Diagnostic utility of endobronchial ultrasound with a guide sheath under the computed tomography workstation (ziostation) for small peripheral pulmonary lesions

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1 # Title page

2 ## Title of article

3 Diagnostic Utility of Endobronchial Ultrasound with a Guide Sheath under the

4 Computed Tomography Workstation (ziostation) for Small Peripheral Pulmonary

5 Lesions

6

7 ## Short title

8 Virtual Bronchoscopy Made by Workstation

9

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Conflicts of interest

7 The authors have stated explicitly that there are no conflicts of interest

8 in connection with this article.

9

Abstract

Background and objective: The application of radial probe endobronchial ultrasound (R-EBUS) and virtual bronchoscopic navigation (VBN) has improved the diagnostic outcome of bronchoscopy for peripheral pulmonary lesions (PPLs). Nonetheless, while existing navigation systems are very useful for selecting the bronchus containing the target lesion, the associated introductory costs are high. Therefore, we focused on virtual bronchoscopy using the workstation, ziostation that was already available in many countries as an adjunct modality.

Materials and methods: Consecutive patients who underwent bronchoscopy with R-EBUS for PPLs (major diameter ≤30 mm) were enrolled. From late June 2013 to November 2013, 121 patients were examined with ziostation, and from September 2012 to early June 2013, 113 patients were examined without ziostation. We compared the diagnostic yield, EBUS detection rate and procedure time between two groups to evaluate the utility of the virtual bronchoscopy.

Results: The ziostation group had significantly higher diagnostic yield than the non-ziostation group (77.7% vs. 64.6%, p = 0.030). Following the

1   multivariate analysis, use of ziostation was a significant factor affecting the

2   diagnostic yield. Meanwhile, EBUS detection rate was significantly higher in the

3   ziostation group (94.2% vs. 75.2%, p < 0.001). And procedure time was

4   significantly shorter in the ziostation group (mean ± SD: 24.0 ± 7.4 min. vs. 26.9

5   ± 7.9 min., p = 0.005).

6   Conclusion: Virtual bronchoscopy offered by the workstation was a

7   valuable tool that facilitated more accurate and rapid bronchoscopy procedure

8   for diagnosis of PPLs.

9

Keywords

11   bronchoscopy; EBUS-GS; radial EBUS; transbronchial lung biopsy; virtual

12   bronchoscopic navigation

13

Ethics

15   This study was approved by the National Cancer Center Institutional

16   Review Board, Japan. The National Cancer Center Research and Development

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18

1 Introduction

2   Globally, lung cancer is the leading cause of cancer-related deaths

3 (1-3). The National Lung Screening Trial (NLST) reported a reduction in lung

4 cancer mortality with low-dose computed tomography (CT) screening, as

5 opposed to radiography screening (4). However, NLST also reported a higher

6 rate of positive lung nodule results in the low-dose CT screening group. As the

7 use of low-dose CT screening has expanded, the detection of peripheral

8 pulmonary lesions (PPLs) that need further evaluation has likewise increased

9 (5).

10   When a PPL is detected, surgery is often recommended if malignancy is

11 suspected; however, there is a risk of unnecessary resection if the lesion is

12 benign (6, 7). Conversely, when the suspicion of malignancy is moderate,

13 transthoracic needle aspiration (TTNA) or bronchoscopy is recommended.

14 Although reports of the diagnostic yield of TTNA have been high; the pooled

15 sensitivity was 90% (95% CI, 88-91%) (8-10), the complication rate has likewise

16 been elevated (10-12). Most notably, the pooled risk of any pneumothorax was

17 15% (95% CI, 14-16%) (10). In contrast, while the performance of bronchoscopy

18 is considered relatively safe, the diagnostic yield is currently low (13). However,

1   the diagnostic value of bronchoscopy has improved since the application of

2   radial endobronchial ultrasound (R-EBUS) (14). Further, guidelines recently

3   established by the American College of Chest Physicians (ACCP) have

4   indicated that the pooled sensitivity of this modality for the detection of lung

5   cancer was 73% (95% CI, 70-76%) (10).

6   Furthermore, ACCP guidelines also recommended electromagnetic

7   navigation (EMN) when the suspected lesion is difficult to reach with

8   conventional bronchoscopy (10). EMN has improved the diagnostic outcomes,

9   especially when combined with R-EBUS (15, 16). However, EMN requires an

10 electromagnetic sensor, which results in prohibitive examination costs (15, 17).

11 Reports have also indicated that the use of virtual bronchoscopic navigation

12 (VBN) results in diagnostic outcomes that are comparable with EMN (18-21).

13 The advantages of VBN include the visualization of the bronchial tree, and the

14 automatic or semi-automatic indication of the route from the trachea to the

15 marked target lesion. However, the extraction of the peripheral bronchi is often

16 insufficient, and VBN sometimes indicates the incorrect route to the target lesion.

17 Moreover, the introduction of VBN to the hospital setting requires additional

18 costs, as VBN machines are specifically designed for bronchoscopy, and are not

8

1   available for use in other fields.

2   As an alternative solution, we focused on the adaptation of a CT

3   workstation that was widely used in the various analyses of coronary artery (22),

4   brain blood flow (23), virtual colonoscopy (24-26) and so on. Previous reports

5   indicated the utility of a workstation in the performance of virtual bronchoscopy

6   (VB) (27). This study showed that use of simulation with VB and an ultrathin

7   bronchoscope (which could not combine with R-EBUS) has improved the

8   diagnostic yield for peripheral lung cancers. Additionally, workstations offer the

9   capability of reconstructing three-dimensional (3D) images, so no additional

10   costs would be associated with use in VB (27).

11   Thus we attempted to use one of a workstation, ziostation to construct

12   VB (zio-VB) since June 2013. In this study, we evaluated the utility of the

13   workstation in performing zio-VB for diagnostic bronchoscopy with R-EBUS.

14

Materials and Methods

Constructing virtual bronchoscopy using the

workstation (zio-VB)

18   Zio-VB was performed by Y.M. using the CT-3D image processing

9

1   workstation commonly used in many hospitals worldwide (ziostation2®, Ziosoft,

2   Tokyo, Japan). In particular, the ziostation2® (including a different version) is

3   already in use in more than 1800 hospitals in Japan. To perform zio-VB, thin

4   section CT (TSCT) is required. The recommended CT parameters are as

5   follows: a) 1 mm or less slice thickness, b) reconstruction factor setting for

6   mediastinal window, and c) half chest field of view at least involving images from

7   the target PPL to the same side main bronchus. Otherwise, it is possible to

8   perform even if these conditions are not met, for example by CT which was

9   taken at previous hospital.

10   Zio-VB was performed using the following procedure: a) the contour of

11   the target PPL was extracted and marked, b) a line was connected from the

12   involved bronchus of the PPL to the same side of the main bronchus or trachea

13   on a multi-planar reconstruction (MPR) oblique plane, c) original CT images

14   were translated into VB images, and d) thumbnails at each bronchial bifurcation

15   were adjusted based on an actual bronchoscopic orientation, and zio-VB was

16   completed as a cine sequence by automatically complementing images between

17   thumbnails (Fig. 1). If it was difficult to identify the involved bronchus within the

18   PPL (especially in negative bronchus sign cases), the route was made by tracing

1 the corresponding pulmonary artery (28). After the zio-VB was uploaded to the

2 in-hospital server, it could be accessed anywhere through an electronic health

3 record system.

4

Subjects

5

6 This was a retrospective study that was approved by the National

7 Cancer Center Institutional Review Board. Written informed consent for the

8 procedure was obtained from all patients.

9 Consecutive patients who underwent bronchoscopy for small PPLs

10 (major diameter ≤30 mm on axial CT images) in the hospital were enrolled. From

11 late June 2013 to November 2013, patients examined with zio-VB were enrolled

12 to the zio-VB (case) group. And from September 2012 to early June 2013,

13 patients examined without any VB were enrolled to the non zio-VB (control)

14 group. In the non zio-VB group, cases without TSCT were excluded to match the

15 study conditions.

16 PPLs were defined as lung parenchymal lesions without visible

17 endobronchial involvement. Poorly-marginated lesions with other surrounding

18 pathologic structures were excluded.

1

The procedure of endobronchial ultrasound with a

guide sheath

4   Bronchoscopies were conducted at the Respiratory Endoscopy unit of

5 the hospital; most of cases, the operator was a resident trainee under the direct

6 supervision of three bronchoscopic expert staff with 13-27 years of experience.

7 The residents were well-trained and the quality of the procedure was assured by

8 the members of the staff. All procedures were performed using endobronchial

9 ultrasound with a guide sheath (EBUS-GS) procedure, as previously described

10 (14, 29, 30). The model of bronchoscope that we used varied among all patients,

11 depending on the case. Briefly, an R-EBUS probe (UM-S20-17S or UM-S20-20R,

12 Olympus, Japan) with a GS (K-201 or K-203, Olympus, Japan) was inserted

13 through the working channel of the bronchoscope to the target PPL, under the

14 X-ray fluoroscopic guidance (VersiFlex VISTA®, Hitachi, Japan). EBUS images

15 were categorized following three patterns by the relationship of the inserted

16 probe and the PPL: a) within: entire circumference of abnormal echogenicity was

17 detected, b) adjacent to: partial circumference of abnormal echogenicity was

18 detected, c) invisible: abnormal echogenicity was not detected. The EBUS

1   detection rate by R-EBUS was calculated as the number of within and adjacent

2   to cases divided by the overall number of cases. After the R-EBUS image was

3   obtained, the probe was removed, and brushing and biopsy were performed

4   sequentially through the GS. While rapid on-site evaluation (ROSE) was

5   combined in all cases, if negative, the biopsy was repeated, or transbronchial

6   needle aspiration (TBNA) was performed through the GS (GS-TBNA), as

7   previously described (31). All cases were performed under local anesthesia with

8   conscious sedation.

9   The diagnostic yield was calculated as the number of cases that were

10   successfully diagnosed by bronchoscopy divided by the overall number of cases.

11   Positive diagnostic criteria were: a) malignant lesion, as determined based on

12   histological features, or class IV/V cytology by Papanicolaou stain, and b) benign

13   lesion, as determined based on histological features, the presence of bacteria by

14   culture, or the reduction in the lesion size during the follow-up period. If the

15   bronchoscopy result was negative but malignancy was suspected, the final

16   diagnosis was confirmed by surgery or TTNA. After more than one year of

17   clinical follow-up with periodic image inspections performed at the discretion of

18   each attending physician, indeterminate cases were excluded from the study.

13

1   Procedure time was measured based on the interval between insertion and

2   removal of the bronchoscope through the vocal cords. Lesion location was

3   assigned based on a study of Baaklini et al (32) but with some modification; with

4   the area around the hilum on CT as reference, lesions in the inner and middle

5   third ellipses were designated as central, whereas lesions in the outer third

6   ellipse were designated as peripheral. Distance from the pleura was calculated

7   as the shortest perpendicular length from the lateral border of the lesion to the

8   costal pleura. The bronchus sign on CT was the discovery of a bronchus leading

9   directly to a PPL (33).

10

Statistical analysis

12   Descriptive statistics were presented as frequency, percentage, and

13   mean ± standard deviation (SD). We investigated the factors affecting diagnostic

14   yield using Fisher Exact Test. Variables with *p* values less than 0.05 were

15   analyzed using logistic regression. All *p* values were two sided and levels ≤ 0.05

16   were considered statistically significant. Statistical analyses were performed with

17   EZR (Saitama Medical Center, Jichi Medical University;

18   http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html; Kanda), a

1 graphical user interface for R (The R Foundation for Statistical Computing,

2 Vienna, Austria, Ver. 2. 13.0) and a modified version of R commander (Ver.

3 1.8-4).

4

Results

6 A total 234 patients were included in this study; 121 were in the zio-VB

7 group, and 113 were in the non zio-VB group. There were no significant

8 differences in the baseline characteristics between the two groups (Table 1).

9 The zio-VB could be constructed in all cases. Figure 2 is a

10 representative case of the zio-VB group. An irregularly shaped PPL was

11 detected in left lower lobe on chest CT. VB was made using the workstation and

12 it reflected the actual bronchoscopic orientation well. Besides, the relationship

13 between the marked PPL and the involved bronchus was reflected as an

14 adequate EBUS image.

15 The zio-VB group had significantly higher diagnostic yield compared to

16 the non zio-VB group (77.7% vs. 64.6%, p = 0.030) (Table 2). Among the

17 non-diagnostic cases, 81.5% in the zio-VB group and 72.5% in the non zio-VB

18 group were diagnosed by additional alternative methods, such as TTNA or

1 surgical biopsy. Following the multivariate analysis, use of zio-VB was a

2 significant factor affecting the diagnostic yield in addition to the distance from

3 pleura and the bronchus sign (Table 3).

4   Meanwhile, EBUS detection rate was significantly higher in the zio-VB

5 group than the non zio-VB group (94.2 % vs. 75.2%, $p < 0.001$) (Table 2). And

6 mean procedure time was also significantly shorter in the zio-VB group (mean ±

7 SD: 24.0 ± 7.4 min. vs. 26.9 ± 7.9 min., $p = 0.005$) (Table 2).

8   Regarding the complications, pneumothorax occurred in two cases

9 (1.7%) in the zio-VB group, whereas there was none in the non zio-VB group.

10 There were no severe complications in both groups.

11

Discussion

13   This study shows the utility of the workstation, ziostation for the

14 performance of virtual bronchoscopy (zio-VB) for diagnostic bronchoscopy with

15 R-EBUS. Some fundamental differences exist between zio-VB and existing VBN.

16 First, and perhaps the greatest difference, VBN is performed from central

17 (trachea) to peripheral (the target PPL) by the automatic extraction of the

18 bronchial tree with some manual adjustment, while zio-VB is performed from

16

1 peripheral to central by the manual selection of the expected bronchi. During

2 VBN, when navigation reaches bronchial branches that could not be

3 reconstructed, the process is sometimes terminated, or an incorrect route is

4 generated within the bronchi that could be reconstructed. In contrast, zio-VB can

5 arrange the route more flexibly, and delete unwanted artifacts along the involved

6 bronchus or corresponding artery. Second, while VBN makes only a simple

7 marking on the target to refer to the location, zio-VB draws a finer contour by

8 using the workstation. Thus, zio-VB allows for more accurate recognition of the

9 target location. Finally, the most important distinction is that while VBN requires

10 specialized equipment, zio-VB can be performed using a multi detector-row CT

11 workstation already available in many hospitals. Additionally, TSCT is required

12 for accuracy in assessing the bronchial tree, which can be accomplished by a

13 workstation at no additional cost. Conversely, the use of zio-VB entails more

14 practice and effort than VBN because of its manual design. In fact, the median

15 creation time with the use of zio-VB was 6.9 minutes (range 4.4–14.3). Therefore,

16 VBN may be preferable when the doctor or radiology technologist does not have

17 enough time.

18   The diagnostic yield in our study was significantly higher in the zio-VB

1   group, and that use of zio-VB was the significant factor in the multivariate

2   analysis. This result was similar to the previous randomized control trial of VBN

3   combined with R-EBUS (80.4% vs. 67.0%, *p* = 0.032) (20). Therefore, we think

4   zio-VB has a comparable potential with VBN as an adjunct modality for

5   diagnostic bronchoscopy of PPLs.

6   Conversely, in the multivariate analysis, the diagnostic yield was lower in

7   the lesions located close the pleura and negative bronchus sign. To reach

8   nearby pleural lesions, it is necessary to trace a longer distance and number of

9   branches. So in general, it is difficult to diagnose such a lesion (34). And the

10   diagnostic outcomes of negative bronchus sign cases are known to be low,

11   because these cases are arduous to approach (33, 35). Especially in metastatic

12   tumors, there is usually no involved bronchus. For these unreachable cases, we

13   often induce a GS to a nearby bronchus by zio-VB, then perform GS-TBNA to

14   breach the intervening bronchial wall (31). Zio-VB can be applied to make an

15   expected route to outside the lesion.

16   Meanwhile, EBUS detection rate in our study was significantly higher in

17   the zio-VB group. The acquisition of an EBUS image during probe insertion

18   meant that the lesion has been reached, indicating that certainly, zio-VB has

18

1   created a correct route. Consequently, EBUS detection has been reported to

2   affect diagnostic yield (21, 29, 36). The position of the probe, especially if within

3   a lesion, is known to be important for PPL diagnosis. If the probe cannot be

4   adjusted to the within position, the intact bronchial wall between the probe and

5   the lesion has to be breached to obtain sufficient tissue (36). Furthermore,

6   precise guidance for a PPL is needed not only for diagnosis but also for

7   therapeutic approach (37).

8   The results of our study also indicated that the zio-VB group had

9   significantly shorter procedure time. Further as with the diagnostic yield, our

10   study was similar to the result of a randomised trial that combined VBN with

11   R-EBUS (20). Accordingly, we believe that both VBN and zio-VB were effective

12   modalities.

13   On the other hand, the occurrence of pneumothorax was more in the

14   zio-VB group. This may be accounted for by the fact that the lesions that

15   necessitated creation of a route by zio-VB were located more distally and near

16   the pleura, compared with the location of the lesions which did not need zio-VB.

17   In fact, in the control period, the occurrence of pneumothorax was also more

18   frequent in the cases that underwent other VBN methods.

1   Nonetheless, this study had several limitations. First, this study was a

2 retrospective, non-randomized study. Second, this study did not compare the

3 utility of zio-VB and VBN directly, so it was impossible to determine which

4 modality was more effective. Third, this study was performed at a single

5 institution. A multi-center trial may be more accurate, because the difference in

6 skill between facilities could prove to be a confounding variable. Therefore, a

7 prospective randomized-control multi-center study would have been more

8 desirable. In the near future, we will start a study (zio-VB vs. non zio-VB) with

9 such design.

10   In conclusion, the performance of VB by CT workstation was a valuable

11 tool that facilitated more accurate and rapid bronchoscopy procedure for

12 diagnosis of PPLs. Thus, we propose that zio-VB is a useful adjunct modality for

13 diagnostic bronchoscopy.

14

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18

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9

Figure Legends

Figure 1. The procedural steps constructing the virtual bronchoscopy using the

workstation (zio-VB).

(A) The contour of the target peripheral pulmonary lesion (PPL) was extracted

and marked (arrowhead). **(B-D)** A line was drawn by connecting the plotted dots

(arrow) from the expected involved bronchus of the PPL to the same side main

bronchus or trachea on the multi-planar reconstruction (MPR) oblique plane. **(E)**

Original CT images were translated into VB images on the made route. **(F)**

Thumbnails at each bronchial bifurcation were adjusted based on an actual

bronchoscopic orientation, and zio-VB was completed as a cine sequence by

automatically complementing images between thumbnails.

1   Figure 2. A representative case of the zio-VB group.

2   **(A)** An irregularly shaped peripheral pulmonary lesion (PPL) was detected in left

3   lower lobe on chest CT. **(B)** The PPL showed a positive bronchus sign. **(C, D)**

4   The virtual bronchoscopy using the workstation (zio-VB) (C) reflected the actual

5   bronchoscopic orientation (D) well. **(E, F)** The relationship between the marked

6   PPL (arrowhead) and the involved bronchus (arrow) (E) was reflected as an

7   adequate EBUS image (F).

Tables

Table 1. Baseline characteristics (n = 234)

	zio-VB (n = 121)	non zio-VB (n = 113)	p value
Age (yr.), no. (%)			0.538
≤ 70	68 (56.2)	68 (60.2)	
> 70	53 (43.8)	45 (39.8)	
Gender, no. (%)			0.733
Male	68 (56.2)	66 (58.4)	
Female	53 (43.8)	47 (41.6)	
Size (mm), no. (%)			0.457
≤ 20	54 (44.6)	45 (39.8)	
> 20	67 (55.4)	68 (60.2)	
Feature, no. (%)			0.619
Solid	88 (72.7)	88 (77.9)	
Mixed GGO	30 (24.8)	22 (19.5)	
Pure GGO	3 (2.5)	3 (2.6)	
Lobe, no. (%)			0.885

30

RUL / LUS	55 (45.5)	55 (48.7)	
RML / Lingula	15 (12.4)	13 (11.5)	
RLL / LLL	51 (42.1)	45 (39.8)	
Location, no. (%)			0.394
Peripheral area	85 (70.2)	85 (75.2)	
Central area	36 (29.8)	28 (24.8)	
Distance from pleura (mm), no. (%)			0.796
≤ 10	78 (64.5)	71 (62.8)	
> 10	43 (35.5)	42 (37.2)	
Bronchus sign, no. (%)			0.289
Positive	96 (79.3)	83 (73.5)	
Negative	25 (20.7)	30 (26.5)	

VB, virtual bronchoscopy; GGO, ground-glass opacity; RUL, right upper lobe;

LUS, left upper segment; RML, right middle lobe; RLL, right lower lobe; LLL, left

lower lobe

Table 2. Examination results (n = 234)

	zio-VB (n = 121)	non zio-VB (n =113)	*p* value
Diagnostic yield, no. (%)	94 (77.7)	73 (64.6)	0.030
EBUS detection rate, no. (%)	114 (94.2)	85 (75.2)	< 0.001
Examination time (mean ± SD, min.)	24.0 ± 7.4	26.9 ± 7.9	0.005

VB, virtual bronchoscopy; EBUS, endobronchial ultrasound
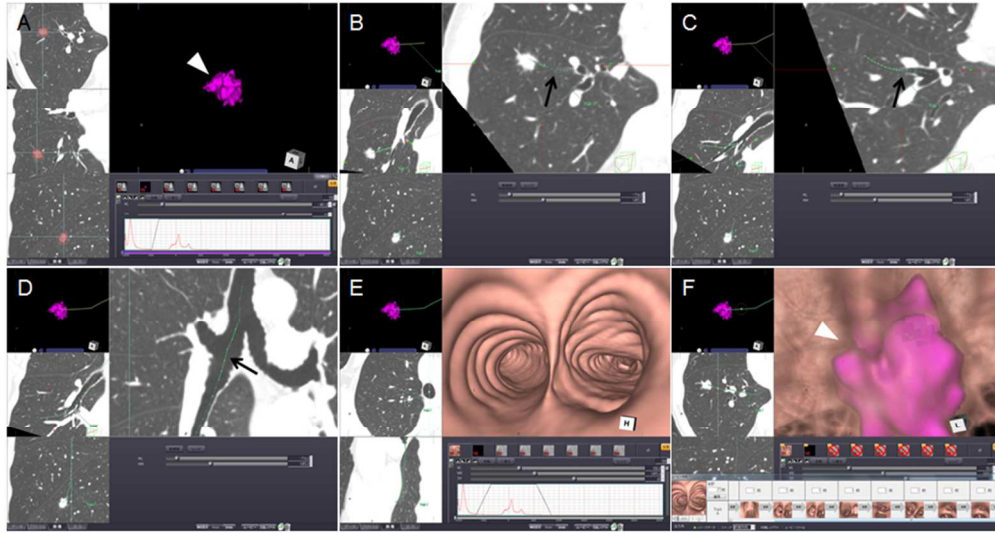
Table 3. Factors affecting the diagnostic yield (n = 234)

	Diagnostic	Non-diagnostic	Univariate	Multivariate	
	(n = 167)	(n = 67)	*p* value	*p* value	Odds ratio
Age (yr.), no. (%)			0.138	-	-
≤ 70	92 (67.6)	44 (32.4)			
> 70	75 (76.5)	23 (23.5)			
Gender, no. (%)			0.689	-	-
Male	97 (72.4)	37 (27.6)			
Female	70 (70.0)	30 (30.0)			
Size (mm), no. (%)			0.025	0.177	-
≤ 20	63 (63.6)	36 (36.4)			
> 20	104 (77.0)	31 (23.0)			
Feature, no. (%)			0.498	-	-
Solid	127 (72.2)	49 (27.8)			
Mixed GGO	37 (71.2)	15 (28.8)			
Pure GGO	3 (50.0)	3 (50.0)			
Lobe, no. (%)			0.510	-	-
RUL / LUS	82 (74.5)	28 (25.5)			

RML / Lingula	18 (64.3)	10 (35.7)			
RLL / LLL	67 (69.8)	29 (30.2)			
Location, no. (%)			0.281	-	-
Peripheral area	118 (69.4)	52 (30.6)			
Central area	49 (76.6)	15 (23.4)			
Distance from pleura (mm), no. (%)			0.005	0.009	2.39
≤ 10	97 (65.1)	52 (34.9)			
> 10	70 (82.4)	15 (17.6)			
Bronchus sign, no. (%)			< 0.001	0.007	2.60
Positive	139 (77.7)	40 (22.3)			
Negative	28 (50.9)	27 (49.1)			
Use of zio-VB, no. (%)			0.027	0.028	1.96
Yes	94 (77.7)	27 (22.3)			
No	73 (64.6)	40 (35.4)			

GGO, ground-glass opacity; RUL, right upper lobe; LUS, left upper segment;

RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe; VB, virtual

bronchoscopy

The procedural steps constructing the virtual bronchoscopy using the workstation (zio-VB).
(A) The contour of the target peripheral pulmonary lesion (PPL) was extracted and marked (arrowhead). (B-D) A line was drawn by connecting the plotted dots (arrow) from the expected involved bronchus of the PPL to the same side main bronchus or trachea on the multi-planar reconstruction (MPR) oblique plane. (E) Original CT images were translated into VB images on the made route. (F) Thumbnails at each bronchial bifurcation were adjusted based on an actual bronchoscopic orientation, and zio-VB was completed as a cine sequence by automatically complementing images between thumbnails.
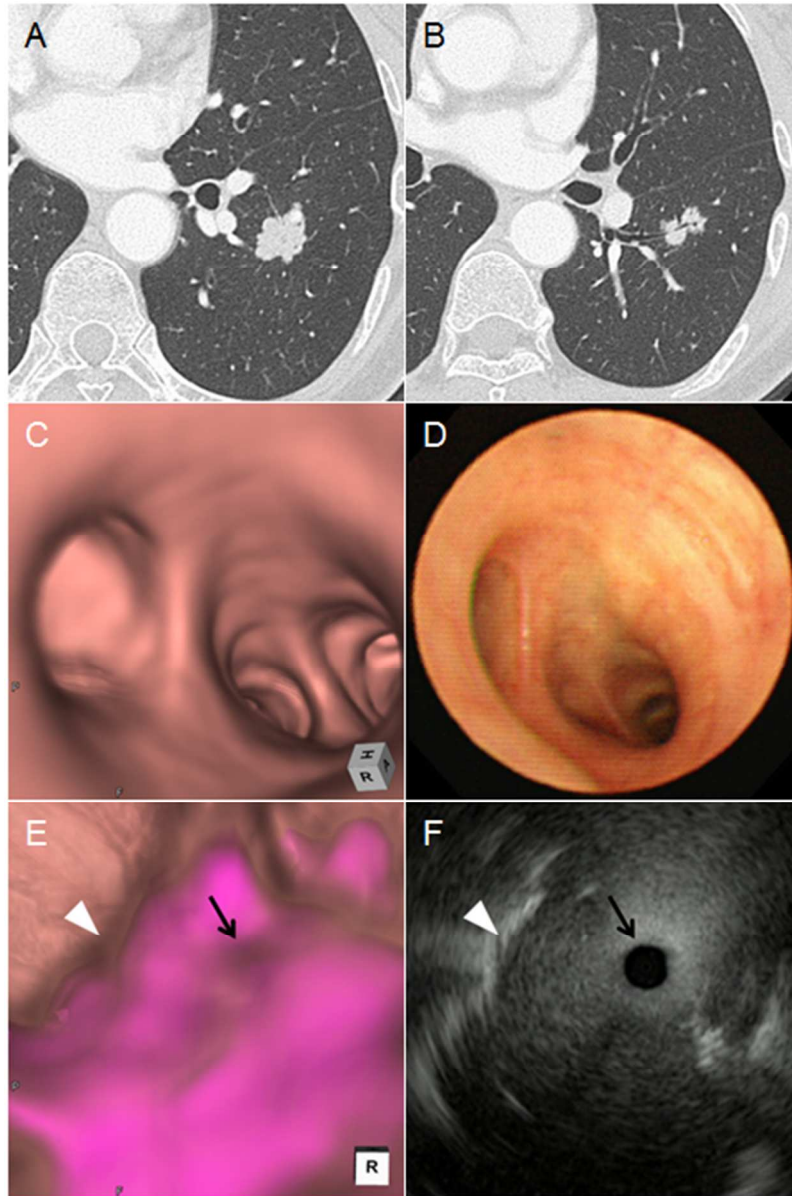
A representative case of the zio-VB group.
(A) An irregularly shaped peripheral pulmonary lesion (PPL) was detected in left lower lobe on chest CT. (B) The PPL showed a positive bronchus sign. (C, D) The virtual bronchoscopy using the workstation (zio-VB) (C) reflected the actual bronchoscopic orientation (D) well. (E, F) The relationship between the marked PPL (arrowhead) and the involved bronchus (arrow) (E) was reflected as an adequate EBUS image (F).