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The diagnostic value of histology and cytology samples during endobronchial ultrasound with a guide sheath

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Abstract

Objective: Endobronchial ultrasound with a guide sheath has been a widely used diagnostic procedure for peripheral pulmonary lesions. After sequential sampling with the usual devices, small portions of the collected specimen remain in the guide sheath and these can potentially contribute to diagnosis. We assessed the diagnostic value of each histological and cytological sample, especially the guide sheath flush, for pulmonary malignancies.

Methods: The medical records of patients who were diagnosed to have peripheral lung cancer by endobronchial ultrasound with a guide sheath in our hospital between January 2014 and May 2014 were reviewed. Separate samples from forceps biopsy, bronchial brushing, device wash, guide sheath flush and bronchial lavage were compared and analyzed.

Results: A total of 106 consecutive patients (54 men, 52 women, median age 69.0 years) were included. The median long axis size of the lesions was 26.0 mm. A definitive diagnosis was made in 90.6% of forceps biopsy samples and in 85.8% of all cytology samples combined. Individual yields were 61.3% from brushing, 77.4% from device wash, 72.6% from guide sheath flush and 32.1% from bronchial lavage. The diagnosis yield from forceps biopsy was significantly higher than each cytological sampling method ($P < 0.05$). Among the cytological sampling methods, yield from bronchial lavage was significantly the lowest ($P < 0.001$).

Conclusions: Forceps biopsy is an important sampling method during endobronchial ultrasound with a guide sheath for peripheral pulmonary lesions. In the collection of diagnostic liquid samples, guide sheath flush is more advantageous than bronchial lavage and provides specimen that may be adequate for molecular testing.

Key words: bronchoscopy, EBUS-GS, radial EBUS, histology/cytology sample, guide sheath flush (GSF)

Introduction

In recent years, the discovery rate of peripheral pulmonary lesions (PPLs) has been increasing with widespread use of computed tomography (CT) examination (1). CT-guided transthoracic needle biopsy (CTNB) and transbronchial biopsy (TBB) are diagnostic options for PPLs but, TBB is less frequently used probably because of its lower diagnostic yield (2–4).

Endobronchial ultrasound with a guide sheath (EBUS-GS) is a sampling procedure that has recently been reported to be useful (5,6). The procedure utilizes a radial EBUS (R-EBUS) probe for PPL

localization and a guide sheath (GS) that enables repetitive sampling from the same site (7).

When bronchoscopic sampling with EBUS-GS is conducted for PPLs, forceps biopsy, brushing and bronchial lavage are usually performed. However, bronchial lavage often causes bouts of coughing during saline instillation and this decreases the level of patient satisfaction during bronchoscopy (8). Additionally, whether bronchial lavage can contribute substantially to specimen collection cannot be ascertained because it is usually performed after removing the GS (7). On the other hand, the GS, which is kept in place during TBB, is located closer to the sampling site compared with the tip of the bronchoscope. Consequently, some portion of the specimen may remain in the lumen of the GS during alternate removal of sampling devices and this may contribute to the diagnostic yield. To our knowledge, there has been no evidence to support this hypothesis.

In this study, we aimed to examine the utility of each sampling method during EBUS-GS, and to investigate if flushing out the residual specimen in the GS (guide sheath flush; GSF) contributes valuably to diagnosis.

Patients and methods

Subjects

This was a retrospective, single-institution study approved by the National Cancer Center Institutional Review Board. A total of 367 consecutive patients who underwent EBUS-GS for PPLs from January 2014 to May 2014 were enrolled; patients who were finally diagnosed with malignant tumor by EBUS-GS were included in this study. PPL was defined as an abnormal lung parenchymal growth that had no visible endobronchial involvement.

Bronchoscopic procedure

All bronchoscopies were performed using the EBUS-GS procedure (9,10) under local anesthesia with mild sedation. Briefly, a R-EBUS probe with a GS was inserted through the working channel of the bronchoscope to the target PPL, under X-ray fluoroscopic guidance (VersiFlex VISTA®, Hitachi, Japan). After tumor localization by R-EBUS, the probe was removed while keeping the GS in place. Rapid on-site evaluation was performed in all cases.

EBUS-GS sampling

While keeping the GS fixed at the position that was localized by R-EBUS, brush (BC-204D-2010 or BC-202D-2010, Olympus Medical Systems Ltd, Tokyo, Japan) and forceps (FB-233D or FB-231D, Olympus Medical Systems Ltd) were alternately inserted through the proximal end of the GS (SG-200C or SG-201C, Olympus Medical Systems Ltd) to collect cytology and histology samples. Usually, brushing was performed two times whereas forceps biopsy was performed until five pieces of specimens were obtained. Glass slides containing smears from the first brushing were usually prepared for cytology examination. After every sampling, the remaining cells in the brush and forceps were rinsed off in saline (device wash). After 2 min of hemostasis, the GS was removed. The residual specimen in the GS lumen was flushed out with 3 ml of saline and collected (GSF). Lastly, bronchial lavage was performed with 20 ml of saline (Fig. 1).

Brushing cytology, device wash, GSF, bronchial lavage and forceps biopsy were performed on all patients. All liquid samples collected from device wash, GSF and bronchial lavage were placed in separate containers for cytology evaluation while forceps biopsy samples were for histology evaluation.

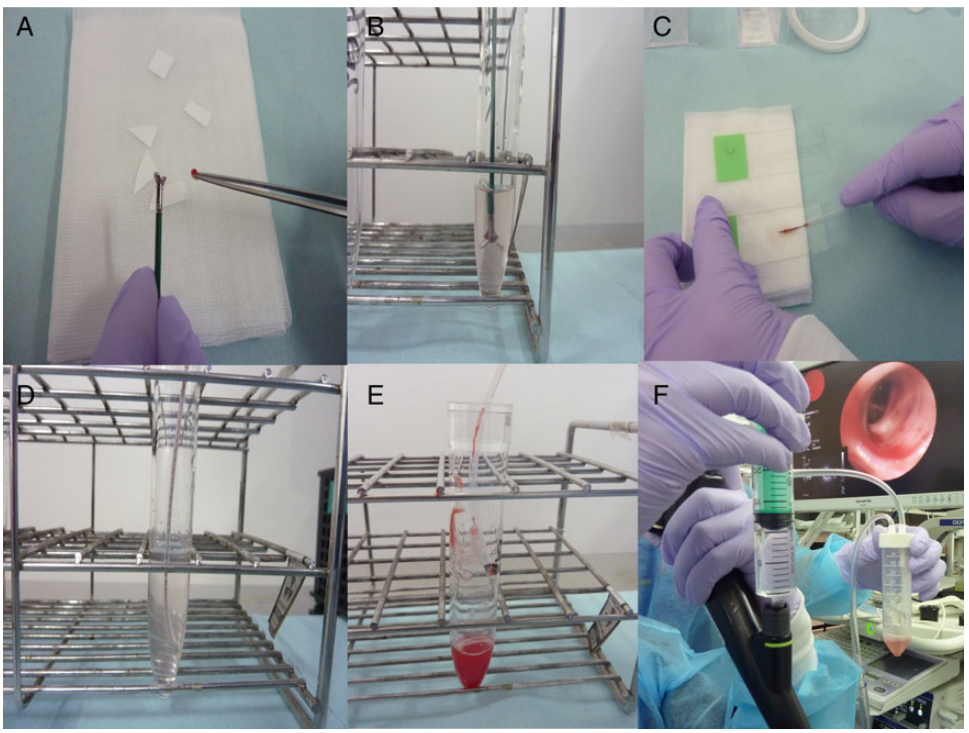

Figure 1. Processing of samples obtained by endobronchial ultrasound with a guide sheath (EBUS-GS). (A) Forceps biopsy; open the biopsy forceps cup and transfer the collected specimen to a vial with formalin. (B) Device wash (forceps); rinse off the remaining cells in a vial with 3 ml saline. (C) Brushing cytology; smear on a glass slide. (D) Device wash (brush); rinse off the remaining cells in the brush in the same vial with 3 ml saline that was used for biopsy forceps rinsing. (E) Guide sheath flush; flush out the guide sheath material into an empty vial using a syringe with 3 ml saline. (F) Bronchial lavage was performed with 20 ml of saline via the working channel of the bronchoscope.

Table 1. Baseline characteristics of the study population

Variable	N = 106 (%)
Median age	
Year (range)	69 (39–84)
Gender	
Male	54 (50.9)
Female	52 (49.1)
Lobar location	
Upper	50 (47.2)
Middle or lingular	15 (14.1)
Lower	41 (38.7)
Feature	
Solid	76 (71.7)
GGO	30 (28.3)
Lesion size (long axis)	
Median size (range, cm)	2.6 (1.0–11.0)
≤3.0 cm	66 (62.3)
>3.0 cm	40 (37.7)
Procedure time (range, min)	21.0 (7.3–39.0)

GGO, ground glass opacity.

Statistical analysis

The yield for diagnostic cytological or histological samples was analyzed per sampling method. Descriptive statistics was presented as frequency, percentage and median (range). The differences among the groups were calculated with Fisher's exact test and *post hoc* test (Holm method 11,12). Data were presented as adjusted *P* values using the Holm method for multiple testing. All *P* values were two sided and a level <0.05 was considered statistically significant. In the multiple tests, statistical significance ($P < 0.05$) was considered after adjustment using the Holm method. Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html; Kanda), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, Ver. 2. 13.0) and a modified version of R commander (Ver. 1.8–4).

Results

Table 1 summarizes the baseline characteristics of 106 consecutive patients (54 men, 52 women, median age 69.0 years) with PPLs that were diagnosed as malignant by EBUS-GS. The median long axis size of the lesions was 2.6 cm, and the tumor locations were upper lobes ($n = 50$), middle/lingular lobes ($n = 15$) and lower lobes ($n = 41$). The median bronchoscopic procedure time was 21.0 min.

Final diagnoses were as follows: adenocarcinoma ($n = 70$), squamous cell carcinoma ($n = 22$), non-small-cell lung cancer ($n = 10$) and small-cell carcinoma ($n = 4$). A definitive cytological diagnosis was made in 65/106 (61.3%) of brushing samples, 82/106 (77.4%) of device wash samples, 77/106 (72.6%) of GSF samples and 34/106 (32.1%) of bronchial lavage samples. Overall diagnostic accuracy from all cytological samples was 91/106 (85.8%). A definitive histologic diagnosis was made in 96/106 (90.6%) of forceps biopsy samples (Table 2). There were two patients who were diagnosed by GSF alone; a representative case is shown in Figure 2.

The differences in diagnostic yield among all sampling methods were significant ($P < 0.01$). In the *post hoc* analysis (Table 3), the diagnostic yield from forceps biopsy was significantly higher than that of each cytological sampling method (adjusted $P < 0.05$) while the yield from bronchial lavage was significantly lower than that of other sampling methods (adjusted $P < 0.001$). Complication observed was pneumonia in two cases.

Table 2. Diagnostic yield of each sampling technique during EBUS-GS

Sampling technique	Diagnostic cases/total cases (%)	*P* value
Forceps biopsy	96/106 (90.6)	<0.01
Brushing	65/106 (61.3)	
Device wash	82/106 (77.4)	
Guide sheath flush	77/106 (72.6)	
Bronchial lavage	34/106 (32.1)	

Data are presented as number and percentage.
EBUS-GS, endobronchial ultrasound with a guide sheath.
Using Fisher's exact test, $P < 0.01$ for each sampling technique.

Discussion

This is the first report to describe the value of each histological and cytological sample during the EBUS-GS for PPLs, especially the utility of GSF sampling method.

In this study, the respective diagnostic yield from every sampling method was significantly different from the others, with forceps biopsy providing the highest yield. This might be related to the characteristics of the study population which included GGO lesions ($n = 30$). Cytological samples may be inadequate for obtaining a diagnosis for GGO (7,13). Therefore, we underscore the importance of obtaining forceps biopsy specimen during EBUS-GS for PPLs that are suspected to be malignant.

A few studies have reported on the diagnosis of lung cancer using catheter suction (14,15). Franke et al. (14) reported a 77% diagnostic yield of catheter aspiration cytology for 28 PPLs that were suspected to be malignant. Eberhardt et al. (15) performed bronchoscopy on 53 PPLs that were suspected to be malignant after inserting a catheter into the extended working channel using electromagnetic navigation and obtained a diagnostic yield of 90% from catheter aspiration cytology. However, both studies were conducted for the purpose of collecting cytology specimens by suction and were carried out by inserting a single catheter into the target bronchi through the working channel of a bronchoscope.

In EBUS-GS procedures, small portions of specimen that remain in the lumen of the GS after sampling may contribute to the diagnostic yield because this material is directly from the tumor site that was confirmed by R-EBUS prior to sampling. Moreover, collecting GSF for cytology does not require additional sampling instruments and time consuming sampling procedures. To date, however, there has been no report comparing this residual specimen in the GS to other bronchoscopic samples obtained during EBUS-GS. On examination, the quality of the cells necessary for making an accurate diagnosis was almost the same in GSF samples and brush cytology samples. This could have important implications in providing adequate samples for molecular analysis (16,17). Furthermore, there were some cases in which the diagnosis was confirmed from the GSF sample but were non-diagnostic by brush cytology, device wash and bronchial lavage combined. This suggests that the diagnostic yield of EBUS-GS for peripheral lung cancer may increase more than ever by incorporating this sampling method.

There are several reports that bronchial lavage significantly increased overall diagnostic yield of bronchoscopy without EBUS-GS

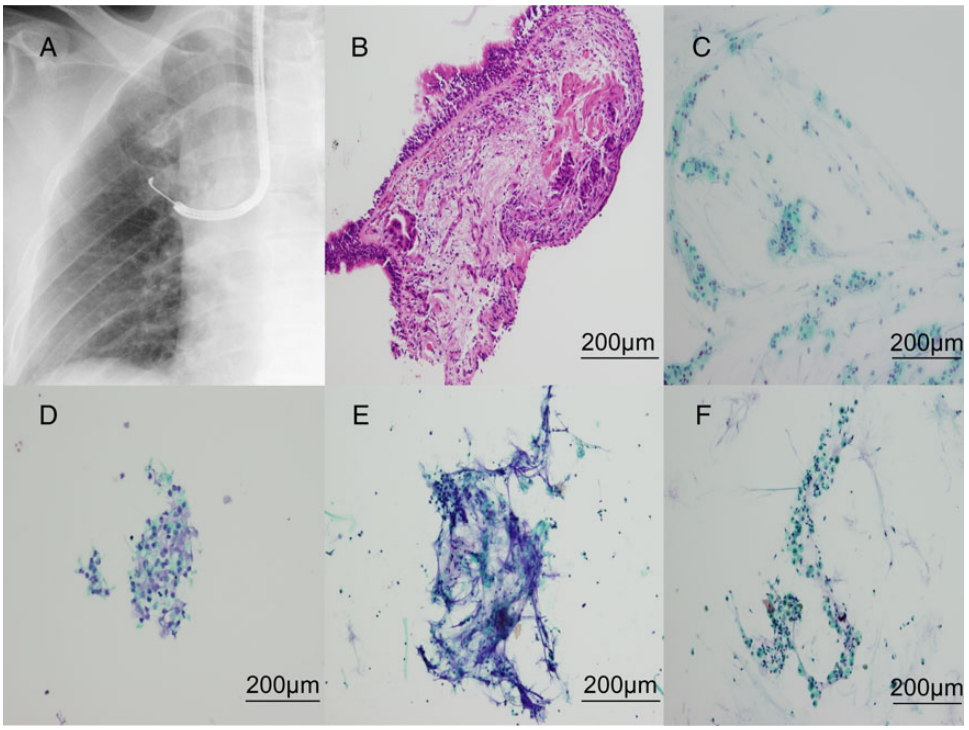

Figure 2. Representative case of a 69-year-old male, who underwent EBUS-GS transbronchial sampling of a solid peripheral pulmonary lesion that was diagnosed by guide sheath flush (GSF) alone. (A) Real-time fluoroscopy imaging during EBUS-GS transbronchial sampling. (B) The specimen from forceps biopsy showed only atypical cells (Hematoxylin–Eosin stain, ×100). (C) The specimen from brushing cytology showed only a few degenerated atypical cells (Papanicalou stain, ×100). (D) The specimen from device wash showed only a few degenerated atypical cells (Papanicalou stain, ×100). (E) The specimen from GSF showed adenocarcinoma (Papanicalou stain, ×100). (F) The specimen from bronchial lavage showed only a few degenerated atypical cells (Papanicalou stain, ×100).

Table 3. Comparison of each sampling technique during EBUS-GS for peripheral pulmonary lesions

Sampling technique	Forceps biopsy	Brushing	Device wash	Guide sheath flush	Bronchial lavage
Forceps biopsy	–	<0.001	0.049	<0.001	<0.001
Brushing	<0.001	–	0.056	0.216	<0.001
Device wash	0.049	0.056	–	0.526	<0.001
Guide sheath flush	<0.01	0.216	0.526	–	<0.001
Bronchial lavage	<0.001	<0.001	<0.001	<0.001	–

Data are presented as adjusted *P* values using the Holm method for multiple testing. Statistically significant ($P < 0.05$) after adjustment for multiple test using the Holm method.

in patients with lung malignancy (18–20). In our study, the diagnostic yield of GSF cytology was significantly higher compared with bronchial lavage cytology (adjusted $P < 0.001$), and there was no patient who was diagnosed by bronchial lavage alone. In addition, bronchial lavage has become one of the factors that decrease the level of patient satisfaction during bronchoscopy because patients often have a coughing fit from saline instillation (8). Since collection of GSF can be performed without causing additional burden on patients, bronchial lavage might be unnecessary and GSF alone might sufficiently serve the purpose of obtaining liquid cytology specimen.

The limitations of this study are its retrospective and single-institution design. Prospective, multi-center trials are ideal and recommended in the future.

Conclusions

Forceps biopsy during EBUS-GS for PPLs is an important sampling method. In the collection of liquid cytology samples, combining GSF with other sampling methods contributes to a highly accurate diagnosis. This could play an important role in the development of a novel treatment for advanced lung cancer patients in the future.

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Conflict of interest statement

None declared.

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