Original Article Open Access

Endobronchial ultrasound-guided transbronchial biopsy for ground-glass opacity-predominant nodules in the lung periphery

Tomoya Horiguchi, MD, Tomoyuki Minezawa, MD, PhD, Takuya Okamura, MD, PhD, Yosuke Sakakibara, MD, Sayako Morikawa, MD, PhD, Yusuke Gotoh, MD, Tomohide Souma, MD, Ken Akao, MD, Toshikazu Watanabe, MD, Sakurako Uozu, MD, Yasuhiro Goto, MD, PhD, Masamichi Hayashi, MD, PhD, Sumito Isogai, MD, PhD, Kazuyoshi Imaizumi, MD, PhD

Department of Respiratory Medicine, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

Abstract

Objectives: Peripheral lung nodules containing ground-glass opacity (GGO), which include both pure GGN (nodules that contain only GGO) and part-solid GGN (nodules that contain both GGO and consolidation), are difficult to diagnose by conventional transbronchial biopsy (TBB) because they are not visible by fluoroscopy. Recently developed endobronchial ultrasound (EBUS)-guided TBB is useful for diagnosing these nodules. This study was performed to clarify the contribution of EBUS to the diagnostic yield of TBB for peripheral lung nodules containing GGO.

Methods: We retrospectively reviewed the medical records of 41 patients (21 male, 20 female; median age, 72 years) with peripheral lung pure GGN or part-solid GGN who underwent EBUS-guided TBB.

Results: The median diameter of the target lesions was 18.6 mm (range, 8.8–46.7 mm). There were seven pure GGN lesions and 34 part-solid GGN lesions. The total diagnostic yield was 65.9% (27/41). EBUS images could be obtained (positive) in 30 (73.1%) patients. Among the clinical factors studied, only a positive EBUS finding was significantly associated with a higher diagnostic yield (p=0.018). Diagnostic yield tended to be higher in patients with a positive CT bronchus sign (presence of a bronchus leading directly to the target lesion) and increased consolidation-to-tumor ratio.

Conclusions: EBUS-guided TBB is useful for diagnosing GGN or part-solid GGN. Obtaining positive EBUS findings is important for successful TBB for lesions containing GGO.

Keywords: Ground-glass opacity, Endobronchial ultrasound (EBUS), CT bronchus sign, Consolidation-to-tumor ratio (CTR)

Introduction

Recent advances in bronchoscopic procedures, such as endobronchial ultrasound (EBUS)-guided transbronchial biopsy (TBB), have improved the diagnostic yield of peripheral lung lesions.[1] As chest computed tomography (CT) screening has become more widespread, smaller peripheral lung lesions have become more readily detected in the daily clinical setting.[2] Similarly, peripheral nodules that contain ground-glass opacity (GGO) can be detected by chest CT, but not by conventional chest X-ray. However, nodules that contain only GGO (pure GGN lesions) and nodules that contain both GGO and consolidation (part-solid GGN lesions) are difficult to diagnose by TBB partly because the lesions are often invisible on fluoroscopy.[3] Additionally, atypia of tumor cells is relatively low in GGO lesions.[4] Therefore, pathological diagnosis of small biopsy samples is sometimes difficult.

We previously reported that the diagnostic yield of EBUS-guided TBB for small peripheral lesions (not only GGO lesions) was significantly associated with the CT bronchus sign (presence of a bronchus leading directly to the target lesion).[5] Ikezawa et al.[6] reported that EBUS-guided TBB is also useful for diagnosing GGO-predominant lesions. They reported that an aberrant EBUS finding could be obtained in many patients with GGN-predominant lesions. In daily clinical practice, however, aberrant EBUS findings are not always easy to recognize.[7] Therefore, the present study was performed to investigate the diagnostic contribution of EBUS during TBB for GGO lesions. We retrospectively reviewed the medical records of patients with pure GGN or part-solid GGN peripheral lung lesions who underwent EBUS-guided TBB in our hospital.

Methods

Patients

We retrospectively reviewed the medical records of consecutive patients who underwent EBUS-guided bronchoscopy for lung lesions containing GGO in Fujita Health University Hospital from April 2015 to March 2017. We selected patients with lesions that contained more than 25% GGO in the tumor on thin-section chest CT (TSCT, 0.5-mm slices) images. The Fujita Health University Institutional Review Board approved this study protocol, which was conducted in accordance with the tenets of

Received 17 June, 2017, **Accepted** 24 August, 2017.
Corresponding author: Kazuyoshi Imaizumi, MD, PhD
Department of Respiratory Medicine, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan
E-mail: jeanluc@fujita-hu.ac.jp

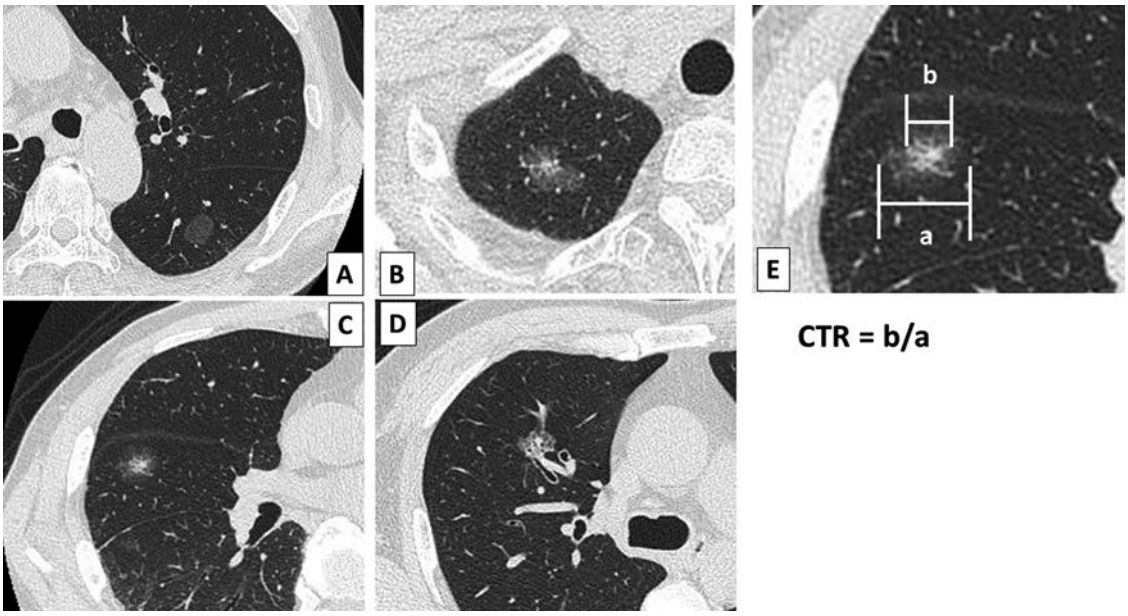

Figure 1 Representative images of classification according to the consolidation-to-tumor ratio (CTR).
(A) CTR=0 (pure GGN; i.e., nodule containing only ground-glass opacity), (B) CTR>0 and ≤25, (C) CTR >25 and ≤50, and (D) CTR >50 and ≤75. (E) The CTR was defined as the ratio of the maximum size of consolidation to the maximum tumor size on thin-slice computed tomography.

the Declaration of Helsinki (approval number: HM 17-060).

Chest CT evaluation

All patients underwent chest TSCT within 1 month before bronchoscopy. TSCT images were generated using a non-enhanced multidetector CT system (Aquilion One Vision Edition; Toshiba Medical Systems, Tokyo, Japan). More than two bronchoscopists carefully evaluated a TSCT image for each patient. We determined the size and location of the lesions and the respective bronchus as well as the number of bronchial branches that reached the target lesion from the trachea before bronchoscopy. We investigated the CT bronchus sign, which was identified as the presence of a bronchus directly leading to the target lesion, as described elsewhere.[5] Briefly, we categorized the relationship between the target lesion and the nearest bronchus into three types of CT bronchus signs (A to C). In type A, the responsible bronchus clearly reached the inside of the target lesion. In type C, no bronchus could be detected in relation to the lesion. When the CT findings could be categorized as neither type A nor C (when the responsible bronchus reached only the edge of the target lesion), the CT bronchus sign was categorized as type B. We also evaluated the consolidation-to-tumor ratio (CTR), which was defined as the ratio of the maximum size of consolidation to the maximum tumor size on TSCT (Figure 1).[8] A pure GGN tumor was defined as a tumor without a solid component (CTR=0). Part-solid GGN tumors (tumors with both GGO and consolidation) were categorized according to the area of GGO lesions in the tumor (CTR≤25, CTR>25 to CTR≤50, and CTR>50 to CTR≤75) (Figure 2). Two pulmonologists independently evaluated the TSCT images and determined the CTR and CT bronchus sign. When the two bronchoscopists recommended different classifications, the final classification was determined by discussion.

Bronchoscopic procedures and evaluation of results

After administration of local pharyngeal anesthesia, all of the patients were sedated with an individually calculated dose of intravenous midazolam, as reported elsewhere.[9] TBB using EBUS was performed according to a modification of the standard Kurimoto method.[10] A 20-MHz radial type ultrasound probe with an external diameter of 1.4 mm (UM-S20-17S; Olympus Medical Systems, Tokyo, Japan) connected to an endoscopic ultrasonography system (EU-M30S; Olympus Medical Systems) was used in all patients. We mainly used a BF-P260F bronchoscope (Olympus Medical Systems) and a guide sheath with an external diameter of 1.9 mm (K-201 kit equipped with a biopsy forceps and cytological brush; Olympus Medical Systems). According to the size or location of the lesion, the operator could add a biopsy using larger biopsy forceps (FB-231D; Olympus

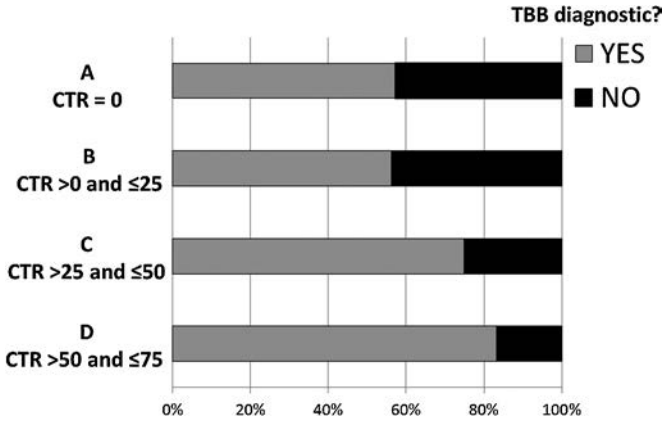

Figure 2 Relationship between the consolidation-to-tumor ratio (CTR) and diagnostic yield of endobronchial ultrasound-guided transbronchial biopsy for lesions containing ground-glass opacity (GGO).
(A) CTR=0 (pure GGN; i.e., nodule containing only GGO), (B) CTR >0 and ≤25, (C) CTR >25 and ≤50, and (D) CTR >50 and ≤75. The diagnostic yield tended to be lower when lesions contained more GGO; however, this difference was not statistically significant ($p=0.3$, χ^2 test). TBB, transbronchial biopsy.

Medical Systems). EBUS findings with hyperechoic fine dots, hyperechoic linear arcs, or a hypoechoic nodule were characterized as positive, and those with a whitish acoustic shadow that represented normal air-filled alveoli were characterized as negative.[6] We took at least nine samples. In this study, we determined successful (diagnostic) bronchoscopy when TBB showed evident malignant findings on histological examination, a distinct histological pattern (e.g., epithelioid granuloma or intra-alveolar organization), or the presence of bacteria accompanied by reasonable radiological and clinical findings.

Statistical methods

Statistical analyses were carried out using JMP software (ver. 8.0; SAS Institute, Inc., Cary, NC). Differences in proportions were evaluated with the χ^2 test. Spearman's rank correlation was used to identify the association between two ordinal variables. A p value of <0.05 was considered to indicate statistical significance. All analyses were two-sided.

Results

Patients' characteristics and details of lesions

Table 1 shows the characteristics of the patients and targeted peripheral lesions containing GGO in this study. Forty-one patients (21 male, 20 female) underwent TBB for pulmonary nodules containing GGO during the study period. The median age of the patients was 72 years (range, 46–80 years). The median diameter of the lesions was 18.6 mm (range, 6.8–46.7 mm). We classified the lesions according to the CTR. Seven (17.1%) lesions had a CTR of 0% (pure GGN lesions), and 68.7% of part-solid GGN lesions had a CTR of ≤50%. Therefore, more than 80% of the studied lesions were GGO-predominant lesions (Figure 1). The number of bronchial branches that reached the target lesion from the trachea ranged from four to eight (median, 6). Type A and B CT bronchus signs (responsible bronchus leading to the lesion) were observed in 34 (82.9%) cases.

Table 1 Characteristics of patients and targeted GGO lesions (n=41)

Variable (patients)		
Age, years		72 (46–80)
Sex		
Male		21 (51.2)
Female		20 (48.8)
Variable (GGN lesions)		
Diameter of lesion, mm		18.6 (8.8–46.7)
Location of lesions		
Upper lobe		21 (51.2)
Lingular lobe or middle lobe		6 (14.6)
Superior segment of lower lobe		8 (19.5)
Lower lobe (except superior segment)		6 (14.6)
Extent of GGO on thin-section CT features		
Pure GGN	CTR*=0	7 (17.1)
Part-solid GGN	0<CTR≤25	16 (39.0)
	25<CTR≤50	12 (29.3)
	50<CTR≤75	6 (14.6)
Number of branches reaching the lesion		
Mean		5.78
4		5 (12.2)
5		14 (34.1)
6		11 (26.8)
7		7 (17.1)
8		4 (9.8)
CT bronchus sign		
Type A		8 (19.5)
Type B		26 (63.4)
Type C		7 (17.1)

Data are presented as median (range), n (%), or n.
GGO, ground-glass opacity; Pure GGN, nodules containing only GGO; Part-solid GGN, nodules containing both GGO and consolidation; CT, computed tomography; CTR, consolidation-to-tumor ratio

Pathological results (diagnostic yield) and outcome of target lesions

Relevant pathological results were obtained in 65.9% (27/41) of the patients (Table 2). Twenty-four patients had adenocarcinoma and three had benign disease (nontuberculous mycobacteriosis and organizing pneumonia). Nineteen patients with adenocarcinoma underwent subsequent surgical resection, leading to a final pathological classification of adenocarcinoma (lepidic or lepidic-predominant pathology constituted the majority). Surprisingly, we were able to diagnose four cases of adenocarcinoma *in situ* by EBUS-guided TBB. However, among 14 (34.1%) patients who could not be diagnosed by TBB, 5 underwent surgery, leading to a final diagnosis of adenocarcinoma. Nine patients were closely followed up.

Factors contributing to the diagnostic yield

We evaluated the contribution of clinical factors to the bronchoscopic diagnostic yield (Table 3). The lesion size and location, number of bronchial branches reaching the lesion, and GGO lesion area (pure GGN or part-solid GGN) were not significantly associated with successful bronchoscopic diagnosis. Among factors associated with the bronchoscopic procedures, the use of large forceps and fluoroscopic visibility were not associated with successful diagnosis of GGO lesions by EBUS-guided TBB. However, whether EBUS images of the lesions could be obtained was significantly associated with successful diagnosis (76.7% when positive EBUS findings could be obtained versus 36.4% when they could not; p=0.018). There appeared to be an increase in diagnostic yield as the CTR increased, but this

Table 2 Final diagnosis of targeted ground-glass opacity-predominant nodules (n=41)

Diagnosed by EBUS-guided biopsy (n=27, 65.9%)	
Lung cancer (adenocarcinoma)	24
Lepidic	4
Lepidic-predominant	7
Papillary	2
Acinar-predominant	2
Adenocarcinoma *in situ*	4
Undetermined	5
Benign diseases	3
Nontuberculous mycobacteriosis	1
Organizing pneumonia	2
Undiagnosed by EBUS-guided biopsy (n=14, 34.1%)	
Lung cancer (adenocarcinoma)	
Papillary	2
Papillary-predominant	1
Lepidic-predominant	1
Adenocarcinoma *in situ*	1
Unknown	9

EBUS, endobronchial ultrasound

Table 3 Contribution of clinical factors to diagnostic yield

Total diagnostic yield		27/41 (65.9%)	
Variables		Diagnostic yield	*p* value
Lesion diameter	<20 mm	13/22 (59.1)	0.32
	≥20 mm	14/19 (73.7)	
Lesion location	Upper lobe or superior segment of lower lobe	17/28 (60.7)	0.29
	Middle or lower lobe[a]	10/13 (76.9)	
Number of bronchial branches reaching the lesion	≥6	14/22 (63.6)	0.74
	≤5	13/19 (68.4)	
GGO lesion area	Pure GGN (CTR=0)	4/7 (57.1)	0.60
	Part-solid GGN (CTR>0)	23/34 (67.7)	
CT bronchus sign	Positive (type A+B)	24/34 (70.6)	0.169
	Negative (type C)	3/7 (42.9)	
Large forceps use[b]	Yes	15/21 (71.4)	0.44
	No	12/20 (60.0)	
Visibility on fluoroscopy	Visible	4/7 (57.1)	0.59
	Invisible	23/34 (67.7)	
EBUS finding	Positive	23/30 (76.7)	0.018[d]
	Negative[c]	4/11 (36.4)	

Data are presented as n (%).
GGO, ground-glass opacity; Pure GGN, nodules containing only GGO; Part-solid GGN, nodules containing both GGO and consolidation; CT, computed tomography; CTR, consolidation-to-tumor ratio; EBUS, endobronchial ultrasound
[a]Except for superior segment of the lower lobe.
[b]Biopsy using larger forceps (Olympus FB231D Disposable Biopsy Forceps®).
[c]No remarkable ultrasound findings were observed.
[d]Statistically significant.

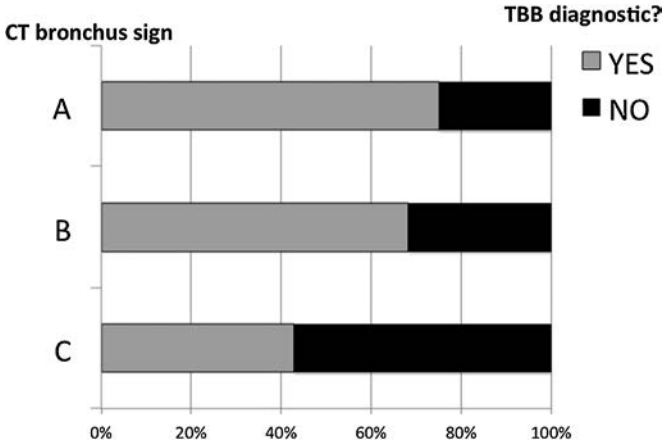

Figure 3 Relationship between computed tomography (CT) bronchus sign and diagnostic yield of endobronchial ultrasound-guided transbronchial biopsy (TBB) for lesions containing ground-glass opacity. When the CT bronchus sign was type A (responsible bronchus clearly recognizable within the target lesion), endobronchial ultrasound-guided TBB showed the highest diagnostic yield. However, the difference was not statistically significant (p=0.064, χ^2 test).

was not statistically significant (p=0.3, χ^2 test) (Figure 2). Additionally, as shown in Figure 3, the diagnostic yield tended to increase according to the CT bronchus sign (A>B>C); however, this was also not statistically significant (p=0.064, χ^2 test). We found no significant association between the EBUS findings and the CTR or CT bronchus sign.

Discussion

In recent years, chest CT has been more widely used for both health checks and screening examinations for lung diseases in Japan.[11] Although CT provides more information than conventional chest X-ray, it often shows small peripheral lung nodules. Therefore, the widespread use of CT screening may cause another clinical issue regarding how these small nodules can be diagnosed. Recently developed EBUS-related techniques, such as EBUS with a guide sheath and EBUS-guided TBB, are useful for diagnosing such small lung lesions.[12] However, the usefulness of EBUS-guided TBB for diagnosis of lesions containing GGO has not been fully determined. Because well-differentiated adenocarcinoma with less atypia often shows GGO density, small TBB specimens are sometimes inadequate for diagnosis. GGO lesions are also frequently invisible on fluoroscopy.[7] For these reasons, lesions containing GGO are thought to be difficult to diagnose by TBB. In this study, we showed that the diagnostic yield for GGO lesions by EBUS-guided TBB was acceptable. This suggests that we should perform TBB for diagnosis of lung peripheral lesions containing GGO.

Because GGO lesions in the lung periphery are often well-differentiated adenocarcinoma,[13] some clinicians perform surgical resection as the first-choice therapeutic procedure.[14] However, our study showed that a small percentage of GGO lesions were benign diseases that did not require surgery. Additionally, a recent increase in the use of chest CT has caused an increase in the number of patients who are unfit for surgery, such as very old patients or those with respiratory insufficiency.[15] For these patients, clinicians should choose an alternative therapy such as radiotherapy or administration of anti-cancer drugs. Establishment of a pathological diagnosis is important for these types of patients. Moreover, establishment of a pathological diagnosis is essential for patients to make decisions regarding their own therapy.

Some previous studies have revealed the usefulness of EBUS-guided TBB for diagnosis of lesions containing various proportions of GGO.[3,6] These studies showed that the tumor size and CT bronchus sign were significantly associated with an

increased diagnostic yield. In the present study, the diagnostic yield tended to be higher for lesions with a positive CT bronchus sign or higher CTR, although the difference was not statistically significant. We speculate that both the CTR and CT bronchus sign may affect the ability to obtain a successful diagnosis by TBB for lesions containing GGO. Our study showed that positive EBUS findings were the only significant factor for successful diagnosis. Ikezawa et al.[6] reported abnormal EBUS findings in more than 90% of cases, although the target lesions containing GGO in their study showed details similar to those in our study. These discrepancies between studies may be due to differences in the sample sizes or technical levels in different institutions. However, our study and other studies have shown that EBUS-guided TBB is useful for diagnosis of GGO[3] and that careful evaluation of EBUS and CT images is essential.

This study has some limitations. First, because this was a retrospective study, patients were selected for EBUS-guided TBB at the physician's discretion. Therefore, patient selection bias is likely to be present. Second, the sample size was small. The CT bronchus sign might have been an important factor associated with higher diagnostic yield for GGO lesions if the sample size had been larger. Third, because considerable training is required for EBUS-guided TBB, the technical skills needed for this procedure might differ among institutions. A prospective, multicenter study with a large number of patients is required in the future.

In conclusion, our study shows that EBUS-guided TBB is useful for GGN lung lesions. Obtaining relevant abnormal findings of the target GGN lesions by EBUS may be important to increase the diagnostic yield.

Abbreviations

CT, computed tomography
EBUS, endobronchial ultrasonography
TBB, transbronchial biopsy
TSCT, thin-section computed tomography
GGO, ground-glass opacity
Pure GGN lesions, nodules containing only GGO
Part-solid GGN lesions, nodules containing both GGO and consolidation
CTR, consolidation-to-tumor ratio

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

TH participated in the design of the study, evaluation of the EBUS images, and drafting of the manuscript. TM and TO participated in evaluation of the TSCT findings. YS, SM, TS, and KA helped to draft the manuscript. YG participated in the design of the study. YS, SM, YG, TS, KA, TW, SU, MH, and SI revised the manuscript. KI participated in the design of the study and performed the statistical analysis. All authors read and approved the final manuscript.

Acknowledgments

The authors thank Mrs. Naomi Maeda for her excellent secretarial help. We also thank Mrs. Chikako Hibiya and Ms. Noriko Hiramatsu for their technical assistance.

References

1. Slavova-Azmanova NS, Lizama C, Johnson CE, Ludewick HP, Lester L, Karunarathne S, Phillips M. Impact of the introduction of EBUS on time to management decision, complications, and invasive modalities used to diagnose and stage lung cancer: a pragmatic pre-post study. BMC Cancer 2016; 16: 44.
2. Morgan L, Choi H, Reid M, Khawaja A, Mazzone PJ. The frequency of incidental findings and subsequent evaluation in low-dose CT scans for lung cancer screening. Ann Am Thorac Soc 2017; 14: 1450–6.
3. Ikezawa Y, Sukoh N, Shinagawa N, Nakano K, Oizumi S, Nishimura M. Endobronchial ultrasonography with a guide sheath for pure or mixed ground-glass opacity lesions. Respiration 2014; 88: 137–43.
4. Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K, Tada H, Mitsudomi T, Tsuboi M, Shibata T, Fukuda H, Kato H; Japan Lung Cancer Surgical Study Group. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol 2011; 6: 751–6.
5. Minezawa T, Okamura T, Yatsuya H, Yamamoto N, Morikawa S, Yamaguchi T, Morishita M, Niwa Y, Takeyama T, Mieno Y, Hoshino T, Uozu S, Goto Y, Hayashi M, Isogai S, Matsuo M, Nakanishi T, Hashimoto N, Okazawa M, Imaizumi K. Bronchus sign on thin-section computed tomography is a powerful predictive factor for successful transbronchial biopsy using endobronchial ultrasound with a guide sheath for small peripheral lung lesions: a retrospective observational study. BMC Med Imaging 2015; 15: 21.
6. Ikezawa Y, Shinagawa N, Sukoh N, Morimoto M, Kikuchi H, Watanabe M, Nakano K, Oizumi S, Nishimura M. Usefulness of endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation for ground-glass opacity lesions. Ann Thorac Surg 2017; 103: 470–5.
7. Sasada S, Izumo T, Chavez C, Tsuchida T. Blizzard sign as a specific endobronchial ultrasound image for ground glass opacity: a case report. Respir Med Case Rep 2014; 12: 19–21.
8. Hattori A, Matsunaga T, Hayashi T, Takamochi K, Oh S, Suzuki K. Prognostic impact of the findings on thin-section computed tomography in patients with subcentimeter non-small cell lung cancer. J Thorac Oncol 2017; 12: 954–62.
9. Ogawa T, Imaizumi K, Hashimoto I, Shindo Y, Imai N, Uozu S, Shimokata T, Ito S, Hashimoto N, Sato M, Kondo M, Hasegawa Y. Prospective analysis of efficacy and safety of an individualized-midazolam-dosing protocol for sedation during prolonged bronchoscopy. Respir Investig 2014; 52: 153–9.
10. Fujita Y, Seki N, Kurimoto N, Inoue K, Miyazawa T, Abe T, Eguchi K. Introduction of endobronchial ultrasonography (EBUS) in bronchoscopy clearly reduces fluoroscopy time: comparison of 147 cases in groups before and after EBUS introduction. Jpn J Clin Oncol 2011; 41: 1177–81.
11. Nawa T, Nakagawa T, Mizoue T, Kusano S, Chonan T, Hayashihara K, Suito T, Endo K. A decrease in lung cancer mortality following the introduction of low-dose chest CT screening in Hitachi, Japan. Lung Cancer 2012; 78: 225–8.
12. Kurimoto N, Miyazawa T, Okimasa S, Maeda A, Oiwa H, Miyazu Y, Murayama M. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest 2004; 126: 959–65.
13. Kudo Y, Matsubayashi J, Saji H, Akata S, Shimada Y, Kato Y, Kakihana M, Kajiwara N, Ohira T, Nagao T, Ikeda N. Association between high-resolution computed tomography findings and the IASLC/ATS/ERS classification of small lung adenocarcinomas in Japanese patients. Lung Cancer 2015; 90: 47–54.
14. Choi SH, Chae EJ, Shin SY, Kim EY, Kim JE, Lee HJ, Oh SY, Lee SM. Comparisons of clinical outcomes in patients with and without a

preoperative tissue diagnosis in the persistent malignant-looking, ground-glass-opacity nodules. Medicine (Baltimore) 2016; 95: e4359.
15. Georgiou HD, Taverner J, Irving LB, Steinfort DP. Safety and efficacy of radial EBUS for the investigation of peripheral pulmonary lesions in patients with advanced COPD. J Bronchology Interv Pulmonol 2016; 23: 192–8.