

Diagnostic contribution of cytological examination to endobronchial ultrasound-guided transbronchial biopsy for lung malignancies

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ABSTRACT

Although endobronchial ultrasound guided transbronchial biopsy (TBB) with a guide sheath (EBUS-GS) is widely used for diagnosis of peripheral pulmonary lesions, the diagnostic contribution of cytology (bronchial brushing, bronchial washing and biopsy forceps rinse) has not been established. To determine the diagnostic contribution of cytological examination to EBUS-GS-TBB, we reviewed medical records of patients with lung malignancies who had undergone TBB with EBUS-GS (EBUS-GS group, $n=187$) or TBB without EBUS-GS (conventional TBB [CTBB] group, $n=197$) at Nagoya University Hospital. Although the mean size of target lesions was significantly larger in the CTBB group than the EBUS-GS group, the total diagnostic rate was equivalent between two groups (EBUS-GS: 73.3%, CTBB: 66.0%). In the EBUS-GS group, cytological procedures increased the diagnostic rate by 9.1% (17/137), compared with only 4.1% (8/130) in the CTBB group. Sensitivity of cytology among biopsy-negative patients was significantly higher in EBUS-GS group than CTBB group ($P=0.022$). Furthermore, in the EBUS-GS group, among 17 patients whose malignant diagnoses could only be established cytologically, bronchial brushing contributed to the malignant diagnosis in 64.7% (11/17). These data may suggest that cytological examination, especially bronchial brushing, may be an important diagnostic contributor in EBUS-GS-TBB.

Keywords: bronchoscopy, guide sheath, cytology, diagnostic yield, bronchial brushing

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INTRODUCTION

Lung cancer remains the leading cause of cancer death, despite recent progress in new diagnostic methods for early detection. Bronchoscopic transbronchial biopsy (TBB) is a mainstay for the pathological diagnosis of various pulmonary diseases, including lung cancer. Endoscopic

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procedures that use ultrasound have recently become more popular. Several studies have shown diagnostic advantages in endobronchial ultrasound with a guide sheath (EBUS-GS).¹⁻⁴ A guide sheath can be introduced to the target peripheral pulmonary lesion, and whether the sheath is located at the center of the target lesion can be confirmed by its depiction on the ultrasound image. Biopsy can be repeated through the guide sheath at exactly at the same point, resulting in a high diagnostic yield.^{5,6} In most cases, cytological examinations, such as bronchial brushing, bronchial washing, or forceps rinsing, are performed simultaneously with EBUS-GS, which potentially help in the diagnosis of lung cancer. However, few reports have discussed the contribution of cytological examination to TBB using EBUS-GS.⁷ In this study, we retrospectively evaluated the contribution of cytological examination to the diagnostic performance of TBB, with and without EBUS-GS.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the clinical records of 266 patients who had undergone TBB with EBUS-GS, at Nagoya University Hospital from April 2011 to June 2012. Collectively, the patients had 137 definite malignant lesions, 32 definite benign lesions, and 97 undiagnosed lesions. From the 97 patients with undiagnosed lesions, twelve patients were excluded because their final diagnoses were undetermined as they were lost to follow-up, and 35 patients were diagnosed as benign by examination methods other than TBB or long-time follow-up (at least three years). Finally, 50 of the 97 patients with undiagnosed lesions were diagnosed with lung cancer by other examination techniques (i.e., false negatives). In total, 187 patients with final diagnoses of malignancy comprised the EBUS-GS group in this study. Between July 2009 and March 2011, we performed TBB without EBUS-GS (conventional TBB [CTBB]) in 313 patients. Of these patients, 130 were diagnosed with malignancies, 46 patients were diagnosed with benign lesions, and 137 were undiagnosed by TBB. Among the 137 undiagnosed patients, 15 patients remained undiagnosed and were excluded because of loss to follow up, and 55 patients were diagnosed with benign disease by examinations other than TBB. Eventually, however, 67 of the 137 patients with undiagnosed lesions by CTBB were diagnosed with malignancies and included in this analysis. In total, 197 patients comprised the CTBB group (Fig. 1). The Nagoya University institutional review board approved this retrospective study.

Bronchoscopy

In EBUS-GS TBB, we used video bronchoscopes (BFp-260F, 4.0-mm outer diameter and BF1T-260, 5.9-mm outer diameter; Olympus, Tokyo, Japan) with an ultrasound scanner (EU-ME-1; Olympus) for the EBUS-GS biopsies. We used guide sheath kits with two sizes (K-201 and K-203 unit; Olympus). Each guide sheath kit consisted of a guide sheath, forceps, and a cytology brush. To detect the target lesion, we used radial endobronchial ultrasound probes (UM-S20-17S, 1.7-mm outer diameter and UM-S20-20R, 2.0-mm outer diameter; Olympus). In the CTBB group, we used several types of bronchoscopes for biopsy (BF260, BF6C260, BFp260F, and BF1T260; Olympus), disposable biopsy forceps (FB-231D; Olympus), and disposable cytology brushes (BC-202D-2010; Olympus).

Procedures

All bronchoscopic procedures were performed under local anesthesia at the pharynx by nebulized lidocaine and conscious sedation by intravenous midazolam.⁸ During EBUS-GS TBB,

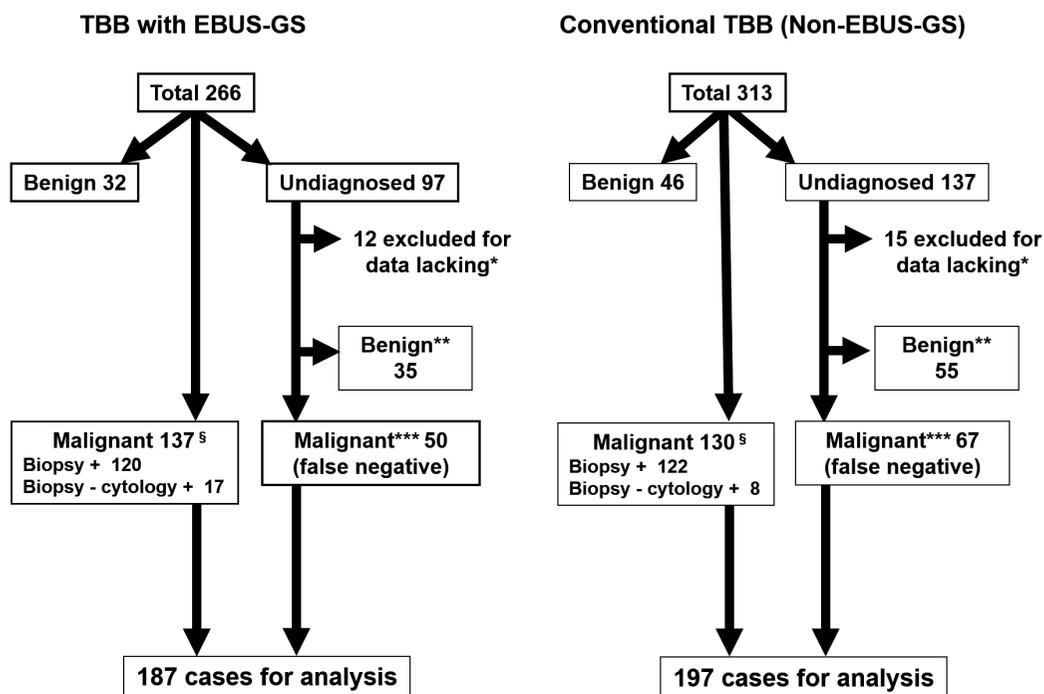


Fig. 1 Schematic of patients included in this study

*Cases with unknown final diagnoses due to loss to follow up were excluded from this analysis.

**Diagnoses were made by methods other than TBB or observation more than three years without remarkable change.

***Diagnoses were made by methods other than TBB.

[§]Biopsy+: malignant diagnosis could be obtained by forceps biopsy; Biopsy-/cytology+: Malignant diagnosis could be obtained only by cytology.

TBB using EBUS-GS: transbronchial biopsy using endobronchial ultrasound with a guide sheath; Conventional TBB: conventional transbronchial biopsy (no guide sheath)

we obtained ultrasound images of peripheral pulmonary lesions by a radial EBUS probe under fluoroscopic X-ray guidance. An EBUS probe was inserted through a guide sheath (K201 or K203; Olympus). When a suitable ultrasound image of the target lesion was obtained, we inserted a biopsy forceps followed by a cytological brush through the guide sheath. After performing biopsies and cytological brushing, 20 ml of saline was injected and retrieved as a bronchial washing. The biopsy forceps were rinsed in saline after each biopsy, and the rinsed saline was used for cytological examination. During each CTBB procedure, we inserted a biopsy forceps and cytological brush into a corresponding bronchus. The biopsies, forceps rinse, brushing cytology, and bronchial washing were performed in the same order as in EBUS-GS. For both periods (July 2009–March 2011, when CTBB had been performed; and April 2011–June 2012, when EBUS-GS-TBB had been performed), years of bronchoscopy experience of operator were equivalent (range: 7–15 years) in our institution.

Statistical analysis

We evaluated the differences in the mean values between two groups using the Mann–Whitney U-test and chi-square test. $P < 0.05$ was considered significant. All statistical analyses were performed with JMP software (ver. 8.0; SAS Institute Inc. Tokyo, Japan).

RESULTS

Patients' characteristics are shown in Table 1. The EBUS-GS group and CTBB group did not significantly differ in age, sex, disease location, or examination times.

Median sizes of target lesion significantly differed between the two groups (EBUS-GS group: 25 mm; CTBB group: 33 mm, $P=0.02$). The total diagnostic yield was equivalent between the EBUS-GS group and CTBB group (73.3%, and 66.0%, respectively; Table 2). The final pathological diagnoses and numbers of patients with false-negative results are shown in Table 2 by histologic type. Except for metastatic cancer, histologic types did not significantly differ among the two groups.

The diagnostic yield of TBB and each type of cytological examination is shown in Table 3.

Table 1 Patient characteristics

	TBB using EBUS-GS	Conventional TBB	<i>P</i>
	(<i>n</i> =187)	(<i>n</i> =197)	
Age (years, mean)	70.6	68.1	NS
Sex (M/F)	119/68	137/60	NS
Lesion location			NS
Right upper lobe	50	67	
Right middle lobe	10	8	
Right lower lobe	43	41	
Left upper lobe	43	42	
Lingular lobe	8	9	
Left lower lobe	33	30	
Lesion size (mm, mean)	25	33	0.02
Procedure time (min, mean)	38	36	NS

TBB using EBUS-GS: transbronchial biopsy using endobronchial ultrasound with a guide sheath; Conventional TBB: conventional transbronchial biopsy (no guide sheath); NS: not significant.

Table 2 Pathological diagnosis and bronchoscopic diagnostic yield

	TBB using EBUS-GS	CTBB
	<i>n</i> =187	<i>n</i> =197
Total diagnosis rate (%)	137/50 (73.3%)	130/67 (66.0%)
Adenocarcinoma	90/27 (76.9)	84/37 (69.4)
Squamous cell carcinoma	19/8 (70.3)	12/11 (52.2)
Small cell carcinoma	10/2 (83.3)	11/0 (100)
Non-small cell carcinoma	9/6 (60.0)	19/14 (57.6)
Metastatic carcinoma	6/7 (46.2)	0/3 (0)
Malignant lymphoma	3/0 (100)	4/2 (66.7)

Data are presented as numbers of bronchoscopic positive cases/false-negative cases with a diagnostic yield (%). Pathological diagnosis was determined by definitive diagnosis.

TBB using EBUS-GS: transbronchial biopsy using endobronchial ultrasound with a guide sheath; CTBB: conventional transbronchial biopsy (no guide sheath)

Cytology in TBB with EBUS-GS

We performed three cytological examination techniques: brushing cytology, bronchial washing, and forceps rinse. Although diagnostic yield did not significantly differ between the two groups for forceps biopsy, forceps rinsing and bronchial washing, the diagnostic yield of bronchial brushing in the EBUS-GS group was significantly higher than that in the CTBB group (52.6% vs. 34.0%, respectively, $P=0.024$; Table 3). In a few cases, none of the three types of cytological examination showed malignancy even though biopsy had proven malignancy (1 in the EBUS-GS group and 2 in the CTBB group). Cytological examinations alone demonstrated malignancy in 17 (9.1%) patients in the EBUS-GS group and 8 (4.1%) in the CTBB group (Table 4a). The diagnostic power of cytological examinations in TBB-negative patients was significantly higher in the EBUS-GS group than in the CTBB group (25.4% vs. 10.7%, respectively; $P=0.022$; Table 4b). In addition, when only cytology was diagnostic (i.e., TBB was not diagnostic), brushing cytology

Table 3 Diagnostic yield of each procedure

	TBB using EBUS-GS	CTBB	<i>P</i>
Procedures			
Forceps biopsy	64.2 (120/187)	61.9 (122/197)	NS
Brushing cytology	52.6 (92/175)	34.0 (65/191)	0.024
Bronchial washing	39.3 (72/183)	37.1 (66/178)	NS
Forceps rinse	46.4 (85/183)	46.6 (88/189)	NS

Data are presented as percentages (number of positive / total number).

TBB using EBUS-GS: transbronchial biopsy using endobronchial ultrasound with a guide sheath; CTBB: conventional transbronchial biopsy (no guide sheath); NS: not significant

Table 4 Contributions of cytological examinations to bronchoscopic diagnoses

(a) Contribution of forceps biopsies and cytological examinations to TBB diagnoses

	TBB using EBUS-GS <i>n</i> =187	Conventional TBB <i>n</i> =197
Both forceps biopsy and cytology positive	120 (64.2)	122 (61.9)
Cytology only*	17 (9.1)	8 (4.1)
Total TBB positive	137 (73.3)	130 (66.0)

* Patients in whom only cytological examination could provide diagnoses of malignant tumors. Data are presented as n (%).

(b) Comparison of cytology sensitivity between EBUS-GS and conventional TBB among biopsy-negative (not diagnostic) patients

	TBB using EBUS-GS <i>n</i> =67	Conventional TBB <i>n</i> =75	<i>P</i> *
Positive (diagnostic)	17 (25.4)	8 (10.7)	0.022
Negative (not diagnostic)	50 (74.6)	67 (89.3)	

*Calculated by the chi-square test. Data are presented as n (%).

TBB using EBUS-GS: transbronchial biopsy using endobronchial ultrasound with a guide sheath; Conventional TBB: conventional transbronchial biopsy (no guide sheath)

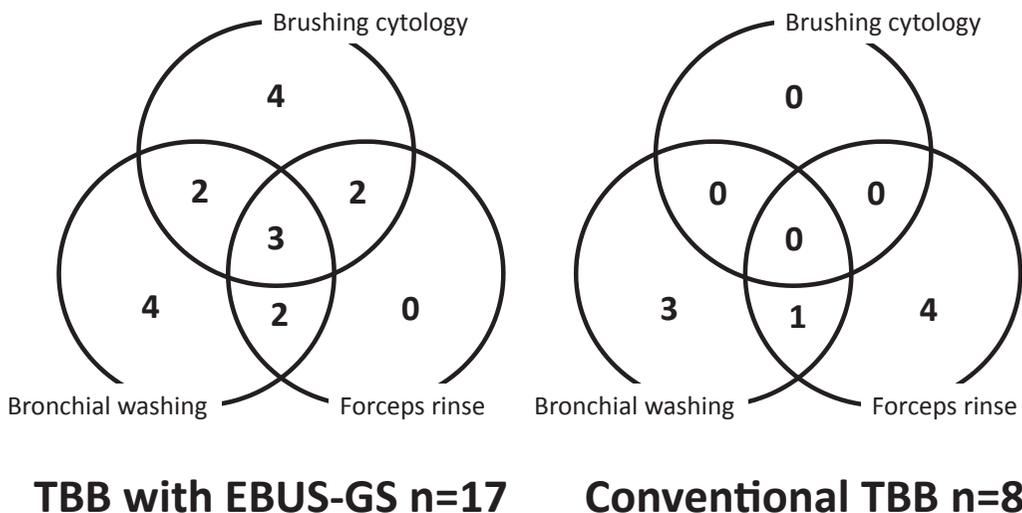


Fig. 2 Contribution of three cytological examination techniques (brushing cytology, bronchial washing, and forceps rinse) in the diagnosis of malignancy in patients for whom diagnoses could be made only by cytological examinations.

In the EBUS-GS group, bronchial brushing contributed to the malignant diagnosis in 64.7% (11/17) patients. TBB using EBUS-GS: transbronchial biopsy using endobronchial ultrasound with a guide sheath; Conventional TBB: conventional transbronchial biopsy (no guide sheath)

provided the largest contribution to the diagnosis of malignancy in the EBUS-GS group (11/17 patients, 64.7%), but not in the CTBB group (Fig. 2). These data show the diagnostic utility of additional cytological examinations, especially bronchial brushing, in TBB with EBUS-GS.

DISCUSSION

The EBUS-GS method was established and first reported by Kurimoto et al in 2004.¹ After the first report, many studies have demonstrated the high diagnostic yield of this method.^{1,2,4,9} Although the diagnostic yield of bronchial biopsy using EBUS-GS is fairly high, it is not always sufficient for the diagnosis of malignancy because the specimens are smaller than those obtained by CTBB. Kunimasa et al demonstrated the diagnostic utility of additional CTBB after TBB using EBUS-GS.¹⁰ An EBUS-GS procedure usually includes forceps biopsy and subsequent cytological examinations, such as bronchial brushing and washing. However, the diagnostic yield of bronchoscopic cytological examinations (bronchial brushing and washing) with EBUS-GS remains uncertain. Notably, forceps biopsy can damage the tissue sample, which may make definite diagnosis of malignancy more difficult. In such cases, cytological examination can sometimes complement the diagnosis of malignancy. Thus, elucidating whether additional bronchoscopic cytological examinations can improve the total diagnostic yield is important. In our retrospective evaluation, twice as many patients in the EBUS-GS could be diagnosed with cancer using cytological examination alone than in the CTBB group (9.1% vs. 4.1%, respectively). In particular, additional bronchial brushing played a central role in improving the diagnostic yield of TBB with EBUS-GS. Bronchial brushing can occasionally provide high-quality cytological samples with minimal crush damage.

As CTBB does not involve a guide sheath, inserting a bronchial brush and biopsy forceps into the same bronchus can be difficult. However, in TBB using a guide sheath, both biopsy and brushing can be performed in the same bronchus. Thus, using a guide sheath would be advantageous for additional bronchial brushing. Our results indicate that an additional bronchial brushing should always be performed after the forceps biopsy in TBB using EBUS-GS. Furthermore, the size of the biopsy forceps in EBUS-GS was frequently smaller (when using an Olympus K201 guide sheath). This might also explain the high number of patients who could be diagnosed only by cytological examination.

This study had some limitations. First, it was a retrospective analysis in a single university hospital. Second, the performance of EBUS-GS or CTBB was dependent upon the date of examination (i.e., not randomized). We introduced EBUS-GS-TBB around the beginning of 2011 and performed EBUS-GS TBB routinely since April in 2011. The backgrounds of the target lesions in the two groups (EBUS-GS or CTBB), including the mean diameters, were not equal. However, although the mean lesion size was significantly smaller in the EBUS-GS than CTBB group, the diagnostic yield was equivalent in both groups. This implies that the diagnostic power of TBB using EBUS-GS for smaller peripheral lung lesions is superior to that of CTBB, and cytological examinations have an important role in achieving high diagnostic yield in EBUS-GS-TBB. A multi-center, prospective, randomized controlled trial would help validate the conclusions of the present study.

In conclusion, bronchoscopic cytological examinations, especially bronchial brushing, may add significant diagnostic value to TBB when using EBUS-GS.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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