Endobronchial Ultrasonography with a Guide Sheath for Pure or Mixed Ground-Glass Opacity Lesions

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Key Words

Lung cancer diagnosis · Bronchoscopy · Endobronchial ultrasonography · Ground-glass opacity

Abstract

Background: Ground-glass opacity (GGO) lesions are difficult to diagnose by transbronchial biopsy (TBB). **Objectives:** We attempted to diagnose solitary peripheral GGO predominant-type lesions by TBB using endobronchial ultrasonography with a guide sheath (EBUS-GS) under X-ray fluoroscopic guidance, and to evaluate several factors associated with diagnostic yield. **Methods:** The medical records of 67 patients with GGO predominant-type lesions who underwent TBB using EBUS-GS under X-ray fluoroscopic guidance were retrospectively reviewed. **Results:** Of the 67 lesions, 38 (57%) were successfully diagnosed by EBUS-GS (5/11 pure GGO lesions and 33/56 mixed GGO lesions). The diagnosable lesions were significantly larger than the nondiagnosable lesions (24 vs. 17 mm, respectively; $p < 0.01$). Regarding the diagnostic yield by signs on computed tomography, the lesions with a bronchus leading directly to a lesion had a significantly higher diagnostic yield than the others ($p < 0.05$). When GGO lesions were confirmed under X-ray fluoroscopic guidance, the diagnostic yield was 79% (vs. 40% in lesions

not visible on X-ray fluoroscopy; $p < 0.05$). **Conclusions:** EBUS-GS is a useful and valuable diagnostic modality, even for GGO predominant-type lesions located at the lung periphery.

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Introduction

Lung cancer is a major health problem world-wide, and the majority of patients are diagnosed with advanced and unresectable disease (stage IIIB/IV) which carries a 5-year survival rate of $<5\%$ [1]. It is important to detect and treat lung cancer at an early stage. Recently, due to advances in computed tomography (CT) and the increase in low-dose helical CT used in lung cancer screening, small nodules including solitary peripheral ground-glass opacity (GGO) lesions are being detected with greater frequency [2, 3]. The diagnosis of peripheral pulmonary lesions has also improved due to the introduction of endobronchial ultrasonography with a guide sheath (EBUS-GS) [4, 5]. A GGO lesion is a finding on high-resolution CT (HRCT) that is defined as hazy increased attenuation of the lung with preservation of bronchial and vascular margins.

Fig. 1. Pure GGO images. **a** Thin-section CT shows a homogeneous focal translucent GGO in the lung window image. **b** Thin-section CT shows no solid component in the mediastinal image. Image of a pure GGO on EBUS shows a delicate high echoic pattern (**c**) compared with a normal lung (**d**).

In terms of radiologic characteristics, two types of GGO predominant-type lesions can be identified. A pure GGO is a lesion which has no solid component, and a mixed GGO is a lesion which consists of heterogeneous attenuation with a solid component [6–8]. Recent studies have reported that some GGO predominant-type lesions, which are unchanged or become larger during clinical follow-up, are likely to be diagnosed as adenocarcinoma or precancerous lesions. These lesions rarely have lymph node metastases, and are expected to be cured by surgical resection [9–12]. Many mixed GGO lesions are caused by adenocarcinoma and tend to become larger and invasive [13–16].

Some studies have reported that when surgical resection is performed without a histologically definitive diagnosis, GGO lesions are finally diagnosed as atypical

adenomatous hyperplasia, adenocarcinoma in situ, adenocarcinoma, infection, focal organizing pneumonia or fibrosis [8–17]. In the event of a pure GGO finding, malignant disease is seen in 34–84% of cases, and benign disease is found in 0–23%. In contrast, with a finding of mixed GGO, malignant disease is found in 94–100% of cases whereas benign disease is found in 0–6% [8, 11, 16]. Most mixed and many pure GGO lesions with a size of >10 mm are malignant; however, a few GGO predominant-type lesions are sometimes benign. This makes it important to diagnose GGO predominant-type lesions before an operation, in order to avoid unnecessary surgery. However, the diagnosis of GGO predominant-type lesions by transbronchial biopsy (TBB) is attended by several methodological problems: (1) the lesion may not be visible under X-ray fluoroscopic guidance, (2) there is difficulty in identifying accessible bronchial routes to reach a peripheral GGO lesion within the time limitation of the procedure, and (3) it is difficult to confirm whether biopsy forceps or a brush has reached the lesion accurately.

The contrast of GGO lesions on EBUS created by the proportion of air surrounding the EBUS probe compared with the image of a normal lung enables accurate confirmation of the position of the lesion with the EBUS-GS procedure. This, in turn, can confer a favorable rate of diagnosis. In this study, we evaluated the diagnostic yield of GGO predominant-type lesions by bronchoscopy utilizing EBUS-GS as well as several factors associated with the diagnosis of the lesions.

Methods

Patients

The medical records of 67 patients with GGO predominant-type lesions who underwent TBB using EBUS-GS under X-ray fluoroscopic guidance between August 2004 and December 2010 at the Hokkaido University Hospital or the Hokkaido Cancer Center were retrospectively reviewed. This study was approved by the institutional review board of Hokkaido University Hospital (project approval No. 009-0312), and all patients provided written informed consent for TBB using EBUS-GS. In this study, GGO predominant-type lesions were defined as having a percent reduction of the maximum tumor area in the mediastinal window image (fig. 1b, 2b) compared to the area in the lung window image (fig. 1a, 2a) on thin-slice CT of $\geq 50\%$ [15]. Among these lesions, pure GGO was defined as described above (fig. 1a, b), and mixed GGO was defined as a lesion consisting of heterogeneous attenuation with any solid components (fig. 2a, b).

CT Signs

CT signs of the lesions were retrospectively reviewed as has been previously reported [18]. The relationship between the lesions and the bronchial or arterial trees was classified into 1 of 5 types according to their radiologic appearance on HRCT: (1) bronchus (with or without pulmonary artery) leading to the center of the lesion, (2) bronchus (with or without pulmonary artery) leading to the edge of the lesion, (3) pulmonary artery alone leading to the center of the lesion, (4) pulmonary artery alone leading to the edge of the lesion and (5) neither bronchus nor artery leading to the lesion. According to these criteria, the medical records of 67 patients who underwent HRCT before TBB were retrospectively reviewed. In order to assess the relationship between the lesions and the bronchial or arterial trees, images on HRCT were reviewed by two of three experienced pulmonologists. When the decision concerning the bronchus-lesion and artery-lesion relationship by two of the pulmonologists was not compatible, the third pulmonologist made the final decision.

TBB Using EBUS-GS

Local anesthesia of the upper respiratory tract was achieved with 4% lidocaine. EBUS was performed using an endoscopic ultrasound system equipped with a 20-MHz mechanical radial-type probe (UM-S20-17R; Olympus Medical Systems, Tokyo, Japan) with an external diameter of 1.4 mm, or else with an endoscopic ultrasound system equipped with a 20-MHz mechanical radial-type probe (UM-S20-20S; Olympus) with an external diameter of 1.7 mm. A flexible fiberoptic bronchoscope with a 2.0-mm diameter working channel (BF-P-260F; Olympus) and a guide sheath with an external diameter of 1.9 mm were used for the 1.4-mm probe, and a flexible fiberoptic bronchoscope with a working channel <2.8 mm in diameter (BF-1T240; Olympus) and a guide sheath with an external diameter of 2.7 mm were used for the 1.7-mm probe. The bronchoscope was inserted as deeply as possible into the target bronchus under direct vision. An EBUS probe was inserted into the guide sheath, and the probe covered with the guide sheath was then inserted through the bronchoscope working channel and advanced to the GGO lesion in order to obtain an EBUS image. EBUS imaging and X-ray fluoroscopy were used to confirm that the probe and guide sheath had reached the lesion [19]. Pure GGO (fig. 1c) and mixed GGO (fig. 2c) provided different images on EBUS compared to a normal lung (fig. 1d). When an EBUS image of the GGO lesion was not obtained, the probe was removed from the guide sheath and a double-hinged curette was inserted into the guide sheath. The appropriate bronchus was then selected by manipulating the curette under fluoroscopic guidance. Once the bronchus was determined, the curette was removed from the guide sheath and the probe was again inserted into the guide sheath in order to obtain an EBUS image. After locating the lesion using EBUS, the probe was removed to leave the guide sheath in the lesion. Biopsy forceps and a bronchial brush were introduced via the guide sheath, and biopsy and brushing were performed under fluoroscopic guidance for pathologic and cytologic examination.

Diagnosis

Each histologic and cytologic specimen was interpreted by an experienced pathologist. Suspicious findings were regarded as negative in our analysis. The final diagnosis was established by pathologic evidence from biopsy including TBB or surgical procedures.

Fig. 2. Mixed GGO images. **a** Thin-section CT shows a homogeneous focal translucent GGO with solid components in the lung window image. **b** Thin-section CT shows some solid components in the mediastinum image. **c** Image of a pure GGO on EBUS shows a low-echoic nodule surrounded by a highly reflective interface produced between the aerated lung and the lesion.

Statistical Analysis

Data were analyzed using the Pearson χ^2 test. Multivariate analysis was used to identify the factors affecting diagnostic yield. All variables reaching a significant level of 5% in the univariate analysis were tested in a logistic regression analysis. Statistical software (SPSS, version 11.0.1; SPSS; Chicago, Ill., USA) was used for all analyses. Statistical significance was established at $p < 0.05$.

Results

Diagnostic Yield of GGO Predominant-Type Lesions by TBB Using EBUS-GS

Of 67 lesions, 11 were found to be pure GGO lesions and 56 were found to be mixed GGO lesions. The mean ($\pm$ SD) diameter of the lesion was 21 ± 8 mm. There were 28 lesions detected in the right upper lobe, 3 in the middle

Fig. 3. Flow diagram to indicate 67 GGO predominant-type lesions.

lobe, 18 in the right lower lobe, 9 in the left upper lobe and 9 in the left lower lobe (table 1). None of the pure GGO lesions and 27 of the mixed GGO lesions were visible on X-ray fluoroscopy (table 2; fig. 3). Of the 67 lesions, 38 (57%) were successfully diagnosed [5/11 pure GGO lesions (46%) and 33/56 mixed GGO lesions (59%)] by TBB using EBUS-GS (table 1; fig. 3). There were no major complications during this procedure in any of the subjects.

EBUS Image of GGO Predominant-Type Lesions

In 44/56 mixed GGO lesions, we could obtain EBUS images, which showed either hyperechoic fine dots (<1 mm in diameter), hyperechoic linear arcs (primarily around the probe) distributed irregularly within the lesions or hypoechoic nodules seen against a background with a delicate change in brightness of the hypoechoic area and hyperechoic fine dots. In contrast, in 6/11 pure GGO lesions, the hyperechoic fine dots were only just evident. These EBUS images enabled us to confirm the presence of the GGO lesions as well as correctly diagnose 37, i.e. 4/6 (67%) pure GGO lesions and 33/44 (75%) mixed GGO lesions (fig. 3).

Pathologic Diagnosis

The diagnosis was adenocarcinoma in the case of 36 lesions, malignant lymphoma in 1 case and inflammation in 1 case. All 36 lesions diagnosed as adenocarcinoma by TBB using EBUS-GS were removed surgically. Of 29 lesions which we could not diagnose, 26 were resected surgically and the remaining 3 were assigned to clinical follow-up. The postoperative final diagnosis for these 26 lesions was adenocarcinoma.

In this study, to verify the importance of conducting biopsy and brushing as well as taking multiple biopsies from GGO lesions using EBUS-GS, we examined detailed hospital records. These were available for 49 patients in the Hokkaido University Hospital where each specimen obtained by TBB using EBUS-GS had been placed separately into a formalin bottle. For all 49 lesions, the diagnostic yield by combining with histology and cytology was 69% (i.e. 34/49). The diagnostic yield for GGO lesion diagnosed by histology was 57% (28/49) and that by cytology was 51% (25/49). There were no significant differences in the diagnostic yields for histology and cytology. Six lesions were diagnosed by cytology only. For the 34 lesions diagnosed by TBB using EBUS-GS, the median number of biopsy specimens was 6 per GGO

Table 1. Characteristics of diagnosed lesions and nondiagnosed lesions

Character	Diagnosed (n = 38)	Nondiagnosed (n = 29)	p value
Age, years ¹	67.5 (42–84)	65.0 (19–82)	0.73
Gender, M/F	17/21	12/17	0.78
Location of lesions			0.35 ²
Right upper lobe	14	14	
Right middle lobe	3	0	
Right lower lobe	15	7	
Left upper lobe	5	4	
Left lower lobe	1	4	
Lesion size, mm ¹	23.9±7.6	16.7±5.4	<0.01
Pure/mixed GGO	5/33	6/23	0.41

¹ Median (range).² Right upper lobe vs. others.

lesion (range 3–8) and the median number of diagnosable biopsy specimens per GGO lesion was 4 (range 1–7). For the 15 lesions not diagnosed by TBB using EBUS-GS, the median number of biopsy specimens was 4 (range 0–9).

Diagnostic Yield by Size of Lesions, CT Signs and Visibility on X-Ray Fluoroscopy

First, the relationship between the characteristics of the lesion and diagnostic yield was analyzed. When the size of diagnosable GGO predominant-type lesions was compared with that of nondiagnosable GGO predominant-type lesions, the former was significantly larger (24 vs. 17 mm, respectively; $p < 0.01$; table 1). The diagnostic yield according to lesion size was 38% (i.e. 6/16) for lesions of <15 mm, 49% (17/35) for lesions of 15–25 mm and 93% (15/16) for lesions of >25 mm (in the mean diameter), respectively (table 3). Next, the relationship between diagnostic yield and CT signs on HRCT was analyzed (see table 2). Lesions with a type 1 CT sign had a significantly higher diagnostic yield than those with the other types ($p < 0.01$). Finally, the relationship between diagnostic yield and the visibility of the GGO predominant-type lesions on X-ray fluoroscopy was analyzed. When the GGO lesions were confirmed on X-ray fluoroscopy, the yield was 79%; however, if confirmation was not possible, the yield decreased to 40% ($p < 0.01$; table 2).

Univariate and Multivariate Analysis of Clinical Factors Predicting Diagnostic Yield

In the univariate analysis, size of the GGO lesion (>25 mm in mean diameter), CT sign (type 1) and visibility on

Table 2. Features associated with diagnostic yield of TBB using EBUS-GS

Variables	Diagnosed by EBUS/ total lesions (%)	p value
CT signs		
Type 1	25/34 (74)	<0.01 ¹
Type 2	5/9 (56)	
Type 3	3/9 (33)	
Type 4	3/7 (43)	
Type 5	2/8 (25)	
X-ray fluoroscopy		
Visible	23/29 (79)	<0.01
Invisible	15/38 (39)	

¹ Type 1 vs. others.**Table 3.** Diagnostic yield of EBUS-GS

Size, mm	EBUS-GS diagnosis		
	total	pure GGO	mixed GGO
<15	6/16 (38%)	1/4 (25%)	5/12 (42%)
15–25	17/35 (49%)	3/6 (50%)	14/29 (48%)
>25	15/16 (94%)	1/1 (100%)	14/15 (93%)
Total	38/67 (57%)	5/11 (45%)	33/56 (59%)

X-ray fluoroscopy were identified as significant factors in predicting diagnostic yield. In the multivariate analysis, the lesion size and visibility on X-ray fluoroscopy remained significant factors in predicting diagnostic yield. The CT sign was not a significant factor but tended toward predicting diagnostic yield ($p = 0.08$; table 4).

Discussion

Although there have been several reports concerning the diagnostic yield for peripheral GGO predominant-type lesions by CT-guided needle biopsy [19–23], this study is the first to demonstrate a promising diagnostic yield for peripheral GGO predominant-type lesions by TBB using EBUS-GS. As a result, 38 of 67 lesions (58%) were successfully diagnosed by EBUS-GS under X-ray fluoroscopy. A surprising result was that 5/11 pure GGO lesions were diagnosed by TBB using EBUS-GS.

Kurimoto et al. [24] have reported in detail on EBUS images of peripheral lesions. Focusing on the homogene-

Table 4. Logistic regression analysis of factors affecting diagnostic yield

Variable	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Lesion size, >25 vs. ≤25 mm	11.0 (2.7–74)	<0.01	6.1 (1.3–44)	0.034
CT sign, type 1 vs. others	4.3 (1.6–12)	<0.01	2.8 (0.9–13)	0.087
Visible vs. invisible	5.9 (2–20)	<0.01	4.3 (1.3–15)	0.018
Pure GGO vs. mixed GGO	0.6 (0.2–2.1)	0.433		

CI = Confidence interval; HR = hazard ratio.

ity of the internal echo image, the patency of the internal blood and the presence of internal air space, they classified these images into type I (benign) and type II/III (malignant), subclassifying the latter into IIa/b and IIIa/b. EBUS images of GGO predominant-type lesions belong to type IIa. In this study, of 50 lesions which we could confirm on EBUS-GS, 37 (74%) were successfully diagnosed. Obtaining the EBUS image was crucial in enabling us to confirm the position of these lesions and to diagnose them.

This method has several advantages. Firstly, the amount of radiation exposure under X-ray fluoroscopic guidance can be much smaller than under CT fluoroscopic guidance [25, 26]. Secondly, TBB using EBUS-GS under X-ray fluoroscopy can be repeatedly performed in a minimally invasive way with local anesthesia, and multiple tissue specimens can be obtained. Percutaneous biopsy under CT fluoroscopic guidance can sometimes not be repeated because of the high risk of pneumothorax associated with this biopsy [19–23]. We reported that the number of biopsy specimens was an important factor in increasing the diagnostic yield [27]. Therefore, obtaining multiple tissue specimens by TBB using EBUS-GS may contribute to a reduction in complications and an improvement in diagnostic yield for GGO predominant-type lesions. Furthermore, it has been reported that EBUS-TBNA is a practical and feasible method for obtaining tissue [28, 29] that can be subjected to multimodal analysis of the echinoderm microtubule-associated protein-like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*) fusion genes in non-small cell lung cancer [30]. Obtaining multiple tissues by EBUS-GS also allows determination of the status of several pertinent mutations such as the epidermal growth factor receptor mutation, the *EML4-ALK* fusion genes and so on. Finally, GGO predominant-type lesions can be diagnosed in patients who could not undergo video-assisted thoracic surgery for diagnosis due to their physical status. Thus, it is expected

that this method will enable physicians to avoid unnecessary surgery or to select a proper therapy (i.e. radiotherapy for lesions at an early stage).

In this study, the relationship between diagnostic yield and lesion characteristics was examined using univariate and multivariate analyses. Lesion size and visibility on X-ray fluoroscopy were significant factors in this relationship, and the CT sign tended toward predicting diagnostic yield. In this study, we diagnosed 15 GGO predominant-type lesions which were not confirmed on X-ray fluoroscopy (the position of the EBUS probe may have contributed to these results). Of these 15 lesions, 14 were detected as being ‘within image’ or ‘adjacent to image’ on EBUS (fig. 3). Taken together, it is important to confirm CT signs in GGO lesions before bronchoscopy.

Our study highlights some important techniques that can be used to confirm the position of pure GGO lesions using EBUS-GS. Firstly, a bronchus leading to a GGO lesion should be examined on HRCT before bronchoscopy, in order to insert the EBUS probe appropriately. Secondly, the position where EBUS image changes should be confirmed. In the case of a pure GGO lesion, there was only a delicate change in brightness on the EBUS image according to when the EBUS probe was in or out of the lesion. However, after becoming familiar with the changes in the EBUS image, the position of a pure GGO lesion can be confirmed. Furthermore, once the EBUS image of a GGO lesion has been obtained, confirmation of the position of the bronchoscope and EBUS probe on X-ray fluoroscopy is important to be able to comprehend the position of the lesion more accurately. There are some limitations to our study. The first is its retrospective nature which might have meant there was a selection bias for the examined cases. The second is that the technique employed by the physicians might have affected diagnostic yield. To try to minimize variability, all bronchoscopic procedures were performed by well-trained bronchoscopists.

In conclusion, EBUS-GS under X-ray fluoroscopy could be a useful modality in clinical practice for the diagnosis of GGO predominant-type lesions located in the peripheral lung. Proper evaluation of size and of the CT bronchus sign of such lesions might be a key factor for improving the diagnostic yield of GGO predominant-type lesions while confirming these lesions under X-ray fluoroscopy.

Financial Disclosure and Conflicts of Interest

All authors have no conflicts of interest to declare.

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