Original Article

Diagnostic usefulness of bronchoscopy for peripheral pulmonary lesions in patients with idiopathic pulmonary fibrosis

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Background: As lung cancers arising in a background of idiopathic pulmonary fibrosis (IPF) are known to show high malignancy grades, early pathologic diagnosis of peripheral pulmonary lesions (PPLs) is important. Meanwhile, the risk of complications associated with diagnostic procedures is high, which prompted us to investigate the role of bronchoscopy, a relatively safe diagnostic procedure. Therefore, we conducted this study to evaluate the usefulness of bronchoscopy for the diagnosis of PPLs in patients with IPF.

Methods: Data of consecutive patients with IPF who underwent bronchoscopy under radial endobronchial ultrasound (R-EBUS) guidance for PPLs at our institution between April 2014 and March 2019 were retrospectively reviewed. IPF was defined as usual interstitial pneumonia (UIP) or probable UIP, in accordance with the classification in the latest global guidelines. The diagnostic outcomes and the factors independently related to the diagnostic yield were analyzed.

Results: A total of 92 patients were included in the analysis. The median (range) size of the target PPLs was 27.1 (11.4–75.3) mm, and the diagnostic yield was 82.6%. Multivariable analysis identified a larger size [P=0.017; odds ratio (OR), 5.33; 95% confidence interval (CI), 1.29–22.01], positive bronchus sign (P=0.035; OR, 4.99; 95% CI, 1.12–22.18), and not involved with UIP/probable UIP pattern (P=0.023; OR and 95% CI, unmeasurable) as being associated with a significantly higher diagnostic yield. Meanwhile, none of the patients developed acute exacerbation of IPF or pneumothorax following the diagnostic bronchoscopy.

Conclusions: Bronchoscopy using R-EBUS was safe and showed an acceptable diagnostic yield for PPLs, even in patients with IPF.

Keywords: Bronchoscopy; diagnosis; endobronchial ultrasound (EBUS); idiopathic pulmonary fibrosis (IPF); peripheral pulmonary lesion (PPL)

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide (1). The International Association for the Study of Lung Cancer took the lead in revising the current 8th TNM staging system for lung cancer, to allow determination of the appropriate treatment and prediction of the prognosis (2). For patients with non-small cell carcinoma, curative treatments such as surgery and radiotherapy have been shown to yield better outcomes in patients with stage I or stage II disease, whereas a multidisciplinary combination (MDD) of surgery, radiotherapy, and drug therapy (i.e., chemotherapy and immunotherapy) is preferred for the treatment of stage III

disease, and appropriate drug therapy and palliative care are adopted, depending on the tumor histology and the patient's general condition for stage IV disease (3,4). In contrast, for patients with small cell carcinoma, surgery is usually performed only in patients with early limited-stage disease without any distant metastases (5).

The prevalence of lung cancer is reported to be high among patients with idiopathic pulmonary fibrosis (IPF), and lung cancers arising in a background of IPF often show higher malignancy grades (6). However, only limited treatment options are available for these patients, due to the high risk of acute exacerbation of IPF (AE-IPF). According to a review article on lung cancer associated with IPF, while surgery is performed in a majority of stage I patients with mild IPF, patients with more advanced malignancy receive chemotherapy or best supportive care, regardless of the severity of IPF (7). Another study reported that during follow-up of patients with interstitial lung disease (ILD), including IPF, tumors need to be identified at an early stage by computed tomography (CT) (8). Thus, early pathological diagnosis of peripheral pulmonary lesions (PPLs) is especially important in patients with IPF, so that lesions that are confirmed as being lung cancer can be treated by curative surgery.

The traditionally used diagnostic techniques for PPLs are bronchoscopy, transthoracic needle biopsy (TTNB), and surgical resection (9). TTNB and surgical resection are superior in terms of the diagnostic yield, but these procedures are also associated with a higher risk of severe complications. A cohort study reported a 9.3% incidence of AE-IPF after surgery for lung cancer, with a 43.9% mortality rate (10). Accordingly, in patients with undiagnosed PPLs, surgery should be avoided, to obviate the unnecessary risk of AE-IPF. In regard to TTNB, although the diagnostic yield is approximately 90%, the pneumothorax rate is about 15%, with at least 7% of the patients requiring chest tube insertion (9). Therefore, TTNB is not the recommended diagnostic tool for patients with IPF, because TTNB, especially for lesions arising in a background of emphysema and/or fibrosis, is associated with a higher risk of pneumothorax (9,11,12).

While the diagnostic yield of traditional semi-blind transbronchial biopsy performed under fluoroscopic guidance was low, ranging from 14% to 63% (13,14), introduction of advanced techniques, such as electromagnetic navigation bronchoscopy, virtual bronchoscopy, radial endobronchial ultrasound (R-EBUS), ultrathin bronchoscopy, and bronchoscopy with the use of a guide sheath (GS), have led to an increase of the diagnostic yield to up to 70% (15). However, reports on the diagnostic outcomes of bronchoscopy for PPLs with a focus on patients with IPF are still scarce. Therefore, we conducted this study to evaluate the diagnostic usefulness of bronchoscopy for PPLs in patients with IPF, and also attempted to identify the factors that could potentially influence the diagnostic yield.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-1067).

Methods

Patients

Data of consecutive patients with IPF who underwent bronchoscopy under R-EBUS guidance for PPLs at our institution between April 2014 and March 2019 were retrospectively reviewed. PPLs were defined as lesions that cannot be directly visualized by bronchoscopy. Among the patients with PPLs, we selected those with IPF, as defined for the purpose of this study as described below.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the National Cancer Center Institutional Review Board (approval No.: 2018–090). The requirement for informed consent was waived due to the retrospective design of the study.

Definition of IPF

IPF is a disease characterized by progressive lung fibrosis and is associated with a poorer prognosis than other ILDs. A recent guideline in 2018 has advocated the use of the following four diagnostic categories based on the patterns observed on high-resolution computed tomographic (HRCT) images: "usual interstitial pneumonia (UIP)", "probable UIP", "indeterminate for UIP", and "alternative diagnosis" (16). IPF can be definitively diagnosed by HRCT alone when the HRCT shows the "UIP" pattern, whereas the histopathological findings should be confirmed by MDD including pathologists when HRCT images show the other three patterns. The "probable UIP" pattern is associated with a greater amount of fibrosis than the "indeterminate for UIP" and "alternative diagnosis" patterns. Thus, the "probable UIP" and "UIP" patterns show similar degrees of fibrosis.

Hence, patients with the HRCT patterns of "UIP"

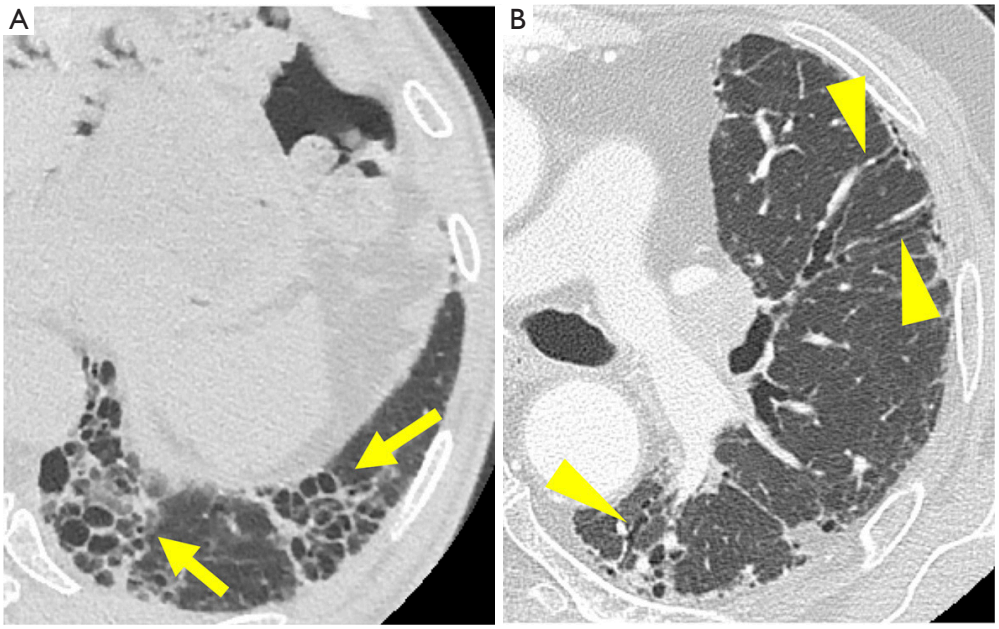

Figure 1 Definition of idiopathic pulmonary fibrosis on high-resolution computed tomography. (A) The usual interstitial pneumonia (UIP) pattern is defined as the heterogeneous distribution honeycombing (arrow) with subpleural and basal predominance. (B) The probable UIP pattern is defined as subpleural, basal-predominant reticular abnormalities with peripheral traction bronchiectasis or bronchiolectasis (arrow head).

and "probable UIP" were extracted as cases of IPF in this study (*Figure 1*). The "UIP" pattern is characterized by heterogeneous distribution of honeycombing, with subpleural and basal predominance, with or without peripheral traction bronchiectasis/bronchiolectasis. The "probable UIP" pattern is characterized by reticular abnormalities, also often distributed heterogeneously, showing subpleural and basal predominance, with peripheral traction bronchiectasis/bronchiolectasis; mild ground-glass opacities may be present. We focused on the presence of honeycombing or bronchiectasis, which directly leads to increased branching and bending of the bronchi and disruption of the structure. In addition, we examined the location of the PPL and the background lung, but not its extent.

Outcomes

The bronchoscopic diagnosis was made as follows. Findings of malignancy on histopathology and/or class IV/V lesions on cytology were defined as malignant lesions. Samples with specific benign features, such as inflammation or granuloma, were classified as benign lesions. The final diagnoses in cases of malignancy were based on the histopathological findings of bronchoscopic biopsy or other interventions. Benign lesions were confirmed by histopathology after surgery or based on the findings of follow-up evaluation, such as reduction of the lesion size on follow-up CT. Successful bronchoscopic diagnosis was defined as a match between the bronchoscopic diagnosis and the final diagnosis.

Safety was examined by extracting every complication that could potentially have been related to the procedure.

Variables

The following clinical factors that could potentially influence the diagnostic yield for PPLs or were characteristic of IPF were collected: size, lobe, location, attachment to the costal pleura, bronchus sign, related bronchial generation, association with UIP/probable UIP, and visibility on X-ray. All imaging factors were evaluated on axial HRCT (1 mm or less slice thickness) images obtained within 4 weeks of the bronchoscopy. The images were displayed in a lung window setting (center, –600 Hounsfield units; width, 1,500 Hounsfield units).

PPLs in a background of IPF are reported to be more likely to occur in the lower lobes and in the lung peripheral

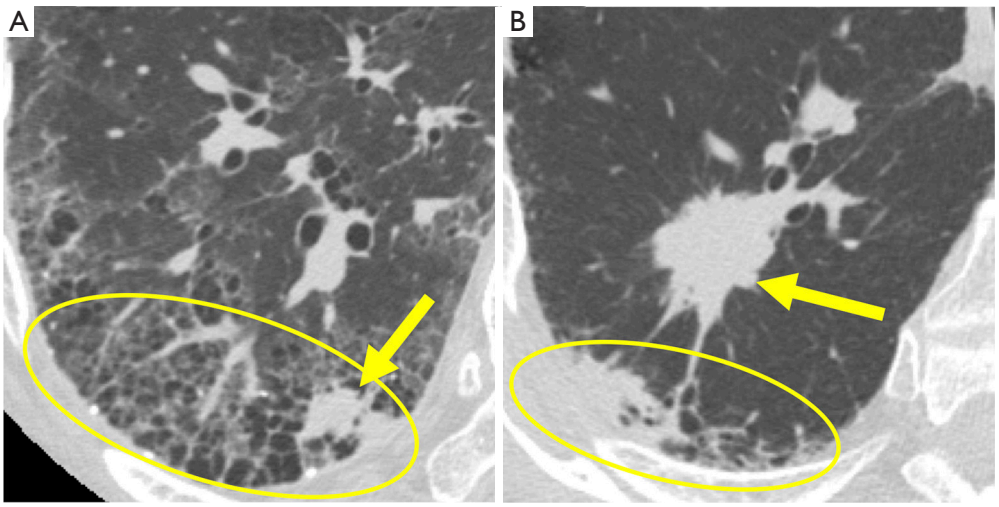

Figure 2 Classification of involved or not involved. The usual interstitial pneumonia (UIP)/probable UIP patterns are shown surrounded by circles. (A) A target lesion (arrow) was classified as "involved" when it was inside or close to an area of the lung showing the UIP/probable UIP pattern. (B) A target lesion (arrow) was classified as "not involved" when it was not within an area of the lung showing the UIP/probable UIP pattern.

regions (17). Therefore, the lobe containing the lesions was classified as "lower" or "others". In addition, we defined the association of the lesion with the UIP/probable UIP pattern. Cases were classified as "involved" or "not involved" depending on whether the target lesion was inside or outside, respectively, the area of the lung showing the UIP/probable UIP pattern (*Figure 2*). Moreover, continuous variables were binarized to account for their median values. Accordingly, each factor was divided into the two groups and analyzed; size (small or large; 20.0 mm as threshold), lobe (upper/middle or lower), location in the lung field (inner 2/3 or outer 1/3), pleural attachment (present or absent), bronchus sign (positive or negative), related bronchial generation (≤6 or >6), association with UIP/probable UIP pattern (involved or not involved), visibility on chest X-ray (visible or invisible).

Procedures

The bronchoscopy in all cases was inserted via the mouth using one of the following bronchoscopes [P260F, P290, Y0053 (18), 1T260; Olympus, Tokyo, Japan] along with an R-EBUS probe (UM-S20-17S or UM-S20-20S; Olympus, Tokyo, Japan), under local anesthesia and conscious sedation. GS kits (K-201 or K-203; Olympus, Tokyo, Japan) were used in some cases. After wedging the bronchoscope against the target bronchus, an R-EBUS probe with or without a GS was inserted through the working channel of the bronchoscope. The R-EBUS findings were classified as "within", "adjacent to", or "invisible" depending on the relationship between the probe location and the lesion, as previously described (19). After identifying the target, subsequent brushing, forceps biopsy, needle aspiration, and/or cryobiopsy were performed under X-ray fluoroscopic guidance (VersiFlex VISTA; Hitachi, Ltd., Tokyo, Japan).

Statistics

Descriptive statistics are presented in numbers, frequencies (percentages), and median values (ranges). The correlations between the diagnostic yield and clinical factors were statistically analyzed using Fisher's exact test. Multivariable logistic regression analysis was used to examine the factors that were independently related to the diagnostic yield. Two-tailed P values of <0.05 were considered as denoting statistical significance. A software was used for the statistical analyses (JMP® ver. 14; SAS Institute Inc., Cary, NC, USA).

Results

During the study period, there were 2,744 patients who underwent diagnostic bronchoscopy for PPLs, of whom 94 with IPF. We excluded 2 cases that were lost to follow-up from the analyses. Finally, a total of 92 patients were

Table 1 Diagnostic yield by each device and technique

Device/technique	Diagnostic cases, n (%)	P value
Total	76/92 (82.6)	–
Brushing		0.802
With	50/60 (83.3)	
Without	26/32 (81.3)	
Needle aspiration		0.253
With	18/24 (75.0)	
Without	58/68 (85.3)	
Cryobiopsy		0.514
With	9/10 (90.0)	
Without	67/82 (81.7)	
Guide sheath		0.854
With	54/65 (83.1)	
Without	22/27 (81.5)	
Virtual bronchoscopy		0.287
With	72/86 (83.7)	
Without	4/6 (66.7)	
Rapid on-site cytologic evaluation		0.031
With	65/75 (86.7)	
Without	11/17 (64.7)	

GS, guide sheath; VBN, virtual bronchoscopy navigation; ROSE, rapid on-site cytologic evaluation.

Table 2 Pathological diagnoses

Diagnosis	Diagnostic, n	Non-diagnostic, n
Malignant		
Squamous cell carcinoma	37	7
Adenocarcinoma	25	2
Adenosquamous carcinoma	3	1
Non-small cell lung carcinoma	5	0
Small cell lung carcinoma	3	2
Metastatic tumor	1	2
Benign		
Inflammation	2	0
Unknown	0	2

included in the final analysis; the median (range) age of the patients was 73 (range, 60–90) years, and 78 patients (84.8%) were male. The median (range) size of the target PPLs was 27.1 (range, 11.4–75.3) mm, 74 lesions (80.4%) showed positive bronchus sign, and 78 lesions (84.8%) were involved with UIP/probable UIP pattern.

The overall diagnostic yield was 82.6% (76/92 cases), and the details are summarized in *Table 1*. No other samplings, in addition to forceps biopsy which was conducted in all cases, were found to have a favorable effect on the diagnostic yield, whereas combined use of rapid on-site cytologic evaluation had a positive effect (diagnostic yield 86.7% *vs.* 64.7%, P=0.031). Meanwhile, the histopathological diagnoses are shown in *Table 2*. Two cases in which a definitive diagnosis could not be made (unknown) continue to remain under close follow-up.

A comparison of the influences of clinical factors on the diagnostic yield is shown in *Table 3*. Multivariable analysis identified the following factors as being associated with a significantly higher diagnostic yield: larger size [P=0.017; odds ratio (OR), 5.33; 95% confidence interval (CI), 1.29–22.01], positive bronchus sign (P=0.035; OR, 4.99; 95% CI, 1.12–22.18), and not involved with UIP/probable UIP pattern (P=0.023; OR and 95% CI, unmeasurable). In addition, when examined separately in association with UIP/probable UIP pattern, the R-EBUS findings were found to significantly affect the diagnostic yield in the involved cases (P<0.001) (*Table 4*).

On the other hand, none of the patients developed respiratory failure necessitating positive pressure ventilation caused by AE-IPF. Although there were 4 cases of bleeding, the bleeding was not serious in any of the cases. Moreover, there was no other complication necessitating intervention or admission, such as pneumothorax or infection.

Discussion

In this study, we investigated the diagnostic usefulness of bronchoscopy for PPLs in IPF patients. To the best of our knowledge, there have been no other reports of such an investigation conducted on a reasonably large number of patients. The diagnostic yield was 82.6%, which was comparable to the rate of 70.6% reported from a meta-analysis of diagnostic bronchoscopy with R-EBUS conducted for PPLs (20).

Multivariable analysis identified a large lesion size, positive bronchus sign, and not involved with UIP/probable UIP pattern as being associated with a significantly higher diagnostic yield. Consistent with these findings, the lesion

Table 3 Clinical factors influencing the diagnostic yield

Variable	Diagnostic cases, n (%)	Univariable	Multivariable	
		P value	P value	Odds ratio (95% CI)
Size[†]		0.006	0.017	5.33 (1.29–22.01)
Small (≤20.0 mm)	19/29 (65.5)			
Large (>20.0 mm)	57/63 (90.5)			
Lobe		0.162	0.385	1.98 (0.40–9.73)
Upper/middle	29/32 (90.6)			
Lower	47/60 (78.3)			
Location		1.000	0.553	1.99 (0.21–18.62)
Inner 2/3	12/14 (85.7)			
Outer 1/3	64/78 (82.1)			
Attachment to the costal pleura		0.781	0.857	1.15 (0.25–5.29)
Present	50/60 (83.3)			
Absent	26/32 (81.3)			
Bronchus sign		0.014	0.035	4.99 (1.12–22.18)
Positive	65/74 (87.8)			
Negative	11/18 (61.1)			
Related bronchial generation[‡]		0.380	0.966	1.03 (0.25–4.30)
≤6	53/62 (85.5)			
>6	23/30 (76.7)			
Association with UIP/probable UIP pattern		0.118	0.023	Unmeasurable
Involved	62/78 (79.5)			
Not involved	14/14 (100.0)			
Visibility on chest X-ray		0.090	0.890	1.11 (0.25–4.97)
Visible	63/73 (86.3)			
Invisible	13/19 (68.4)			

[†], median [range]: 27.1 [11.4–75.3] mm; [‡], median [range]: 6 [2–12]. CI, confidence interval; UIP, usual interstitial pneumonia.

Table 4 Diagnostic yield associated with each radial endobronchial ultrasound finding

R-EBUS finding	Involved with UIP/probable UIP pattern		Not involved with UIP/probable UIP pattern	
	Diagnostic cases, n (%)	P value	Diagnostic cases, n (%)	P value
Within	44/47 (93.6)	<0.001	10/10 (100.0)	1.000
Adjacent to	17/27 (63.0)		4/4 (100.0)	
Invisible	1/4 (25.0)		–	

R-EBUS, radial endobronchial ultrasound; UIP, usual interstitial pneumonia.

size and bronchus sign have been reported from previous studies as predictors of the diagnostic yield of bronchoscopy (15,20). In contrast to previous studies, in this study, we investigated the influence of the relationship of PPLs with areas of the lung showing the UIP/probable UIP pattern on the diagnostic yield. We estimated the following reasons for the poor diagnostic yield for PPLs within lung areas showing the UIP/probable UIP pattern.

First, when the target lesion is within an area of the lung showing changes of IPF, it is often difficult to identify the bronchus leading to the lesion. The pathology of UIP is characterized by inflammation and repair, resulting in remodeling and dense fibrosis of the lungs and peripheral airways (16). This causes the bronchi to be pulled and dilated, resulting in bent bronchi, which do not show normal branching on CT. The lung parenchyma also becomes fibrotic and cystic, making it difficult to distinguish between bronchi and cysts. Furthermore, pulmonary fibrosis and pulmonary emphysema are similar with respect to destruction of the architecture of the lung parenchyma. The diagnostic yield of bronchoscopy for PPLs in patients with severe emphysema has been reported to be worse than that in patients with normal or mild emphysema (21). This is because in patients with advanced emphysema, the destruction of the lung parenchyma makes it difficult to detect the bronchus sign, and the same may be true in patients with IPF. In fact, when we examined the diagnostic yield of each R-EBUS finding, which was strongly related to the presence/absence of the bronchus sign, separately according to the location of the lesion relative to areas of the lung showing the UIP/probable UIP pattern, we found significant differences in the diagnostic yield depending on the R-EBUS findings in the involved cases, but not in the not involved cases (*Table 4*). This may be due to the fact that it was relatively difficult to identify the orientation of the bronchus towards the lesion by R-EBUS in the involved cases, as the boundary of the lesion with the background lung was obscured in these cases.

Second, target lesions within lung areas with IPF might be difficult to detect by X-ray fluoroscopy. It has been reported that lung cancers associated with IPF are often centered in fibrotic areas of the lung (8,17), and lesions overlapping the reticular shadows of IPF often cannot be visualized on a chest X-ray (22). In addition, most PPLs in patients with IPF are found in the lower lobe (17), sometimes in a position hidden by the diaphragm. We show a representative case of a PPL with IPF that was invisible on X-ray fluoroscopy (*Figure 3*). Although there was no statistically significant difference in the visibility on chest X-ray, lesions within areas of IPF, as in this case, can often not be visualized on chest X-ray or X-ray fluoroscopy, which may explain the lower diagnostic yield.

On the other hand, the R-EBUS findings of IPF might be different from those of the normal parenchyma, as the lung structure is destroyed and replaced by fibrosis. The difference in the findings of R-EBUS between normal lung parenchyma and honeycomb lung has been investigated in autopsy lungs (23). Normal lungs showed relatively regular and fine granular hyperechoic patterns, whereas honeycomb lungs exhibited a gross patchy combination of hyperechoic and hypoechoic patterns. In fact, as shown in *Figure 3C*, the R-EBUS findings of lesions involved in IPF were relatively difficult to identify. Nevertheless, the diagnostic yield was the highest when the R-EBUS probe was within the lesion, consistent with previous reports (15,20) (*Table 4*). Although the R-EBUS findings may vary somewhat, the sufficient detection of target PPLs (i.e., within the lesion) could improve the diagnostic yield, even in patients with IPF.

In terms of complications, there were no cases of pneumothorax requiring treatment in this study, whereas a previous meta-analysis reported an incidence rate of pneumothorax of 1.5% (15). The possibility of sampling at the location of the lesion identified by R-EBUS is thought to account for the safety of the procedure. On the other hand, the diagnostic yield was low in cases where the lesions could not be identified clearly by R-EBUS or chest X-ray, which could possibly be related to the fact that sampling was not enforced in these cases. In addition, there was no case of AE-IPF. Although there are no reports of the risk of AE-IPF when bronchoscopy is performed for the diagnosis of PPLs in cases of IPF, a certain degree of risk has been reported when bronchoscopy is performed for the diagnosis of ILD (24). Thus, our results suggest that bronchoscopy for PPLs in patients with IPF can be performed safely without serious complications.

The present study had several limitations. First, it was a retrospective, non-randomized study conducted at a single cancer institution. Although we enrolled consecutive cases, there might be some bias in the selection of the study subjects. In fact, most cases were diagnosed as having malignant tumors, which may have contributed to the high diagnostic yield (20,25). Second, we did not compare the diagnostic yield between patients with and without IPF. Third, selection of the bronchoscopes and devices to be used were left to the discretion of each operator. In this retrospective setting, we could not determine if

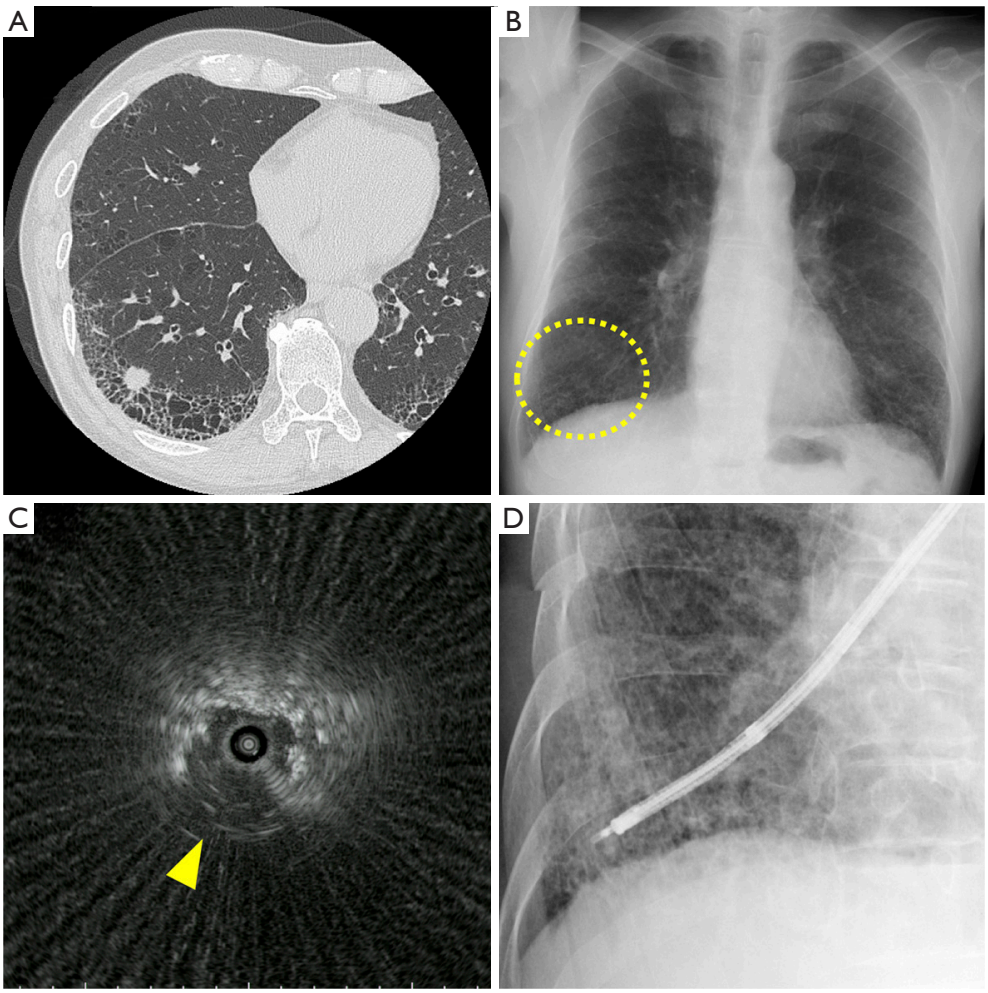

Figure 3 Representative case of a peripheral pulmonary lesion in a case of idiopathic pulmonary fibrosis. (A) The patient was a 71-year-old man with a solid nodule on his right S^9 measuring 15.8 mm in diameter. (B) The target lesion could not be visualized on the chest X-ray (circle). (C) A radial endobronchial ultrasound (R-EBUS) showed an image of the probe adjacent to the lesion (arrowhead). (D) As the lesion could also not be visualized on X-ray fluoroscopy, we performed forceps biopsy in the right anterior oblique view in line with the position detected by R-EBUS, and diagnosed the tumor as a squamous cell carcinoma.

the differences in the scopes/devices selected might have influenced the results. Therefore, a prospective study is warranted for further clarification of the findings.

Conclusions

Bronchoscopy using R-EBUS is safe and provides an acceptable diagnostic yield for PPLs, even in patients with IPF.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013). This human study was approved by the National Cancer Center Institutional Review Board (approval: No. 2018–090). The requirement for informed consent was waived due to the retrospective design of the study.

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