Factors Affecting the Diagnostic Yield of Transbronchial Biopsy Using Endobronchial Ultrasonography with a Guide Sheath in Peripheral Lung Cancer

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Abstract

Objective Endobronchial ultrasonography with a guide sheath (EBUS-GS) and virtual bronchoscopic navigation (VBN) improves the diagnostic yield in patients with peripheral pulmonary lesions (PPLs). Most previous reports on EBUS-GS-guided transbronchial biopsy (TBB) have included patients with benign and malignant diseases. We aimed to determine the factors that predicted a successful diagnosis by EBUS-GS-guided TBB diagnostic in patients with small peripheral lung cancer, with a focus on the high-resolution computed tomography (HRCT) findings before bronchoscopy.

Methods We retrospectively reviewed the medical records of 173 consecutive patients with 175 small (≤ 30 mm) PPLs who were diagnosed with primary lung cancer between June 2010 and October 2013 at Nagoya University Hospital. All patients underwent EBUS-GS-guided TBB with VBN using a ZioStation computer workstation (Ziosoft, Osaka, Japan). We analyzed the patient characteristics, HRCT findings, diagnostic yield, and the diagnostic factors in small peripheral lung carcinoma.

Results The EBUS probe position was within the PPL in 83 of the 175 lesions (47%) and 112 (64.0%) cases were successfully diagnosed by EBUS-GS-guided TBB. A univariate analysis revealed that the following factors were associated with a significantly higher diagnostic yield: CT bronchus sign positivity, a lesion of >20 mm in diameter, a solid nodule, and a probe position that was within the lesion. The following factors were not significant: the lesion location, the number of biopsies, and the lung cancer histology. A multivariate analysis revealed that the following factors significantly affected the diagnostic yield: CT bronchus sign positivity [odds ratio (OR) =2.479]; a probe position that was within the lesion (OR=2.542); and a solid nodule (OR=2.304).

Conclusion The significant factors that were significantly associated with a successful diagnosis using EBUS-GS-guided TBB in small peripheral lung carcinoma were as follows: CT bronchus sign positivity, a solid nodule, and a probe position that was within the lesion.

Key words: EBUS-GS, lung cancer, virtual bronchoscopic navigation, diagnostic factor, CT bronchus sign

(Intern Med 55: 1705-1712, 2016)

(DOI: 10.2169/internalmedicine.55.6341)

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Received for publication August 10, 2015; Accepted for publication September 16, 2015

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Introduction

Lung cancer is the leading cause of cancer death worldwide. Most lung cancer patients already have advanced disease at the time of their diagnosis. Advances in computed tomography (CT) equipment have resulted in the improved detection of peripheral pulmonary lesions (PPLs) and lung cancers (1). An early histological diagnosis is essential for the optimal treatment and management of lung carcinoma. Several diagnostic modalities, including conventional transbronchial biopsy (TBB) using fluoroscopy, CT-guided TBB, endobronchial ultrasonography with a guide sheath (EBUS-GS)-guided TBB, virtual bronchoscopic navigation (VBN), transthoracic needle aspiration (TTNA), and surgical biopsy, can be applied to the diagnosis of PPL. Although the diagnostic yield of TTNA is high in the case of peripheral lung malignancies, it is associated with a higher incidence of pneumothorax, and occasionally causes air embolism and tumor seeding (2, 3). EBUS-GS and VBN have improved the PPL diagnostic yield (4, 5). The diagnostic yield of EBUS-GS-guided TBB in small (≤ 30 mm) PPL has been reported to be 63-79% (4-8). The factors which affect the EBUS-GS diagnostic yield in PPL have been reported; however, some reports have indicated that the probe position is the only independent predictor of the EBUS-guided TBB diagnostic yield (7, 8). It is also controversial whether the findings from high-resolution computed tomography (HRCT) before bronchoscopy (e.g., lesion size, location, and CT bronchus sign) are significant diagnostic factors that can be used in addition to the EBUS image. Furthermore, most previous studies have included patients with various benign and malignant diseases, including tuberculosis, nontuberculous mycobacterial infection, organizing pneumonia, lymphoma, and metastatic lung tumors (4, 5, 7, 8). We therefore assessed the diagnostic yield of EBUS-GS-guided TBB and VBN using a computer workstation, ZioStation (Ziosoft, Osaka, Japan) in a study population that only included patients with small peripheral primary lung cancer, and examined the factors that affected EBUS visualization and diagnostic success, particularly in the evaluation of CT findings before bronchoscopy.

Materials and Methods

Subjects

Two hundred seventy-one small (≤ 30 mm) peripheral pulmonary lesions were examined in 269 patients who underwent EBUS-GS-guided TBB between June 2010 and October 2013 at Nagoya University Hospital. Ninety-six lesions which were diagnosed as lung metastases or benign diseases were excluded, and 175 lesions which were subsequently diagnosed as primary lung cancer in 173 patients were included (Fig. 1). At the time of the retrospective analysis, we recorded the characteristics of the nodules, including the

size, location, the structure of the lesion, and the presence or absence of the CT bronchus sign (i.e., the finding of a bronchus leading directly to a PPL) (Fig. 2a and b) based on the HRCT findings (9). We divided PPLs into the following three groups according to their structures: solid nodule, pure ground-glass nodule (GGN), and part-solid nodule (Fig. 2c-e). PPLs were defined as lesions that were surrounded by the pulmonary parenchyma and which were not visible on bronchoscopy. The term “sub-solid nodule” was defined as a combination of pure GGN and part-solid nodule. Medical records were retrospectively reviewed in two groups: lesions that were diagnosed by EBUS-GS-guided TBB ($n=112$, diagnosed group) and undiagnosed lesions ($n=63$, undiagnosed group). The definitive diagnoses of lung cancer were established in the undiagnosed lesions by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), TTNA, video-assisted thoracoscopic surgery, or thoracotomy. Institutional review board approval was obtained (2014-0372). Individual patient informed consent was not required because of the retrospective nature of the study. Informed consent was obtained from each patient prior to bronchoscopy.

CT examination and virtual bronchoscopic navigation

CT scans were performed at total lung capacity (inspiratory breath-hold) using 16-row or 64-row non-enhanced multi-detector CT (Aquilion; Toshiba Medical Systems, Tokyo, Japan). The HRCT data were reconstructed at 1 mm or 0.5 mm slice thickness with 0.5 mm or 0.4 mm intervals (16-row or 64-row, respectively) using a standard reconstruction algorithm. An individual CT dataset for each patient was sent to a ZioStation computer workstation. An experienced chest radiologist (S. Iwano) constructed all of the VBN images (from the carina tracheae to the leading bronchus of the objective lesion). The bronchoscopy operator could manipulate the VBN images (6). The pulmonary artery closest to the bronchus was used to predict the paths when the bronchus to the lesion was not visible on HRCT (10).

The procedure and sedation

Radial EBUS was performed using an endoscope ultrasonography system (EU-ME1; Olympus, Tokyo, Japan) equipped with 20 MHz mechanical radial-type probes measuring 1.4 mm (UM-S20-17S; Olympus) or 1.7 mm (UM-S20-20R; Olympus) in diameter. A thin bronchoscope (BF-P260; Olympus, channel diameter: 2.0 mm) and guide sheath (K-201; Olympus, external diameter: 1.95 mm) were used for the 1.4-mm probe, and a thicker bronchoscope (BF-1T260; Olympus, channel diameter: 2.8 mm) and guide sheath (K-203; Olympus, external diameter: 2.55 mm) were used for the 1.7-mm probe. The probe and bronchoscope were selected by the operator.

The GS-covered EBUS probe was inserted through the working channel of the bronchoscope and advanced to the

Figure 1. Flow diagram. Two hundred seventy-one small (≤ 30 mm) peripheral pulmonary lesions were examined by EBUS-GS-guided TBB. Ninety-six lesions, which were diagnosed as lung metastases or benign diseases, were excluded. The 175 lesions that were subsequently diagnosed as primary lung cancer were included in the present study.

PPL to obtain an EBUS image. The GS position was adjusted by radiographic fluoroscopy. If an EBUS image of PPL could not be visualized, the probe was removed from the GS and an angulated double-hinged curette (CC-6DR-1; Olympus) was used to reach the PPL. After the PPL was located on the EBUS image, the probe was removed to leave the guide sheath in the PPL. Biopsies were performed using forceps, with bronchial brushing, and washing through the GS under fluoroscopic guidance to obtain histological and cytological specimens; biopsies were repeated until an adequate number of specimens had been collected. As a rule, we obtained nine samples for each case. At all times during the procedure, the operators were able to refer to three monitors, which showed the actual bronchoscopic image, the VBN image, and the fluoroscopic image at the same time. All procedures were performed under local anesthesia and a safe method of sedation with individually calculated doses of intravenous midazolam (11, 12).

We classified the EBUS probe positions into the following three groups as described previously: [1] “within” (the probe was located within PPL); [2] “adjacent to” (the probe was located adjacent to PPL); and [3] “outside” (the probe was located outside PPL) (Fig. 2f-h) (8, 13, 14).

In this study, we considered lesions with positive cytological findings or evident malignant findings on histological examination to have been positively diagnosed using EBUS-GS-guided TBB.

Statistical analysis

Mann-Whitney *U* tests (or *t*-tests if data were normally distributed) and Pearson’s chi-square tests were used for the statistical analyses of continuous and categorical variables, respectively, to compare the diagnosed and undiagnosed lesions. Univariate and multivariate logistic regression analyses were performed to elucidate significant predictors of positive results on EBUS-GS-guided TBB or the “within” PPL EBUS probe position. The variables that were analyzed in relation to diagnosis using EBUS-GS-guided TBB were as follows: location (S1/S2/S1+2/S6 or the others), structure (solid nodule or sub-solid), size (>20 mm or ≤ 20 mm), CT bronchus sign status (positive or negative), and EBUS image (within or adjacent to/outside). The variables that were analyzed in relation to the visualization of the EBUS image were as follows: location (S1/S2/S1+2/S6 or the others), structure (solid nodule or subsolid), size (>20 mm or ≤ 20 mm), and CT bronchus sign status (positive or negative). The diagnostic factors were compared using receiver operating characteristic (ROC) curves. *p* values of <0.05 were considered to be statistically significant. All of the analyses were performed using the SPSS software program (version 22, IBM Corp., Armonk, USA).

Results

The characteristics of the lesions are shown in Table 1. Of

Figure 2. (a) A chest CT image revealing a bronchus leading directly to a PPL (CT bronchus sign-positive). (b) A chest CT image revealing a bronchus that does not lead directly to a PPL (CT bronchus sign-negative). (c-e) We divided PPLs into the following three groups according to their structures: solid nodule (c), pure GGN (d), and part-solid nodule (e). (f) The EBUS probe is located within a PPL. (g) The EBUS probe is located adjacent to a PPL. (h) The EBUS probe is located outside a PPL.

the 175 lesions, 112 (64%) were diagnosed using EBUS-GS-guided TBB. The median age of the patients was 70 years, and 112 (64%) were male. Ninety-three lesions (53%) were located in the upper lobes. The CT appearances of the lesions were as follows: pure GGN (n=7), part-solid nodules (n=31), and solid nodules (n=137). The median longest diameter of the lesions was 21 mm (range: 10-30), and 81 (46%) of the lesions were ≤ 20 mm. One hundred forty-four lesions (82%) were CT bronchus sign-positive. Regarding the position of the probe, the probe was within the PPL in 83 (47%) cases, adjacent to the PPL in 61 (35%), and outside the PPL in 31 (18%). One hundred sixty-four (94%) procedures were performed using the 1.4-mm probe. The median number of biopsy specimens was nine (range 2-14),

and 120 (69%) lesions were diagnosed as adenocarcinoma. There were no significant differences between the diagnosed and undiagnosed groups in terms of gender, location, EBUS probe, number of biopsies, or pathological diagnosis (Table 1).

A univariate analysis revealed that the structure of the lesions (solid nodule vs. sub-solid nodule), lesion size (>20 mm vs. ≤ 20 mm), CT bronchus sign (positive vs. negative), and EBUS image ("within" vs. "adjacent to" and "outside") were significant diagnostic factors. A multivariate analysis revealed that solid nodules [odds ratio (OR) =2.304; 95% confidence interval (CI) =1.069-4.968; $p=0.033$], CT bronchus sign positivity (OR=2.479; 95% CI=1.072-5.734; $p=0.034$), and the "within" probe position (OR=2.542; 95%

Table 1. Characteristics of the Lesions (n=175).

		Total (n=175) 70 (44-89)	Diagnosed (n=112) 71 (44-89)	Undiagnosed (n=63) 70 (56-85)	p value
Age	Median (range)				0.567
Gender					
	Male	112	71	41	0.79
	Female	63	41	22	
Location					
	Upper	93	61	32	0.662
	Middle or lingular	17	12	5	
	Lower	65	39	26	
Structure					
	Pure GGO	7	3	4	0.061
	Part-solid nodule	31	15	16	
	Solid nodule	137	94	43	
Size	Median (range)	21 (10-30)	22 (10-30)	19 (10-30)	0.012
	≤20 mm	81	45	36	0.031
	21-30 mm	94	67	27	
CT bronchus sign					
	Positive	144	99	45	0.005
	Negative	31	13	18	
EBUS image					
	Within	83	64	19	< 0.001
	Adjacent to	61	42	19	
	Outside	31	6	25	
EBUS probe					
	1.4-mm probe	164	105	59	0.979
	1.7-mm probe	11	7	4	
Number of biopsy	Median (range)	9 (2-14)	9 (2-12)	9 (3-14)	0.548
Diagnosis					
	Adenocarcinoma	120	78	42	0.36
	Squamous cell carcinoma	24	16	8	
	Non-small cell carcinoma	14	9	5	
	Small cell carcinoma	14	9	5	
	Large cell carcinoma	2	0	2	
	Adenosquamous cell carcinoma	1	0	1	

GGN: ground-glass nodule, CT: computed tomography, EBUS: endobronchial ultrasonography

Table 2. Logistic Regression Analysis of Factors Affecting Diagnostic Yield of EBUS-GS.

Variables		Univariate OR (95%CI)	p value	Multivariate OR (95%CI)	p value
Location	S1, S2, S1+2 and S6 (n=85)	1.402 (0.715-2.605)	0.285	—	—
	The others (n=90)	1 (ref)			
Structure	Solid nodule (n=137)	2.429 (1.168-5.050)	0.017	2.304 (1.069-4.968)	0.033
	Subsolid nodule (n=38)	1 (ref)		1 (ref)	
Size	>20 mm (n=94)	1.985 (1.062-3.712)	0.032		
	≤20 mm (n=81)	1 (ref)			
CT bronchus sign	Positive (n=144)	3.046 (1.375-6.750)	0.006	2.479 (1.072-5.734)	0.034
	Negative (n=31)	1 (ref)		1 (ref)	
EBUS image	Within (n=83)	3.088 (1.603-5.947)	0.001	2.542 (1.285-5.026)	0.007
	Adjacent to or outside (n=92)	1 (ref)		1 (ref)	

EBUS-GS: endobronchial ultrasonography with a guide sheath, OR: odds ratio, CI: confidence interval, ref: reference, CT: computed tomography

CI=1.285-5.026; p=0.007) were significant predictors of a successful diagnosis using EBUS-GS-guided TBB (Table 2).

The probe position was within the PPL in 83 of the 175 (47%) lesions. The univariate analysis showed that a positive CT bronchus sign (vs. negative) and lesion size >20 mm

(vs. ≤20 mm) were significantly associated with an EBUS finding of “within” PPL. These two factors were also found to be statistically significant in the multivariate analysis. The lesion location and structure were not significantly associated with successful EBUS visualization (Table 3).

Table 3. Logistic Regression Analysis of Factors for Visualization of EBUS.

Variables		Within (n = 83)	Adjacent to or outside (n = 92)	Univariate OR (95%CI)	p value	Multivariate OR (95%CI)	p value
Location	S1, S2, S1+2 and S6 (n=85)	42	43	0.857 (0.4737-1.552)	0.61	—	—
	The others (n=90)	41	49	1 (ref)			
Structure	Solid nodule (n=137)	69	68	1.739 (0.830-3.643)	0.142	—	—
	Subsolid nodule (n=38)	14	24	1 (ref)			
Size	>20 mm (n=94)	26	55	3.259 (1.747-6.079)	<0.001	3.120 (1.649-5.905)	<0.001
	≤20 mm (n=81)	57	37	1 (ref)		1 (ref)	
CT bronchus sign	Positive (n=144)	76	68	3.832 (1.553-9.456)	0.004	3.568 (1.407-9.048)	0.007
	Negative (n=31)	7	24	1 (ref)		1 (ref)	

EBUS: endobronchial ultrasonography, OR: odds ratio, CI: confidence interval, ref: reference, CT: computed tomography

Figure 3. (a) ROC curves comparing the EBUS image with a combination of three CT findings (structure, CT bronchus sign, and size) in relation to the EBUS-GS-guided TBB diagnostic yield. (b) The areas under the ROC curves for the EBUS image, the three variables, and the combination of the EBUS image and the three variables were 0.635, 0.670, and 0.708, respectively.

Fig. 3 shows the ROC curves comparing the EBUS image with a combination of three CT findings (structure, CT bronchus sign status, and size) in relation to the EBUS-GS-guided TBB diagnostic yield. The areas under the ROC curves for the EBUS image, the three variables, and that the combination of the EBUS image and three variables were

0.635, 0.670, and 0.708, respectively.

Discussion

Although there are previous reports which identify some of the factors that affect the EBUS-GS diagnostic yield,

most previous studies have included patients with benign and malignant diseases or with lesions of >30 mm. Several previous reports have revealed a difference in the diagnostic yield in patients with benign and malignant diseases (8, 15). In the present study, we therefore restricted our patient selection to patients with small (≤ 30 mm) primary lung carcinoma. The results of our study revealed that the overall diagnostic yield was 64%, and that a solid nodule structure, CT bronchus sign positivity, and the “within” PPL probe position were independently associated with a successful diagnosis. Furthermore, we showed that both the HRCT and EBUS findings were important for a successful diagnosis using the ROC curves.

Rivera et al. reported that conventional flexible bronchoscopy for peripheral lesions ≤ 20 mm and >20 mm in diameter showed sensitivities of 34% and 63%, respectively, whereas TBB using radial-EBUS showed a 56% diagnostic yield in lesions of ≤ 20 mm and 78% in lesions of >20 mm in a recently performed meta-analysis (2). The probe position was an important factor in predicting the diagnostic yield of EBUS-GS-guided TBB. Previous reports have indicated the probe position to be the only significant diagnostic factor (7, 8). In the multivariate analysis of the present study, the “within” PPL probe position was found to be significantly associated with a successful diagnosis using radial EBUS (OR=2.542; $p=0.007$). With regard to EBUS imaging, Huang et al. reported that lesion size (≤ 20 mm or >20 mm) is a significant factor affecting PPL visualization using EBUS; however, the CT bronchus sign was not included in their univariate or multivariate analyses (15). In the present study, a lesion size of >20 mm and CT bronchus sign positivity were found to significantly associated with the successful visualization of the probe position within the lesion in the multivariate analysis ($p<0.001$ and $p=0.007$, respectively).

Our institution previously reported that the internal opacity of lesions is a significant diagnostic factor for PPL; however, the sensitivity of this factor was low for small non-solid type lung carcinoma (6). Because GGNs are usually difficult to identify using radiographic fluoroscopy or EBUS, the TBB diagnostic yield may be low. Recently, some reports described the use of TBB with EBUS-GS, including different types of EBUS images, for the diagnosis of GGNs (16, 17). Izumo et al. investigated radial EBUS images, and showed a correlation between the blizzard sign (a subtle, but noticeable increase in intensity and a radius with a whitish acoustic shadow) and pure GGNs (16). The diagnostic yield of EBUS-guided TBB may be improved in GGNs with the use of new data.

Previous reports have revealed a higher conventional TBB diagnostic yield for patients with peripheral lung lesions in whom the CT bronchus sign is present (9, 18). CT bronchus sign positivity is significantly associated with visualization of the lesion using EBUS and a successful bronchoscopic diagnosis using EBUS-GS (19-21). In the present study CT bronchus sign positivity was found to be significantly asso-

ciated with a successful diagnosis and with EBUS visualization in both the univariate and multivariate analyses.

Although multivariate analyses of two previously published studies indicated that lesion size is a statistically significant factor for the bronchoscopic diagnosis of PPL (17, 22), other studies have failed to corroborate these findings (7, 8). The univariate analysis of the present study showed that the diagnostic yield was significantly higher in lesions of >20 mm in diameter in comparison to those of ≤ 20 mm in diameter; however, the multivariate analysis did not show any significance. Only 32% (25/79) of the lesions with diameters of ≤ 20 mm were visualized with the EBUS probe within the lesion. In contrast, 61% (57/94) of the lesions with diameters of >20 mm were visualized with the EBUS probe ($p<0.001$). Although EBUS visualization is difficult in smaller PPLs, a successful diagnosis may be achieved, particularly in lesions that are visible using EBUS.

Shinagawa et al. reported that lesions located in the left S6 segment had significantly lower diagnostic sensitivity in comparison to lesions in other locations using an ultrathin bronchoscope under CT guidance (23). Yoshikawa et al. found that the diagnostic yields were significantly high for PPLs located in the right-middle lobe and the left lingular segment (22). Other studies indicate that it is difficult to reach lesions in the right-upper lung because the tips of EBUS catheters are relatively long and stiff, and are difficult to maneuver in tortuous airways (14, 24). We therefore divided the lesion locations into S1, S2, S1+2, and S6 or others, based on the assumption that it is not easy to reach lesions in the former segments; however, we did not find any significant differences in the diagnostic yield among the different locations.

Although the EBUS image is a highly significant factor for a successful diagnosis using EBUS-GS, we showed that HRCT findings before bronchoscopy are important. The area under the curve for the combined EBUS image and three factors regarding the HRCT findings were superior to those for the EBUS image or the three factors alone (area under the curve 0.708 vs. 0.635 and 0.670, respectively; Fig. 3). Thus, CT and EBUS findings are important for the successful diagnosis of small peripheral lung cancer using EBUS-GS-guided biopsy. The lung cancer diagnostic yield was 84.4% when pre-procedure HRCT revealed a solid and larger nodule with CT bronchus sign positivity and the EBUS image during bronchoscopy showed a “within” PPL probe position. This is a considerably high diagnostic yield; however, there were some unsuccessful cases. It is therefore essential to consider additional diagnostic modalities based on multidisciplinary discussions when anticipated results are not obtained.

Virtual bronchoscopy (VB) is a CT-based imaging technique which allows a noninvasive intraluminal evaluation of the tracheobronchial tree and which is used as a guide to navigate the bronchoscope near a target lesion (4, 6, 10). Ishida et al. reported that VBN improved the diagnostic yield while decreasing the overall duration of the examina-

tion (25). In a recent study, Asano et al. revealed that VBN improved the diagnostic yield for lesions showing involved bronchi on CT images (21). In the present study, all patients underwent bronchoscopy with VBN and CT bronchus sign positivity was independently associated with a successful diagnosis.

Our study is associated with some limitations. Our conclusions may not be generalized because the study was retrospective in nature and because it was performed at a single medical institution. Our study included only seven pure GGN lesions and no lesions of <10 mm in diameter. Smaller lesions (<15 mm) and pure GGN cases have a lower diagnostic yield (6, 8, 17). It is therefore possible that lesions that were fit for TBB-based diagnosis were selected.

Conclusion

In conclusion, the CT findings, including CT bronchus sign positivity and lesion structure and EBUS visualization for EBUS-GS-guided biopsy were significant diagnostic factors in patients with small peripheral lung cancer. Therefore, chest physicians must carefully evaluate patients' HRCT findings on an individual basis before performing bronchoscopy to assess the best way to diagnose a PPL.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We are indebted to all of the participating clinicians. The present study was supported in part by a Grant-in-Aid for scientific research from the Japan Society for the Promotion of Science (Grant Number 15K19282).

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