

Conclusions: The introduction of endobronchial ultrasound increases the diagnostic yield of the nucleic acid amplification tests, acid-fast bacillus smear, and *M tuberculosis* culture from bronchoalveolar lavage fluid in patients with pulmonary tuberculosis who have negative sputum smear or no sputum production. (J Thorac Cardiovasc Surg 2010;139:1554-60)

The definitive diagnosis of active pulmonary tuberculosis (TB) usually requires the isolation of *Mycobacterium tuberculosis* from respiratory secretions. It may take up to 6 weeks to identify *M tuberculosis* from cultured specimens,¹ although the detection time may be shortened when automated and semiautomated liquid culture systems are used.^{2,3} Thus, it is common practice to commence early expectant treatment for pulmonary TB on the basis of clinical evidence even before culture confirmation. Among this clinical evidence, sputum examination is the most useful method for diagnosing active pulmonary TB.⁴ However, between 25% and 60% of patients with pulmonary TB have negative sputum smears or no spontaneous sputum production.⁵ Thus, the diagnosis of TB may be missed initially in

these patients. This error may incur delays in the treatment of pulmonary TB until the return of positive culture results. As a result, delays in diagnosis and treatment have been recognized as an important cause of death due to pulmonary TB.⁶ The utility of rapid diagnostic tests in the early detection of smear-negative TB is, therefore, an important clinical consideration. It is also of considerable interest to public health.

Nucleic acid amplification tests (NAATs) are rapid, sensitive, and specific for the detection of *M tuberculosis* complex DNA or RNA in respiratory specimens.⁷ NAATs have higher sensitivity than acid-fast or fluorochrome smears in detecting culture-positive samples because their detection threshold is as low as 1 organism per 100 mL of sample. They have a sensitivity and specificity greater than 95% in smear-positive specimens.⁸ However, in smear-negative samples the sensitivity of polymerase chain reaction (PCR) is between 40% and 77% but the specificity remains high.⁹ The wide range of sensitivity may be explained by the use of different samples such as bronchoalveolar lavage fluid (BALF) versus sputum. In fact, a recent study has disclosed that a combined use of BALF smears and *M tuberculosis* NAATs has a good diagnostic yield in patients with sputum smear-negative TB or those without sputum production.¹⁰

Bronchoscopy with an acid-fast bacillus (AFB) smear and a culture for *M tuberculosis* of BALF have been introduced to

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This project is supported by NSC 97-2314-B-182A-088-MY3, National Science Council, Taiwan, Republic of China.

Disclosures: None

Received for publication Aug 19, 2009; revisions received Nov 22, 2009; accepted for publication Feb 9, 2010.

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0022-5223/\$36.00

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doi:10.1016/j.jtcvs.2010.02.019

Abbreviations and Acronyms

AFB	= acid-fast bacillus
AMTD	= Amplified Mycobacterium Tuberculosis Direct
BAL	= bronchoalveolar lavage
BALF	= bronchoalveolar lavage fluid
CI	= confidence intervals
CT	= computed tomography
EBUS	= endobronchial ultrasonography
NAATs	= nucleic acid amplification tests
OR	= odds ratios
PCR	= polymerase chain reaction
TB	= tuberculosis

obtain a bacteriologic diagnosis of TB in smear-negative patients or patients unable to expectorate.¹¹ Endobronchial ultrasonography (EBUS), a newly introduced technique, has also been applied to assess peripheral lung lesions.¹² Compared with conventional bronchoscopy, EBUS offers the benefits of visualizing the parabranchial structure, confirming the precise location of peripheral lung lesions, and therefore improving the diagnostic yield of lung cancer.^{13,14} However, few studies have investigated the role of EBUS in the diagnosis of benign lung lesion. Our recent study has demonstrated that the addition of EBUS to a diagnostic bronchoscopy increases the incidence for proving the presence of TB in a population of patients with negative AFB smear or no sputum production.¹⁵ The study analyzed all subjects with pulmonary TB. Therefore, the sensitivity, specificity, and positive and negative predictive values could not be determined. In addition, the role of bronchoscopy with the aid of EBUS in the positive yield of NAATs for pulmonary TB in sputum-negative patients is still undetermined.

This study was designed to compare the diagnostic yields of AFB smear, NAATs, and *M tuberculosis* culture in BALF for pulmonary TB by bronchoscopy, with or without EBUS, in patients with a negative sputum smear or without sputum production. The contributions of EBUS-guided procedures on the early diagnosis of pulmonary TB were also determined.

PATIENTS AND METHODS

Study Subjects

This study retrospectively analyzed patients who underwent bronchoscopy at Chang Gung Memorial Hospital, a university-affiliated, 3300-bed hospital in Taiwan. With the capability of performing Amplified Mycobacterium Tuberculosis Direct (AMTD) test since 2006, the institutional guideline recommended that patients with symptoms or chest radiographs suggestive of pulmonary TB may receive bronchoalveolar lavage (BAL) for AFB smear, *M tuberculosis* culture, and AMTD test. Before introduction of the guideline, patients with suspected pulmonary TB received bronchoscopy for BAL and transbronchial lung biopsy.¹⁵ In contrast, no patients received biopsy in the present study. The inclusion criteria were symptoms or

FIGURE 1. Analysis of patients with suspected pulmonary tuberculosis. BAL, Bronchoalveolar lavage; BALF, bronchoalveolar lavage fluid; BAL with EBUS, endobronchial ultrasound; BAL without EBUS, conventional bronchoscopy; PCR, polymerase chain reaction.

chest radiographs suggestive of pulmonary TB in patients who received BAL because of their lack of spontaneous sputum or a negative AFB smear in 3 consecutive daily sputum specimens. The exclusion criteria were failure to receive a complete BAL procedure or sputum smears that were positive for AFB. From June 2006 to July 2007, a total of 347 patients with symptoms or chest radiographs suggestive of pulmonary TB were referred to our bronchoscopic center for BAL because of their lack of spontaneous sputum or a negative AFB smear in 3 consecutive daily sputum specimens (Figure 1). There are 2 bronchoscopy rooms in the bronchoscopic center but only 1 of them is equipped with the EBUS system. Patients referred to the bronchoscopic center received bronchoscopy with or without EBUS depending on the availability of the room equipped with the EBUS system. Among the 347 patients, 99 had a positive culture for *M tuberculosis* in sputum or BALF, whereas the absence of *M tuberculosis* in both BALF and sputum was found in the other 248 patients. Patients who received bronchoscopic examination with EBUS guidance were defined as the EBUS group. The other patients underwent bronchoscopic examinations during the time period when EBUS was not available. They received bronchoscopic examination without EBUS guidance and were designated as the non-EBUS group. The diagnostic yields of the BALF AFB smear, AMTD test, and culture for *M tuberculosis* were compared between both groups. None of them was infected with human immunodeficiency virus. Informed consent to undergo bronchoscopy was obtained from all the subjects, and this study was approved by the hospital internal review board. Patients' baselines included age, gender, location and size of lesion, and radiologic appearance. Their underlying medical history was also collected, including diabetes mellitus, hypertension, history of malignancy, chronic airway obstructive disease, and previous TB infection.

Procedure and Equipment of Bronchoscopy

The bronchoscopic examinations were performed by experienced bronchoscopists who had performed more than 200 bronchoscopic procedures each year. To ensure the quality of EBUS in the study, we retrieved the EBUS group after each of the bronchoscopists had performed more than 50 EBUS procedures. The probable location of the lesion was determined initially by traditional posteroanterior chest radiography with and without chest computed tomography (CT). A flexible fiberoptic bronchoscope (BF-P240 or BF-40; Olympus, Tokyo, Japan) was then inserted via the nostril after anesthetizing with a local spray of 2% lidocaine (Xylocaine). In

TABLE 1. Characteristics of 347 patients undergoing bronchoscopy

Variables	No. (%)
Age, y (mean $\pm$ SD)	54.9 $\pm$ 12.8
Female gender (n, %)	166 (47.8%)
Size of lesion, cm (mean $\pm$ SD)	3.7 $\pm$ 1.9
Lobe distribution of lesions (n, %)	
Right upper lobe	145 (41.8%)
Right middle lobe	32 (9.2%)
Right lower lobe	28 (8.1%)
Left upper lobe	128 (36.9%)
Left lower lobe	14 (4.0%)
Benign lesions (n, %)	213 (61.4%)
Tuberculosis	99 (28.5%)
Pneumonia or other infection disease	58 (16.7%)
Fibrosis	41 (11.8%)
Organizing pneumonia	15 (4.3%)
Malignant lesions (n, %)	134 (38.6%)
Non-small cell lung cancer	121 (34.9%)
Small cell lung cancer	13 (3.7%)
Metastatic cancer	10 (2.9%)

SD, Standard deviation.

patients who received bronchoscopy with EBUS, a 20-MHz radial mechanical type ultrasound probe (model UM-S20-S20R; Olympus) and an ultrasound unit (Endoscopic Ultrasound System; Olympus) were used in the procedure. To assess lesions in the periphery of the lung, we advanced the EBUS catheter into the fourth- to sixth-order bronchi. Once the lesion was located by EBUS, the neighboring bronchiolar orifices were also examined to ensure the precise location of lesions. Each EBUS image was evaluated for 3 features including the continuous margin of the lesion, the presence of an air bronchogram, and heterogeneous echogenicity of the internal structure.¹³ The EBUS procedure was performed without a guide sheath.

Specimen Processing

In the EBUS group, BAL was performed via the bronchiolar orifice determined by the EBUS image. In the conventional bronchoscopy group, the location of the lesion was determined by chest radiographs or CT and BAL was performed as far as the bronchoscope could advance. BAL was performed by infusion of 6 aliquots of 50 mL normal saline.¹⁶ The return was submitted for the AFB smear, AMTD tests, and culture. Lavaged specimens were processed by standard methods and stained with fluorochrome.¹¹ The specimens were decontaminated with *N*-acetyl-L-cysteine-NaOH (BBL MycoPrep; Becton Dickinson, Cockeysville, Md). Positive smears were confirmed by Ziehl-Neelsen staining. Specimens were cultured with BACTEC 12B vials (radiometric BACTEC 460TB system; Becton Dickinson, Franklin Lakes, NJ) and Lowenstein-Jensen media (Bio-Rad, Marnes-la-Coquette, France). PCR testing for *M tuberculosis* complex was performed with the AMTD test kit (Gen-Probe, San Diego, Calif) according to the instructions of the manufacturer.¹⁷ The specimen results were read in a Leader 450 luminometer (Gen-Probe); a cutoff value of 30,000 relative light units or more was used for diagnosing positive specimens. Positive and negative controls were included in every run. The primary diagnosis of TB was made by a positive AFB smear or NAATs in BALF; the definitive diagnosis was confirmed by the presence of *M tuberculosis* cultured in sputum or BALF. The treatment of TB was started if a positive AFB smear or NAATs in BALF were obtained. For those with a negative AFB smear and NAATs in BALF, anti-TB treatment was started until the results of positive *M tuberculosis* cultured in sputum or BALF were obtained. The time to diagnosis and treatment of TB was measured from the patient's first visit to the medical center to the diagnosis and treatment of TB.

Statistical Analysis

Data are expressed as either group percentages (categorical variables) or mean $\pm$ standard deviation (continuous variables). Data were compared between patients who received bronchoscopy with versus without EBUS. Categorical variables were compared by χ^2 or Fisher's exact test. Odds ratios (OR) and their 95% confidence intervals (CI) were used to assess the difference of diagnostic yields between the 2 groups. We applied the *t* test to compare continuous variables with normal distribution and the Mann-Whitney test for continuous variables not distributed normally ($P < .05$ for all). All analyses were performed with SPSS software version 10.0 (SPSS, Inc, Chicago, Ill)

RESULTS

Patient Characteristics

A total of 347 patients were analyzed in the study (Table 1). In 99 patients TB was diagnosed owing to the presence of *M tuberculosis* cultured in sputum or BALF. The group comprised 166 women and 181 men with a mean age of 54.9 $\pm$ 12.8 years. The mean lesion size was 3.7 $\pm$ 1.9 cm. Two hundred thirteen patients had benign lesions and 134 patients had malignant lesions. The baseline characteristics of patients with culture-confirmed TB are summarized in Table 2. There were no significant differences between groups regarding demographic variables, size of lesion, percentage of retrieved BALF, chest CT scan, location of lesion, radiologic appearance, and chronic coexisting conditions. For the EBUS groups, 51 (91.1%) lesions could be localized by EBUS. The presence of air bronchograms was observed in 44 (78.6%) patients; lesions with a complete margin and homogeneous echogenicity were detected in 22 (39.3%) and 40 (71.4%) patients, respectively. Diabetes mellitus was the most frequent chronic comorbidity in the 2 groups. The overall mean time for procedure was 11.1 $\pm$ 2.3 minutes for the EBUS group and 9.7 $\pm$ 2.3 minutes for the non-EBUS group.

Sensitivity, Specificity, and Predictive Values of BAL for the Diagnosis of Pulmonary TB

Sensitivities, specificities, and predictive values of AFB smear and NAATs for the diagnosis of culture confirmed pulmonary TB in BALF are shown in Table 3. The sensitivity of AFB smear in BALF was 30.4% in the EBUS group and 9.3% in the non-EBUS group. The positive predictive value was 85% in the EBUS group and 66.7% in the non-EBUS group. The specificities and negative predictive values were similar in both groups. The sensitivity of NAATs in BALF was 89.3% in the EBUS group and 65.1% in the non-EBUS group. The specificities and positive and negative predictive values were similar in the 2 groups.

The Yield of Sputum and Lavage Specimen for Culture-Confirmed TB Diagnosis

The diagnostic yields of the NAATs in BALF (89.3%, 50/56; OR, 4.46; 95% CI, 1.56–12.81; $P = .006$), AFB smear in BALF (30.4%, 17/56; OR, 4.25; 95% CI, 1.31–13.78;

TABLE 2. The characteristics of patients with culture-confirmed pulmonary tuberculosis

Baseline characteristics	Without EBUS (n = 43)	With EBUS (n = 56)	P value
Age, y (mean ± SD)	48.4 ± 21.9	53.6 ± 19	.210
Female sex, no. (%)	12 (27.9%)	20 (35.7%)	.517
Size of lesion, cm (mean ± SD)	3.8 ± 1.9	4.3 ± 1.7	.174
Percentage of retrieved BALF	39.2 ± 22	39.4 ± 19.8	.535
Lesion localized by EBUS, no. (%)	NA	51 (91.1%)	NA
With computed tomography	14 (32.6%)	26 (42.4%)	.216
Location of lesion			
Right upper lobe	21 (48.8%)	22 (39.3%)	.415
Right middle lobe	4 (9.3%)	6 (10.7%)	1.00
Right lower lobe	1 (2.3%)	6 (10.7%)	.135
Left upper lobe	17 (39.5%)	20 (35.7%)	.834
Left lower lobe	0 (0%)	2 (4.7%)	.504
Radiologic appearance			
Alveolar consolidation	18 (41.9%)	22 (39.3%)	.838
Fibronodular infiltration	16 (37.2%)	20 (35.7%)	1.00
Cavity	6 (14%)	8 (14.4%)	1.00
Multiple nodules or mass	4 (9.3%)	7 (12.5%)	.752
With lymphadenopathy	4 (9.3%)	3 (5.4%)	.464
Miliary shadowing	2 (4.7%)	1 (1.8%)	.578
Lower lung field TB	1 (2.3%)	3 (5.4%)	.631
Echoic features by EBUS			
Presence of air bronchogram	NA	44 (78.6%)	NA
Complete margin	NA	22 (39.3%)	NA
Homogenous echogenicity	NA	40 (71.4%)	NA
Chronic coexisting condition, no. (%)			
Diabetes mellitus	6 (14%)	8 (14.3%)	1.00
Hypertension	6 (14%)	5 (8.9%)	.525
Chronic renal insufficiency	5 (11.6%)	2 (4.7%)	.234
Cancer	0 (0%)	2 (4.7%)	.504
COPD	5 (11.6%)	4 (7.1%)	.496
Previous TB infection	1 (2.3%)	2 (4.7%)	1.00

EBUS, Endobronchial ultrasound; SD, standard deviation; TB, tuberculosis; COPD, chronic obstructive pulmonary disease; NA, not available.

$P = .013$), and *M tuberculosis* in BALF culture (67.9%, 38/56; OR, 2.43; 95% CI, 1.07–5.53; $P = .041$) were significantly higher in EBUS patients. Diagnostic yields in those who underwent conventional bronchoscopy were 65.1% (28/43), 9.3% (4/43), and 46.5% (20/43), respectively (Table 4). In contrast, similar incidences of positive sputum *M tuberculosis* culture were found in both groups. There was a higher proportion of patients in the conventional group whose TB diagnosis was documented only by positive culture (32.6%, either from BALF or sputum) than among EBUS patients (8.9%; $P = .004$) (Figure 1). Combining BALF smear and NAATs allowed a rapid diagnosis of pulmonary TB to be made in 51 (91.1%) of the 56 EBUS patients and 29 (67.4%) of the 43 remaining patients who received conventional bronchoscopy. With the aid of EBUS, the overall diagnostic yield for TB by bronchoscopic

procedures (smear, NAATs, and culture of BALF) was higher (92.9%) than that for those who did not undergo EBUS (74.4%; OR, 4.47; 95% CI, 1.31–15.23; $P = .021$). In contrast, pulmonary TB was diagnosed only by sputum culture of *M tuberculosis* in 4 (7.1%) of the 56 EBUS patients and 11 (25.6%) of the 43 non-EBUS patients.

The Effects of CT, Location, and Size of Lesion on NAATs Yields

The use of EBUS in bronchoscopy had higher diagnostic yields of NAATs than conventional bronchoscopy in patients with (22/26, 84.6% vs 7/14, 50%; OR, 5.5; 95% CI, 1.23–24.52; $P = .029$) or without (28/30, 93.3% vs 21/29, 72.4%; OR, 5.33; 95% CI, 1.02–27.77; $P = .042$) chest CT scan before the bronchoscopic procedures. In patients in whom the lesion was smaller than 3 cm in size, bronchoscopy with EBUS ($n = 40$) had a higher diagnostic yield of NAATs (36/40, 90% vs 15/23, 65.2%; OR, 4.8; 95% CI, 1.25–18.39; $P = .022$) in BALF than conventional bronchoscopy ($n = 23$). Despite the lack of statistical significance, bronchoscopy with EBUS ($n = 16$) seemed to have a higher yield of NAATs (14/16, 87.5% vs 15/23, 65%; OR, 3.8; 95% CI, 0.66–21.56; $P = .245$) in BALF compared with conventional bronchoscopy ($n = 20$) in those in whom the lesion was larger than 3 cm in size.

The Treatment of Pulmonary TB

The time to diagnosis of TB in EBUS patients (18.6 ± 18.4 days) was shorter than that in non-EBUS patients (28.7 ± 24.7 days; $P = .022$). Similarly, the time to initiate treatment in patients receiving bronchoscopy with EBUS (26.0 ± 17.7 days; $P = .013$) was shorter than that in patients receiving conventional bronchoscopy (36.8 ± 24.6 days). In our study, most of the patients received bronchoscopy in the outpatient clinic rather than during hospitalization. Therefore, the time lag between diagnosis of TB and initiation of treatment may be due to the schedule of the next clinic visit.

Complications

Pneumothorax occurred in 2 (1.2%) patients of the conventional bronchoscopy group and resolved spontaneously, but no pneumothorax developed after the EBUS procedure. No major bleeding with hemodynamic instability developed during the procedure in either group.

DISCUSSION

This study has demonstrated that the introduction of EBUS increases the diagnostic yield of the NAATs, AFB smear, and *M tuberculosis* culture from BALF in patients with pulmonary TB who have a negative sputum smear or no spontaneous sputum production. Combining the BALF smear and NAATs, bronchoscopy with EBUS allows for

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TABLE 3. Sensitivity, specificity, and predictive values of BALF smear and AMTD test for the diagnosis of culture confirmed pulmonary TB

Procedure	Final diagnosis (no. positive/tested)		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
	TB	Non-TB				
BALF smear						
With EBUS	17/56	3/130	30.4	97.7	85	76.5
Without EBUS	4/43	2/118	9.3	98.3	66.7	74.8
BALF AMTD						
With EBUS	50/56	5/130	89.3	96.2	90.9	95.4
Without EBUS	28/43	3/118	65.1	97.5	90.3	95.4

BALF, Bronchoalveolar lavage fluid; AMTD, Amplified Mycobacterium Tuberculosis Direct; TB, tuberculosis; EBUS, endobronchial ultrasound.

a higher rate of rapid diagnosis of TB than conventional bronchoscopy in those patients. In addition, the time to diagnosis and time to treatment of TB in EBUS patients was shorter than that in non-EBUS patients.

The clinical application of EBUS began in the early 1990s.¹² EBUS was documented in improving the diagnostic yield for lung cancer; the EBUS image pattern might offer clues for differentiating benign lesions from malignant peripheral lung lesions.¹³ Apart from its role in the diagnosis of lung cancer, our previous study had shown that EBUS increased the diagnostic yield of BAL and transbronchial lung biopsy in TB patients with negative sputum smear.¹⁵ However, that study analyzed all subjects with pulmonary TB; therefore, the sensitivity, specificity, and positive and negative predictive values could not be determined. The present study recruited patients with symptoms or chest radiographs suggestive of pulmonary TB. In 99 of the 347 patients, TB was diagnosed owing to the presence of positive *M tuberculosis* culture. The present study provided the sensitivity, specificity, and positive and negative predictive value of BAL smear and NAATs in the diagnosis of pulmonary TB. A recent study has shown the good diagnostic yield for pulmonary TB by NAATs in BALF obtained by conventional bronchoscopy.¹⁰ Our study further disclosed that EBUS increased the sensitivity of NAATs in BALF for the diagnosis of pulmonary TB in patients with sputum smear-negative condition or those without sputum production.

The sputum-negative conditions in patients with pulmonary TB have been reported to be the major causes of treatment delay for TB.⁵ To avoid delay in treatment, physicians

have been using fiberoptic bronchoscopy for obtaining lower respiratory tract sections in those patients.¹⁸ Once the lesion is not visible by conventional bronchoscopy, BAL is performed in a best-guess fashion or with the aid of a fluoroscope.¹⁹ In the lesions that are not visualized by conventional bronchoscopy, EBUS images allow confirmation of the precise location of lesions by direct visualization. Therefore, with the aid of EBUS to accurately localize the lesion, bronchoscopy-guided BAL for AFB smear and NAATs increased the overall diagnostic yield for pulmonary TB to more than 90%. Pneumothorax is an unusual complication of BAL. The development of pneumothorax after BAL had been reported in patients with obstructive airway disease.²⁰ Compatible with a previous report, our study showed that pneumothorax developed after BAL in 2 patients with chronic obstructive pulmonary disease.

When conventional bronchoscopy is performed, knowledge of the CT appearance may improve the diagnostic yield of lung cancer by better targeting suspicious lesions. This applies to both endobronchial diseases visible with the bronchoscope with transbronchial biopsy specimens and washings taken from the periphery of the lung.²¹ However, our study demonstrated that the higher diagnostic yield of NAATs in EBUS groups than the non-EBUS group was unaffected by having a CT scan or not. This discrepancy could be caused by the difference of disease (TB in our study versus lung cancer in previous studies) and the different procedures used in these studies (NAATs in BALF in our study versus transbronchial lung biopsy and washing in previous studies). In addition, bronchoscopy with EBUS had a higher

TABLE 4. Comparison of results of AMTD, AFB smears, and *M tuberculosis* cultures in BALF and sputum from patients with culture confirmed pulmonary TB

	With EBUS (n = 56)	Without EBUS (n = 43)	OR	95% CI	P value
Positive BALF AMTD	50 (89.3%)	28 (65.1%)	4.46	1.56–12.81	.006
Positive AFB smear of BALF	17 (30.4%)	4 (9.3%)	4.25	1.31–13.78	.013
Positive BALF <i>M tuberculosis</i> culture	38 (67.9%)	20 (46.5%)	2.43	1.07–5.53	.041
Positive sputum <i>M tuberculosis</i> culture	24 (42.9%)	24 (55.8%)	0.59	0.27–1.32	.228
Positive BALF AMTD and/or AFB smear	51 (91.1%)	29 (67.4%)	4.92	1.61–15.07	.004
Positive BALF smear, AMTD, or culture	52 (92.9%)	32 (74.4%)	4.47	1.31–15.23	.021

AMTD, Amplified Mycobacterium Tuberculosis Direct; AFB, acid-fast bacillus; BALF, bronchoalveolar lavage fluid; TB, tuberculosis; EBUS, endobronchial ultrasound; OR, odds ratio; CI, confidence interval.

diagnostic yield of NAATs in BALF than conventional bronchoscopy, especially in lesions less than 3 cm in diameter. In those patients with small-sized lesions, it was difficult to obtain the diagnosis while pulmonary TB was suspected. Our results provide the evidence for the usefulness of bronchoscopy with EBUS in the diagnosis for TB among patients with small-sized lesions. Owing to the small sample size in the subgroup with a lesion size of less than 3 cm, the role of EBUS in the diagnostic yield of NAATs deserves further investigation.

The value of NAATs in respiratory samples to obtain a rapid diagnosis of pulmonary TB has been described in many studies.^{10,22} A positive NAAT result may be valuable in the early detection of active TB cases that are smear-negative.²³ One previous study reported a sensitivity of 53% and a specificity of 93% in comparison with the culture when NAAT was applied to smear-negative specimens²⁴; this suggests that a potentially significant number of cases of smear-negative TB could be quickly detected with the expanded use of NAATs. In a patient with clinically suspected TB who has a negative AFB smear and a positive NAAT, therapy can be started sooner and contact investigation can be initiated.²⁵ By combined use of bronchoscopy and NAATs, Tueller and associates¹⁰ have reported that NAATs in BALF had a sensitivity of 78% for detection of pulmonary TB in sputum smear-negative patients or patients without sputum production. Our results have shown that the NAATs of BALF offered rapid evidence for TB infection in 89.3% of the patients in the EBUS group, but only in 65.1% of the patients who received conventional bronchoscopy. Combining AFB smear and NAATs in BALF as the rapid evidence for diagnosis, only 8.9% of the patients in the EBUS group needed to wait until a positive culture as the only evidence for TB diagnosis. In contrast, 32.6% of the patients in the conventional group had culture as the only clue for TB diagnosis. The high diagnostic yield of EBUS-guided bronchoscopy for early diagnosis of TB infection may therefore avoid a delay in administration of anti-TB treatment or the need for further invasive procedures such as CT-guided or surgical biopsy to reach a definite diagnosis.

Some limitations of this study need to be mentioned. First, results of BALF smear and NAATs may be false positive; therefore, *M tuberculosis* cultures in BALF or sputum are still required for a definite diagnosis. In addition, the study only recruited patients with negative AFB smear or no sputum production. Therefore, the results of our study could not be extended to all the patients with suggestive TB lesions.

In conclusion, sputum AFB smears and *M tuberculosis* cultures should be performed first in patients in whom pulmonary TB is suspected. Once a negative sputum AFB smear or no spontaneous sputum production occurs, the introduction of EBUS increases the diagnostic yield of the NAATs, AFB smear, and *M tuberculosis* culture from

BALF. By means of a BALF smear and NAATs, bronchoscopy with EBUS allows for a higher rate of rapid diagnosis of TB than conventional bronchoscopy in patients with negative sputum smear or no spontaneous sputum production.

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