

# Predictive factors for a successful diagnostic bronchoscopy of ground-glass nodules

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## Abstract:

**INTRODUCTION:** Since the National Lung Screening Trial demonstrated the utility of low-dose computed tomography screening for lung cancer, the detection rate of ground-glass nodules (GGNs) has increased. Endobronchial ultrasound with a guide sheath (EBUS-GS) is widely performed to diagnose peripheral pulmonary lesions, but there are not enough reports on the predictive ability of EBUS-GS in diagnosing GGNs. The aim of this study is to investigate the predictive factors for a successful diagnostic bronchoscopy for GGNs.

**METHODS:** Consecutive patients who underwent diagnostic bronchoscopy for GGNs from September 2012 to January 2016 were enrolled in this study. From these, cases who underwent EBUS-GS were selected. They were reviewed and analyzed to examine the association between the diagnostic yield and the following clinical factors: lesion size, lobar position, location, consolidation-to-tumor ratio, visibility on X-ray, use of virtual bronchoscopy, bronchus sign, guide sheath size, and number of biopsies.

**RESULTS:** We enrolled 254 cases, of which 167 were diagnosed using EBUS-GS (65.7% diagnostic yield). Univariate analysis indicated that a positive bronchus sign was a significant factor for higher diagnostic yield (72.9% vs. 34.0%;  $P < 0.001$ ). The use of virtual bronchoscopy also tended toward a higher yield, but the result was not significant (69.0% vs. 54.4%;  $P = 0.058$ ). However, multivariate analysis indicated that both were significantly associated with higher diagnostic yield ( $P < 0.001$ , odds ratio [OR]: 5.35;  $P < 0.001$ , OR: 1.97, respectively).

**CONCLUSIONS:** Our results suggest that a positive bronchus sign and the use of virtual bronchoscopy are positive predictive factors for successful diagnostic bronchoscopy of GGNs.

## Keywords:

Bronchoscopy, ground-glass nodule, lung cancer, radial endobronchial ultrasound with a guide sheath, virtual bronchoscopy

Since the National Lung Screening Trial demonstrated the utility of low-dose computed tomography (CT) screening,<sup>[1]</sup> the detection and diagnosis rate of solid peripheral pulmonary lesions (PPLs) has increased.<sup>[2]</sup> Accordingly, diagnoses of ground-glass nodules (GGNs), including part-solid and nonsolid nodules, have also increased. Although localized GGNs exhibit a high incidence of lung cancer,<sup>[3]</sup> GGNs can also represent benign conditions. Therefore,

a definitive diagnosis is important for determining the appropriate treatment for GGNs. Diagnostic modalities for GGNs include surgery, transthoracic needle biopsy, and bronchoscopy.

When there is a strong suspicion that the GGN is malignant, surgery is recommended. However, this involves the risk of unnecessary resections of benign lesions.<sup>[4]</sup> Another diagnostic option is transthoracic needle biopsy. According to the guidelines of the American College of

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Chest Physicians,<sup>[5]</sup> the diagnostic yield of transthoracic needle biopsy for PPLs is at least 90%. Similarly, a recent meta-analysis demonstrated the validity of transthoracic needle biopsy for GGNs as well as solid lesions<sup>[6]</sup> although it was associated with a 29.8% risk of pneumothorax. Moreover, transthoracic needle biopsy carries serious risks of hemoptysis, hemothorax, tumor seeding, and air embolism.<sup>[7]</sup>

In contrast, bronchoscopy is a well-established and safe procedure for diagnosing PPLs. The most frequent complication of bronchoscopy is pneumothorax, with an incidence of only 1.5%.<sup>[8]</sup> However, while bronchoscopy has greater safety, until recently its diagnostic value was insufficient. However, the diagnostic yield of bronchoscopy for PPLs has improved since the advent of new guided techniques such as radial endobronchial ultrasound (R-EBUS), guide sheath, virtual bronchoscopy, electromagnetic navigation bronchoscopy, and ultrathin bronchoscopy.<sup>[9,10]</sup> In these reports, diagnostic bronchoscopy is acknowledged to be more difficult for GGNs than for solid nodules, for several reasons. First, it is not easy to detect GGNs on chest X-rays or real-time X-ray fluoroscopy. Second, identifying accessible routes to the target GGNs during the procedure is difficult. Third, GGNs often represent minimal changes in histology, such as adenocarcinoma *in situ*, minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma.<sup>[11]</sup> Thus, it is difficult to confirm overt malignancy. However, the diagnostic efficacy of bronchoscopy for GGNs with a new guided technique, R-EBUS, has recently been reported.<sup>[12-14]</sup> To avoid invasive procedures for diagnosing GGNs, it is important to improve the diagnostic yield of bronchoscopy for GGNs and therefore to confirm the predictive factors for successful transbronchial diagnoses of GGNs.

The aim of this study was to clarify the predictive factors for successful transbronchial diagnoses of GGNs using a radial endobronchial ultrasound with a guide sheath (EBUS-GS).

## Methods

### Study design and objectives

Consecutive patients who underwent diagnostic bronchoscopy with EBUS-GS for GGNs in our institution from September 2012 to January 2016 were enrolled in this study. This study was approved by the National Cancer Center Institutional Review Board (No. 2012-278). Written informed consent was obtained from all patients before they underwent bronchoscopy. All GGNs were defined as PPLs with an area of increased attenuation and preservation of the underlying vessels and bronchi. They were divided into two types depending on the presence

of solid components. A nonsolid nodule was defined as a lesion with no solid components, and a part-solid nodule was defined as a lesion having heterogeneous attenuation with some solid components. If malignancy was suspected when a definitive diagnosis was not established by bronchoscopy, the lesion was diagnosed by additional procedures, i.e., either transthoracic needle biopsy or surgery. The diagnostic yield of bronchoscopy was defined as the proportion of positive diagnostic cases to the number of overall cases. Among those patients, the clinical variables were analyzed to investigate the predictive factors for successful bronchoscopy. The clinical variables analyzed were as follows: lesion size ( $\leq 20$  mm or  $>20$  mm), lobar position (right upper lobe/left upper segment, right middle lobe/left lingula, or bilateral lower lobes), location area (outer or inner), the consolidation-to-tumor ratio ( $\leq 25\%$  or  $>25\%$ ), visibility on a chest X-ray (fine, equivocal/invisible, or not taken before bronchoscopy), use of virtual bronchoscopy (Ziostation2<sup>®</sup>, Ziosoft, Tokyo, Japan; LungPoint<sup>®</sup>, Bronchus, Mountain View, California, USA; or Bf-NAVI<sup>®</sup>, Olympus, Tokyo, Japan) (used or not), the bronchus sign on thin-section CT (TSCT) (positive or negative), the guide sheath size (small or large), and number of biopsies taken ( $\leq 5$  or  $>5$ ).

All patients underwent a TSCT scan with a thickness of  $\leq 1$  mm within 1 month of the bronchoscopy. The size of the lesion was determined based on the major diameter on axial TSCT images. Lesion location area was defined based on a previous study and was designated as "outer" if the lesion was in the outer third ellipse or "inner" if the lesion was in the inner- or middle-third ellipses.<sup>[15]</sup> The consolidation-to-tumor ratio was defined as the maximum diameter of consolidation to the maximum lesion diameter. The bronchus sign on TSCT, defined as a CT finding of bronchi leading directly to or contained within the target lesion,<sup>[16,17]</sup> was evaluated.

### Procedures and equipment

All bronchoscopies were performed through the oral route, under local anesthesia with conscious sedation. On reaching the target bronchus, the guide sheath (K-201 or K-203, Olympus, Tokyo, Japan) in combination with an R-EBUS probe (UM-S20-17S or UM-S20-20S, Olympus, Tokyo, Japan) was inserted through the working channel of the bronchoscope and advanced toward the target GGN under real-time X-ray fluoroscopic guidance (VersiFlex VISTA<sup>®</sup>, Hitachi, Japan). When the target GGN could not be detected on the chest X-ray or through real-time X-ray fluoroscopy, we utilized virtual fluoroscopy as a reference for forceps guidance.<sup>[18]</sup> If the EBUS image could not be visualized, as in cases of solid lesions, we manipulated the probe under fluoroscopic guidance until a whitish acoustic shadow, which we previously reported as

blizzard sign or mixed blizzard sign, was generated.<sup>[12]</sup> When evaluating the location of the probe against the GGN, EBUS images were divided into three groups according to a previously published report:<sup>[19]</sup> “within” (the probe was located in the bronchus inside the GGN), “adjacent to” (the probe was located in the bronchus alongside the GGN), or “invisible” (the probe was located in the bronchus, but the GGN could not be seen). After confirming the location of the target GGNs through R-EBUS, transbronchial sampling through the guide sheath was repeated using forceps, brush, and transbronchial needle aspiration (TBNA).<sup>[20,21]</sup>

### Diagnostic criteria in bronchoscopy

The samples obtained through bronchoscopy were considered diagnostic when malignant histology findings or Class IV/V cytology findings were confirmed. Cases of benign lesions were diagnosed when the samples showed specific benign findings (e.g., granuloma, fibrotic change, and inflammation on histopathology or the presence of bacteria in microbial culture) and when subsequent clinical outcomes were consistent after a 12-month follow-up period. Bronchoscopy was considered nondiagnostic if the sample was inadequate (e.g., peripheral lung tissue and peribronchial tissue).

### Statistical analysis

Descriptive statistics presented in this study are frequency, percentage, and median (range). We investigated the factors influencing the diagnostic yield using Chi-square test. Variables selected through univariate analyses ( $P < 0.20$ ) were analyzed using multivariate logistic regression. All statistical tests were two-sided, and a  $P < 0.05$  was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),<sup>[22]</sup> which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

## Results

A total of 254 patients were enrolled and analyzed; a summary of patient characteristics is shown in Table 1. The diagnostic yield of bronchoscopy with EBUS-GS was 65.7% (167 of 254 GGNs). Table 2 shows the histology of the GGNs. Of 21 benign lesions, 14 were successfully diagnosed through bronchoscopy (66.7% diagnostic yield), and one was diagnosed as nontuberculous mycobacteria through surgery. The remaining six lesions were clinically diagnosed as inflammation, based on the reduction or complete disappearance of the lesions after anti-inflammatory therapy.

Of 233 malignant lesions, 153 were successfully diagnosed through bronchoscopy (65.7% diagnostic yield). In the nondiagnostic cases, diagnosis was established through

**Table 1: Baseline characteristics of patients with ground-glass nodules diagnosed with malignancy (n=254)**

Variables	No. patients (%) <sup>a</sup>
Age, median (range), years	67 (42-87)
Sex, n (%)	
Male	119 (46.9)
Female	135 (53.1)
Lesion size, median (range), mm	19.7 (7.2-60.1)
Lobe, n (%)	
Right upper lobe/left upper segment	141 (55.5)
Right middle/left lingula	32 (12.6)
Right lower/left lower	81 (31.9)
Location, n (%)	
Outer area	199 (78.3)
Inner area	55 (21.7)
Consolidation-to-tumor ratio, n (%)	
≤25	78 (30.7)
>25	176 (69.3)
Visibility on chest X-ray, n (%)	
Fine	152 (59.8)
Equivocal or invisible	94 (37.0)
Not taken before bronchoscopy	8 (3.1)
Using of virtual bronchoscopy, n (%)	
Yes	197 (77.6)
No	57 (22.4)
Bronchus sign, n (%)	
Positive	207 (81.5)
Negative	47 (18.5)
Guide sheath kit type, n (%)	
K-203, large	176 (69.3)
K-201, small	78 (30.7)
Biopsy times, median (range)	5 (1-10)

<sup>a</sup>Unless otherwise specified

**Table 2: The results of bronchoscopy using endobronchial ultrasound with a guide sheath for evaluation of ground-glass nodules**

	Diagnostic (n=167)	Nondiagnostic (n=87)
Malignant		
Adenocarcinoma	145	71
Adenosquamous carcinoma of the lung	-	2
Small cell lung carcinoma	1	-
Squamous cell carcinoma	-	1
Minimally invasive adenocarcinoma	2	2
Adenocarcinoma <i>in situ</i>	1	2
Other malignant tumors	4	2
Benign		
Organizing pneumonia	2	-
Mycobacterium tuberculosis	1	-
Nontuberculous mycobacteria	1	1
Inflammation	10	6
Diagnostic yield	65.7% (167/254)	

surgery in 77 patients and transthoracic needle biopsy in 3 patients. Of these cases, almost all were invasive

adenocarcinoma (216/233, 92.7%). There were six other malignant tumor cases: three of malignant lymphoma and one each of adult T-cell leukemia, metastasis of renal cancer, and metastasis of pancreatic cancer. With respect to complications, 2 patients (0.8%) had small self-limiting pneumothorax and another 2 (0.8%) had mild bleeding. There were no severe complications during this study.

The clinical factors associated with the diagnostic yield are shown in Table 3. In the univariate analysis, a positive bronchus sign was a significant factor for a higher diagnostic yield (72.9% vs. 34.0%,  $P < 0.001$ ). The use of virtual bronchoscopy also tended to have a higher yield, but there was not a significant difference (69.0% vs. 54.4%,  $P = 0.058$ ). Conversely, in the multivariate analysis, the use of virtual bronchoscopy and a positive bronchus sign were both significantly associated with a higher diagnostic yield ( $P < 0.001$ , odds ratio [OR]: 1.97, 95% confidence interval [CI]: 1.04–3.72, and  $P < 0.001$ , OR: 5.35, 95% CI: 2.70–10.60, respectively).

Figure 1 is a representative case of a successful bronchoscopy for GGN evaluation.

## Discussion

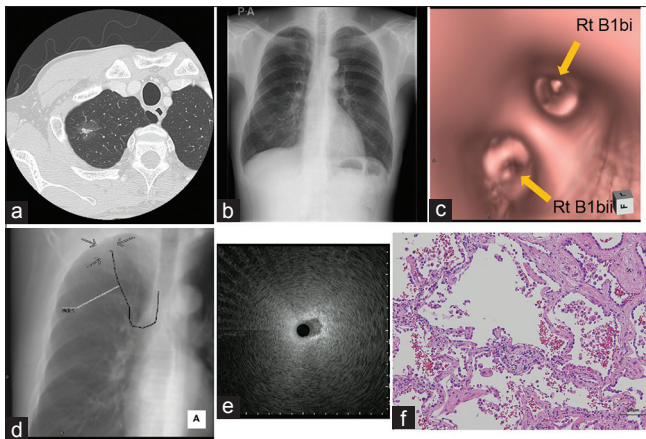
Although several groups have reported the utility of EBUS-GS for diagnosing GGNs,<sup>[12,14,23]</sup> few reports have investigated the clinical factors affecting the diagnostic yield of this procedure. Our study showed that the diagnostic yield (167/254, 65.7%) and the complication rate (4/254, 1.6%) were comparable to those for solid nodules reported in previous studies.<sup>[8,9,24,25]</sup> Positive bronchus signs on TSCT and the use of virtual bronchoscopy were positive predictive factors of EBUS-GS for GGNs, which may be helpful when choosing a diagnostic modality.

Previous studies have reported a relationship between a CT bronchus sign and the diagnostic yield for diagnosing PPLs through EBUS-GS.<sup>[17,26,27]</sup> Similarly, in the present study, the CT bronchus sign was significantly associated with successful diagnosis, according to both the univariate and multivariate analyses. The diagnostic yield of positive bronchus sign cases was 72.9%. Considering its diagnostic effectiveness and safety, bronchoscopy with EBUS-GS seems to be a feasible first modality for undiagnosed

**Table 3: Clinical factors affecting diagnostic yield of endobronchial ultrasound with a guide sheath available before bronchoscopy**

Variables	Univariate analysis		Multivariate analysis	
	Diagnostic yield (%)	<i>P</i>	OR (95% CI)	<i>P</i>
Lesion size, mm				
≤20	85/130 (65.4)	0.951	-	
>20	82/124 (66.1)			
Lobe				
Right upper lobe/left upper segment	97/141 (68.8)	0.513	-	
Right middle/left lingula	20/32 (62.5)			
Lower	50/81 (61.7)			
Location				
Outer area	131/199 (65.8)	1	-	
Inner area	36/55 (65.5)			
Consolidation-to-tumor ratio				
≤25	52/78 (66.7)	0.951	-	
>25	115/176 (65.3)			
Visibility on chest X-ray				
Fine	103/152 (67.8)	0.208	-	
Equivocal or invisible	61/94 (64.9)			
Not taken before bronchoscopy	3/8 (37.5)			
Use of virtual bronchoscopy				
Yes	136/197 (69.0)	0.058	1.97 (1.04-3.72)	<0.001
No	31/57 (54.4)			
Bronchus sign				
Positive	151/207 (72.9)	<0.001	5.35 (2.70-10.60)	<0.001
Negative	16/47 (34.0)			
Guide sheath kit type				
K-203, large	120/176 (68.2)	0.278	-	
K-201, small	47/78 (60.3)			
Number of biopsies taken				
≤5	104/155 (67.1)	0.666	-	
>5	63/99 (63.6)			

OR = Odds ratio, CI = Confidence interval



**Figure 1:** A 59-year-old male with a part-solid ground-glass nodule in the right upper lobe. Computed tomography showed part-solid nodule located at right segment 1b (a), but invisible on X-ray (b). We approached it referring to virtual bronchoscopy (c) and virtual fluoroscopy (d), and radial endobronchial ultrasound showed blizzard sign (e). The biopsy specimen revealed lepidic predominant adenocarcinoma (f)

GGNs with a positive bronchus sign. For solid lesions with a negative bronchus sign, TBNA, which directly punctures the lesion through the bronchial wall, has been generally recommended.<sup>[28]</sup> We previously demonstrated the diagnostic utility of TBNA for PPLs.<sup>[20,21]</sup> In the same way, if the GGN shows negative bronchus sign, TBNA may be a useful way to improve the diagnostic yield.

We highlight virtual bronchoscopy as an important technique for diagnosing GGNs because it was significantly related to successful bronchoscopy in the multivariate analysis. In addition, virtual fluoroscopy constructed with virtual bronchoscopy facilitates confirmation of the location of the GGN even if the GGN cannot be detected on chest X-rays or by real-time fluoroscopy.<sup>[18]</sup> In such cases, using this technique, we can move the bronchoscope as close as possible to the target lesion through the preplanned bronchial route generated by the virtual bronchoscopy and select the biopsy site based on virtual fluoroscopy guidance and EBUS images. The use of virtual bronchoscopy and virtual fluoroscopy would resolve the problems (e.g., complicated access routes to the target and poor visibility in fluoroscopy) that make transbronchial diagnosis for GGNs difficult. Although Ikezawa *et al.* have reported that the size and visibility of GGNs affect the diagnostic yield,<sup>[14]</sup> our study did not reveal any significant relationship of this kind. We assume that this difference was the result of our use of virtual bronchoscopy.

Our study has several limitations. First, it was a retrospective, nonrandomized study in a single cancer center, so there may have been a bias in patient selection. For example, the rate of benign lesions in all GGNs was much lower than that of malignant lesions (8.3% vs. 91.7%). Second, the bronchoscopy procedures were not all performed by the same bronchoscopist. The

effect of differences in bronchoscopist's skill levels on lesion visibility and diagnostic yield was not measured. Instead, teaching staff supervised all procedures performed by residents and ensured that the quality of the procedures was maintained. Third, the type of bronchoscope and sampling devices (e.g., forceps, brush, and needle) was independently decided in each case. Finally, the effect of the use of rapid on-site examination during the procedure on the diagnostic yield was not evaluated. The latter method has the potential to improve the diagnostic yield of bronchoscopy with EBUS-GS.<sup>[29,30]</sup> Prospective, randomized studies are recommended in the future.

## Conclusions

This study demonstrated that a positive bronchus sign on TSCT and the use of virtual bronchoscopy are positive predictive factors for successful diagnosis of GGNs using bronchoscopy with EBUS-GS. We therefore suggest that physicians consider using virtual bronchoscopy and evaluating the bronchus sign on TSCT.

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## Conflicts of interest

There are no conflicts of interest.

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