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Virtual bronchoscopic navigation as an aid to CT-guided transbronchial biopsy improves the diagnostic yield for small peripheral pulmonary lesions

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SUMMARY AT A GLANCE

CT-guided transbronchial biopsy (CT-TBB) is one of several procedures used to diagnose small peripheral pulmonary lesions (PPLs) although its diagnostic yield is unsatisfying. We now report that a combined approach in which virtual bronchoscopic navigation (VBN) is used to assist CT-TBB improves the diagnostic yield for small PPLs.

ABSTRACT

Background and objective: Virtual bronchoscopic navigation (VBN) entails the provision of a virtual display of the bronchial routes that lead to small peripheral pulmonary lesions (PPLs). It has been predicted that a combination of CT-guided transbronchial biopsy (CT-TBB) with VBN might improve the diagnostic yield for small PPLs. This study sought to investigate that prediction.

Methods: A total of 100 patients with small PPLs (<20 mm) were enrolled for CT-TBB and randomly allocated to either a VBN+ or VBN- group (50 subjects per group). Group results were then compared in terms of diagnostic yield, whole procedure time, times at which the first CT scan and biopsy were taken, and the number of lung biopsy specimens retrieved.

Results: The diagnostic yield for small PPLs was significantly higher in the VBN+ group versus (vs.) VBN- group (84% vs. 58%, respectively (p=0.013)), with no significant difference in (whole) examination time between groups (VBN+: 32:53 (32 min and 53 seconds) ± 12:01 vs. VBN-: 33:06 ± 10:08 (p=NS)). However, the time periods between commencing the examination and either the first CT scan, or first biopsy, were significantly shorter for the VBN+ group, while the net biopsy time tended to be longer for this group with a significantly higher number of specimens collected (VBN+: 3.54 ±

1.07 specimens vs. VBN-: 2.98 ± 1.06 specimens (p=0.01)).

Conclusion: Combining VBN with CT-TBB significantly improved the diagnostic yield for small PPLs.

KEY WORDS

Bronchoscopy and interventional techniques

Clinical trials

Lung cancer

Radiology and other imaging

Histology/Cytology

SHORT TITLE

Diagnostic yield with VBN and CT-TBB

INTRODUCTION

The development of computed tomography (CT)-related health screening now makes it possible to detect small peripheral pulmonary lesions (PPLs) including lesions that are invisible by X-ray fluoroscopy.[1-3] As many as 57% of non-small cell lung cancer screened using low-dose CT are at stage IA. As a result, the early detection of these lesions has reduced mortality for lung cancer patients.[1] The diagnostic yield of small PPLs with diameters of less than 20 mm remains problematic, with estimates of less than 30% when using conventional bronchoscopy under X-ray fluoroscopy[4-6]. To improve the diagnostic yield of PPLs, advanced methods for diagnosing small PPLs including endobronchial ultrasound with a guide sheath (EBUS-GS), electromagnetic navigation bronchoscopy (ENB), CT-guided transbronchial biopsy (CT-TBB) have been developed[2]. Transthoracic percutaneous needle aspiration (TTNA) is an alternative and reliable diagnostic method[7]. Despite satisfactory diagnostic yields using TTNA and surgical resection, their associated complications (e.g. air embolus, pneumothorax, haemoptysis, etc.) can be fatal[7]. In contrast, transbronchial biopsy (TBB) is a relatively safe procedure and rarely provokes severe complications[2]. We previously reported that CT-TBB has an advantage with few occurrences of adverse effects[8]. However, the diagnostic yield of PPLs by CT-TBB is relatively low. No reliable data has been available for virtual bronchoscopic navigation

(VBN) supplemented CT-TBB. Therefore, we sought to apply VBN as an aid to CT-TBB with the expectation of improving the diagnostic yield for PPLs.

METHODS

Study Design

Patients were prospectively assigned to either VBN+ or VBN- groups. The VBN+ was referred to the bronchoscopic procedure of CT-TBB with aid of VBN, alternatively, VBN- was referred to the bronchoscopic procedure of CT-TBB without the aid of VBN. The senior doctors in our department recruited the patients for this study. Patients with small PPLs (<20 mm in diameter) were recruited consecutively in Shinshu University Hospital from November 2011 to November 2014 (until 100 cases were collected). Every week one patient recruited for the study underwent CT-guided bronchoscopy. Patients were assigned to either the VBN+ or VBN- study group dependent on when they underwent CT-guided bronchoscopy. CT-guided bronchoscopy with aid of VBN was performed every other week and patients scheduled for CT-guided bronchoscopy in those week were assigned to the VBN+ study group. Patients undergoing CT-guided bronchoscopy during the weeks in between were assigned to the VBN- study group, which makes the study not truly randomized. However no arbitrary manipulation interfered with this assignment.

The primary endpoint was to improve the diagnostic yield of PPLs. Clinical patient data (medical histories, clinical presentation, laboratory examinations, electrocardiograms, tests of pulmonary function, and high-resolution CT scans) were carefully reviewed. Written informed consent was obtained for each patient prior to bronchoscopy, following the approval of our protocol by the Shinshu University Ethical Committee (permission number: 2170). We also obtained this interventional trial registration by the University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR: registration number: UMIN000032484).

Small PPL lesions

All small PPLs (<20 mm in diameter) were detected by chest X-ray, CT scan, or by a follow-up CT scans for other underlying disease. The definition of PPLs are generally considered as lesions in the peripheral one-third of the lung although a precise definition and radiographic anatomical landmarks separating central and peripheral lesion does not exist[2, 6], and are not detectable beyond the visual segmental bronchi by flexible bronchoscopy[6, 8, 9]. The selection criteria for PPL included PPLs that were invisible or unlikely to be detected by X-ray fluoroscopy, PPLs that went undiagnosed despite

examination by conventional bronchoscopy, and difficult-to-access PPLs in terms of conventional bronchoscopy. Patients were assigned in turn to either the VBN+ or VBN- groups for the CT-TBB examination (50 per group).

Definition of the CT-bronchus sign (CT-BS)

The CT-bronchus sign (CT-BS) was used to describe the positional relationship of a PPL relative to a nearby bronchus[10]. For example, the term CT-BS 0 indicates no bronchus in proximity to the PPL whereas CT-BS 1 indicates a bronchus adjacent to the PPL, and CT-BS 2 indicates a bronchus within the PPL. CT-BS classifications were evaluated prior to CT-TBB. Given that PPLs with a CT-BS designation of 0 were unlikely to receive a definitive diagnosis (as according to our previous study)[11] only PPLs with classifications of CT-BS 1 or 2 were included in the present investigation.

Patient preparation before the CT-guided bronchoscopy

The patients were prepared for the CT-TBB as per previous description[11]. Briefly, topical anesthesia with 2% lidocaine and conscious sedation with intramuscular pethidine hydrochloride were administered before the procedure, which was then monitored by pulse oximetry and ECG.

CT-guided transbronchial biopsy assisted by virtual bronchoscopic navigation

VBN images were constructed from high resolution CT scans by a navigation system (LungPoint Satellite Planning System®, Bronchus Technologies, Inc., Mountain View, CA, USA) according to a previously described methodology[12]. Prior to examination, the bronchoscopist confirmed the virtual route to the target lesion by VBN. The examination was then performed in a room equipped with CT apparatus. Bronchoscopists with substantial expertise performed the CT-TBB assisted with VBN.

Bronchoscopy was performed as a routine procedure with a BF-type P260F (4.0-mm outer diameter, 2.0-mm channel diameter, Olympus; Tokyo, Japan) flexible bronchofibervideoscope. Instead of X-ray fluoroscopy, a multi-detector CT (Aquilion™ 16; Toshiba; Tokyo, Japan) was used to guide the procedure. The application of VBN was as per previous description[12] and in Supplementary Appendix S1**.** The position of the target lesion with respect to the tip of the biopsy forceps (FB-211D, Olympus; Tokyo, Japan) was confirmed by the first real-time multislice CT fluoroscopy (tube voltage: 120 kV; tube current: 10 mA; rotation time: 0.5 s; slice thickness: 2 mm). We repeated a subtle positional change of the forceps each time after a set of CT scanning within a narrow range containing both the lesion and the forceps, until we were sure that the tip of the

forceps could capture the target. The biopsy was then performed as previously described[8]. The final procedure was to perform a bronchial wash using 10 ml of normal saline, with the bronchial lavage collected for cytological and bacterial analyses.

We tried to perform as many biopsies as possible until the patients felt fatigue and within the empirical length of examination time. The examination time was measured from the start of bronchoscopy to the termination of the procedure. In addition, the time intervals between beginning bronchoscopy and taking either the first CT scan or first biopsy were recorded[13].

The biopsy lung tissues were fixed with formalin for histological diagnoses. Lung tissue retrieved from the tips of the forceps was also evaluated by cytology. In this study, rapid on-site cytological examinations, cell-block, and liquid based cytology were not performed.

CT dose index

The CT dose index (CTDI) is a metric that quantifies the radiation output from multiple contiguous CT scans. In the present study, we used the CTDI to estimate radiation exposure during the procedure of CT-guided bronchoscopy.

Diagnostic criteria

The diagnostic criteria of PPLs were as described previously[11] and in Supplementary Appendix S1.. The definition of diagnostic yield in this paper was the percentage of the number of patients who obtained the definitive diagnosis by CT-TBB out of the total number of the patients in the given group.

Statistical analysis

We used Z-test with pooled variance of PASS 15.0.5 (NCSS, LLC Kaysville, Utah, USA) for a sample size estimation. Based on our previous study of CT-TBB yield of 52.2%[11] and VBN-assisted EBUS yield of 80.4%[14] as a reference yields of the study, we calculated the sample size with the statistical power of 0.80 and 5% on both sides to be a total of 100 subjects considering that there would be no drop out because all the recruited patients had agreed to perform the bronchoscopic examination in their informed consents.

Statistical analyses were with SPSS 14.0 (SPSS Inc., Chicago, IL, USA) for Windows (Microsoft Inc., Redmond, WA, USA). Performed statistical analyses are described in the Supplementary Appendix S1.

RESULTS

Trial profile and basic characteristics of the patient cohort

The trial profile of this study was illustrated in **Figure 1**. As shown in **Table 1**, there were 23 men and 27 women in each of the groups (VBN+ and VBN-). No significant difference was found in the PPL diameter between the two groups.

Diagnostic yield of small PPLs

Diagnostic yields were 84.0% in the VBN+ group and 58.0% in the VBN- group, with a significant difference in diagnostic yield between the two groups (P=0.013; **Fig. 2**). We performed brushing in two cases and TBNA on one case in VBN+ group, but all the diagnostic yield was based on the biopsies and bronchial wash after biopsy. As a result, 47 patients in the VBN+ and 40 patients in the VBN- groups had final definitive diagnoses (**Fig. 3**).

Factors that affect diagnostic yield

As shown in **Table 2**, the number of biopsy specimens was significantly greater for the VBN+ group (n = 3.54 ± 1.07) vs. VBN- group (n = 2.98 ± 1.06, P=0.01). There was no

significant difference in terms of whole examination time between groups (P=NS). However, time elapsed before the first CT, and the first biopsy, was significantly shorter for the VBN vs. VBN- group (P<0.01). There was no statistically significant difference in CT dose index between the two groups (P=NS).

Complications and adverse events

Complications were observed in 6 cases in the VBN+ group and 4 cases in the VBN- group. There was no serious adverse event in both groups. The details of the complications were reported in Supplementary Appendix S2**.**.

DISCUSSION

CT images enable fine visualization of a tiny positional gap between a small PPL and the forceps just before biopsy. In addition, the real time CT can inspect the proper bronchus for the bronchoscopic route, with an aid of VBN to further confirm the route reaching the PPL. This is the first prospective, single centre trial to examine the value of using a VBN system to assist CT-TBB in the diagnosis of PPLs.

Likewise, CT-guided bronchoscopy, EBUS-GS is a reliable diagnostic procedure for small PPLs with a diagnostic yield of 58% to 77% for all lesion sizes[15-17]. In particular, for those cases with PPLs with positive CT-bronchus sign, diagnostic yields of 77% to 89% have been reported[15, 16, 18].

Previous studies have reported that VBN might be used to guide biopsy forceps to small PPLs[19, 20]. Ishida et al. reported a greater diagnostic yield when using VBN-assisted EBUS-GS for small PPLs of <30 mm (80.4% vs. 67.0% with and without VBN, respectively (P=0.032)). The diagnostic yield of PPLs <20 mm in size was 75.9% vs. 59.3%, with and without VBN respectively, when calculated from this study[14].

The present investigation demonstrated that VBN could be used to increase the diagnostic yield for PPLs of less than 20 mm in diameter using CT-TBB. The diagnostic yield of small PPLs was 84.0% in the group with VBN vs. 58.0% for the group without VBN. The improved diagnostic yield of 84.0% for VBN-assisted CT-TBB (in the present investigation) exceeds that achieved (80.4%) when combining EBUS-GS with VBN[14].

The diagnostic yield of lesions <2cm by percutaneous CT-guided biopsy is also high; the diagnostic accuracy is 92.8% with a sensitivity for malignancy at 92.3%[21], but this technique carries the risk of complications such as pneumothorax, bleeding[22], air embolism[23,24], and even an increased risk of pleural recurrence in stage I lung cancer[25].

Therefore, in our opinion, the PPLs of negative CT-BS or undiagnosed PPLs by CT-TBB should be considered an alternative choice of the diagnostic procedure to perform TTNA. Using TBNA during CT-guided bronchoscopy might be an alternative procedure in cases of negative CT-BS. Mondoni et al. reported that using TBNA under X-ray fluoroscopy brought about good yield of 0.70 in CT-BS (+) nodule in size > 3cm [8]. However, there are some differences from our study. Firstly, our targets were the PPLs in size smaller than 20mm; second, it was not preferred to obtain samples by using TBNA during CT-guided bronchoscopy because the CT fluoroscopy could not follow the tip of the needle in real time while the needle was advanced to the target lesion, and thus the risk of pneumothorax was increased, which was proved in our previous study[11].

CT-TBB is especially applicable to those cases of PPL that are unresectable because of physical or mental problems, for which there is a strong suspicion of lung carcinoma. In fact, up to 60% of the nodules were not malignant in some studies[26]. Indeed, in our study, 52 of the 100 cases necessitated confirmation of a definitive diagnosis prior to resection because of poor cardiopulmonary condition (15 cases), a history of other pulmonary cancer (7 cases), multiple lung cancer (7 cases), a possibility of benign disease (2 cases), a suspicion of metastatic lung cancer (3 cases), refused surgical procedure (6 cases), multiple comorbidities (10 cases), and severe mental disease (2 cases). In addition, 33

individuals in this 100-patient cohort were over 75 years of age.

The examination time was controlled to be as short as possible in order to reduce radiation exposure. There was no significant difference in the average examination time between groups (**Table 2**). On the other hand, the time elapsed prior to the first biopsy was longer for the VBN- group (**Table 2**), such that a greater proportion of the examination time could be used to collect biopsy material for the VBN+ group, with more biopsies collected. In a previous study of the diagnostic yield for PPL transbronchial biopsy suggested that larger specimen numbers might lead to an improved diagnostic yield[27]. In our previous study, although the diagnostic yield did not differ significantly between PPLs involving one biopsy vs. those involving multiple specimens, there was a tendency for an increased specimen number to lead to a better diagnostic yield[11].

We anticipated that VBN assisted bronchoscopy might lead to a reduction in radiation exposure. However, there was no significant difference in radiation exposure for the VBN+ vs. VBN- groups (**Table 2**). Larger numbers of biopsy specimens might cause an increase in CT scans. To reduce radiation exposure in CT-guided bronchoscopy, other methods (e.g. rapid on-site cytological evaluation) might be of benefit in shortening the examination time.

The CT-apparatus can be used for CT-TBB in few hospitals. In our hospital, we have

one CT apparatus that is designated only for the invasive examinations. In the insurance system of Japan, CT-TBB costs 450 dollars per examination, EBUS-GS costs 410 dollars and no cost-charge for using VBN. We believe the use of CT-TBB is likely to be cost-effective, but are now studying and the advantages of CT-TBB over EBUS-GS in the diagnosis of small PPLs, to help guide the appropriate future use of CT-TBB.

The limitation of the study is that the patients were assigned alternatively to either VBN+ or VBN- groups, which was not true randomization in clinical study. Additionally, patients with CT-BS 1 and 2 only were included. Based on our previous study, CT-BS 0 were not recommended to perform the CT-TBB because of the low diagnostic yield at 2.9%[11]. Nevertheless, excluding the CT-BS 0 might be a limitation to have bias in the patient selection.

In conclusion, VBN significantly improved the diagnostic yield of small PPLs in CT-guided bronchoscopy.

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FIGURE LEGENDS

Figure 1. Trial profile. Total of 1336 patients were performed bronchoscopic examination in the study period. Among of them, 430 patients were performed bronchoscopy for the diagnoses of PPLs. Of which, 308 patients were examined with conventional bronchoscopy or EBUS-GS. The rest of 122 patients were performed the CT-TBB. Among of the 122 patients, 22 patients were excluded in the recruitment including 3 patients with PPLs in size more than 20mm, 9 cases with PPLs of CT-BS 0, and 10 patients whose clinical data (e.g. examination time, CT-dose index etc.) were unqualified. As a result, 100 patients were recruited in the study and assigned in turn into VBN+ (n=50) and VBN- (n=50) group.

Figure 2. Diagnostic yield. The diagnostic yield for the VBN (+) group was significantly greater than that of the VBN (-) group.

Figure 3. Final diagnosis. In the VBN+ group, of those 42 cases who got definitive diagnosis, 41 were malignant tumor (38 cases of adenocarcinoma, two of squamous cell carcinoma, and one of metastatic lung carcinoma), and one were inflammation. Of those 8 cases who could not obtain the diagnosis, five had surgery and diagnosed with

adenocarcinoma, one received radiation therapy and two were followed up periodically by CT scanning. In the VBN- group, of those 29 cases who got definitive diagnosis, 27 were malignant tumor (26 cases of adenocarcinoma and one of metastatic lung cancer) and two were inflammation. Of those 21 cases who could not obtain the diagnosis, 11 had surgery diagnosed with adenocarcinoma, one received radiation therapy as lung cancer, eight were followed up periodically by CT scanning, and one went to another hospital and lost of following up. Number in the blanket indicates the number of patients.

Table 1. Basic characteristics of the patient cohort

	VBN+ Group	VBN- Group	P value
Age (years)* Range (years)	67.9±10.2 (49-85)	71.4±7.7 (49-88)	NS (0.07)
M:F (n)	23:27	23:27	NS
PPL lesion diameter* (millimetres)	13.3±3.9	14.6±3.3	NS (0.07)
Final diagnosis (n)			
adenocarcinoma	43	37	NS
squamous cell carcinoma	2	0	
metastatic lung cancer	1	1	
inflammation	1	2	
undiagnosed	3	10	
Prior diagnostic work-up (none/ conventional bronchoscopy/EBUS-GS/ conventional CT-TBB) (n)	(45/2/2/1[#])	(46/3/1/0)	NS
CT-BS classification (0/1/2) (n)	(0/31/19)	(0/30/20)	NS

M, male; F, female; VBN, virtual bronchoscopic navigation; NS, not significant; n, number

* Age and PPL lesion diameter were expressed as mean ± standard deviation (SD)

[#]: This patient was performed the conventional CT-TBB (=without VBN) before the present study.

Table 2. Examination time, biopsy number, and CT dose index

	VBN+ Group	VBN- Group	P value
Biopsy number (n)	3.54±1.07	2.98±1.06	0.01
Entire examination time (mins)	32:53±10:2	33:06±7:7	0.921
Time to first CT (mins)	10:32±2:41	12:56±3:52	0.003
Time to first biopsy (mins)	15:16±6:46	19:36±9:02	0.008
CT dose index (mGy)	134.8±179.0	98.4±38.8	0.17

VBN, virtual bronchoscopic navigation; mGy, milli gray

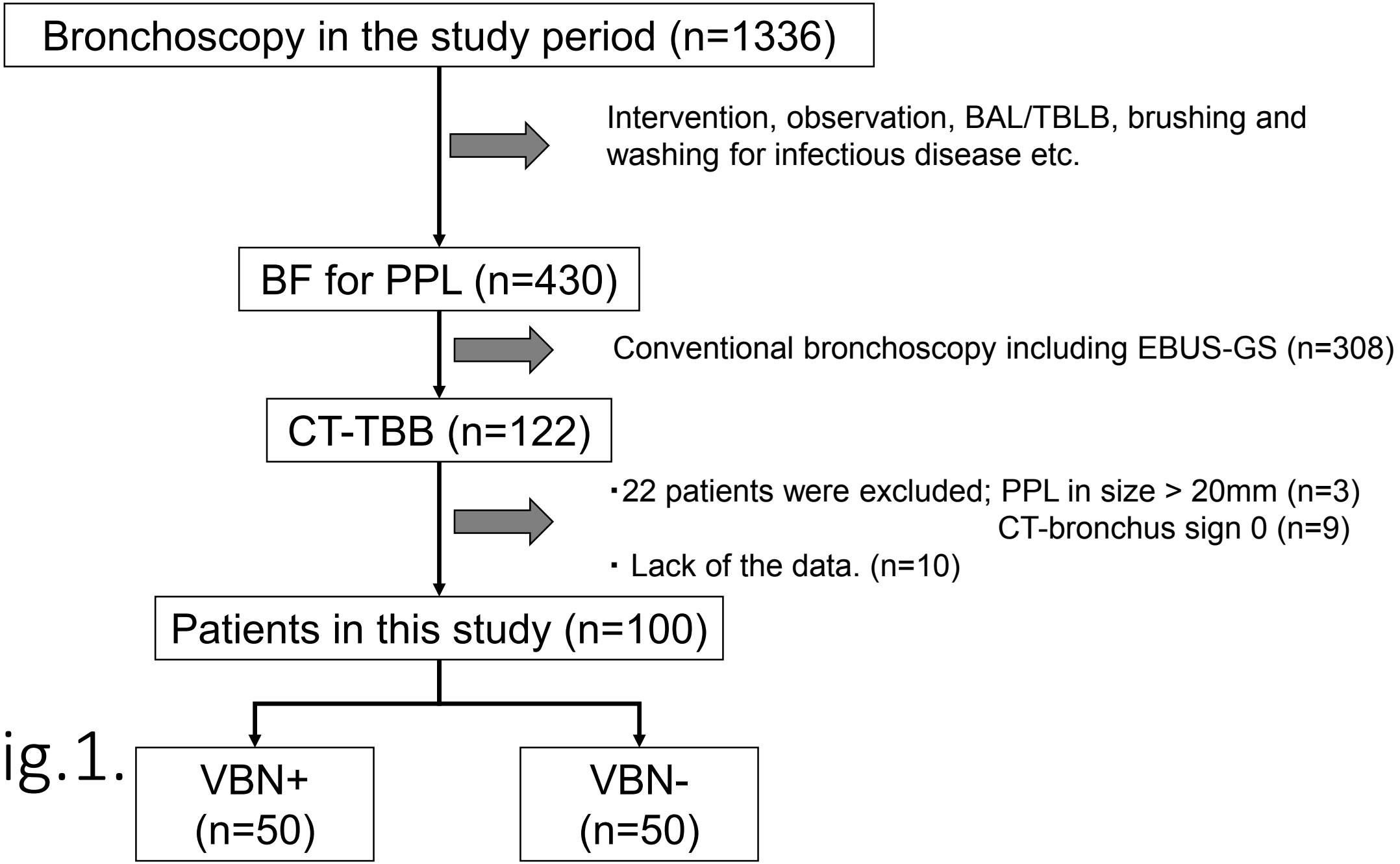

Bronchoscopy in the study period (n=1336)
Intervention, observation, BAL/TBLB, brushing and washing for infectious disease etc.
BF for PPL (n=430)
Conventional bronchoscopy including EBUS-GS (n=308)
CT-TBB (n=122)
・22 patients were excluded; PPL in size > 20mm (n=3)
CT-bronchus sign 0 (n=9)
・ Lack of the data. (n=10)
Patients in this study (n=100)
VBN+ (n=50)
VBN- (n=50)

Fig.1.

Fig.2.

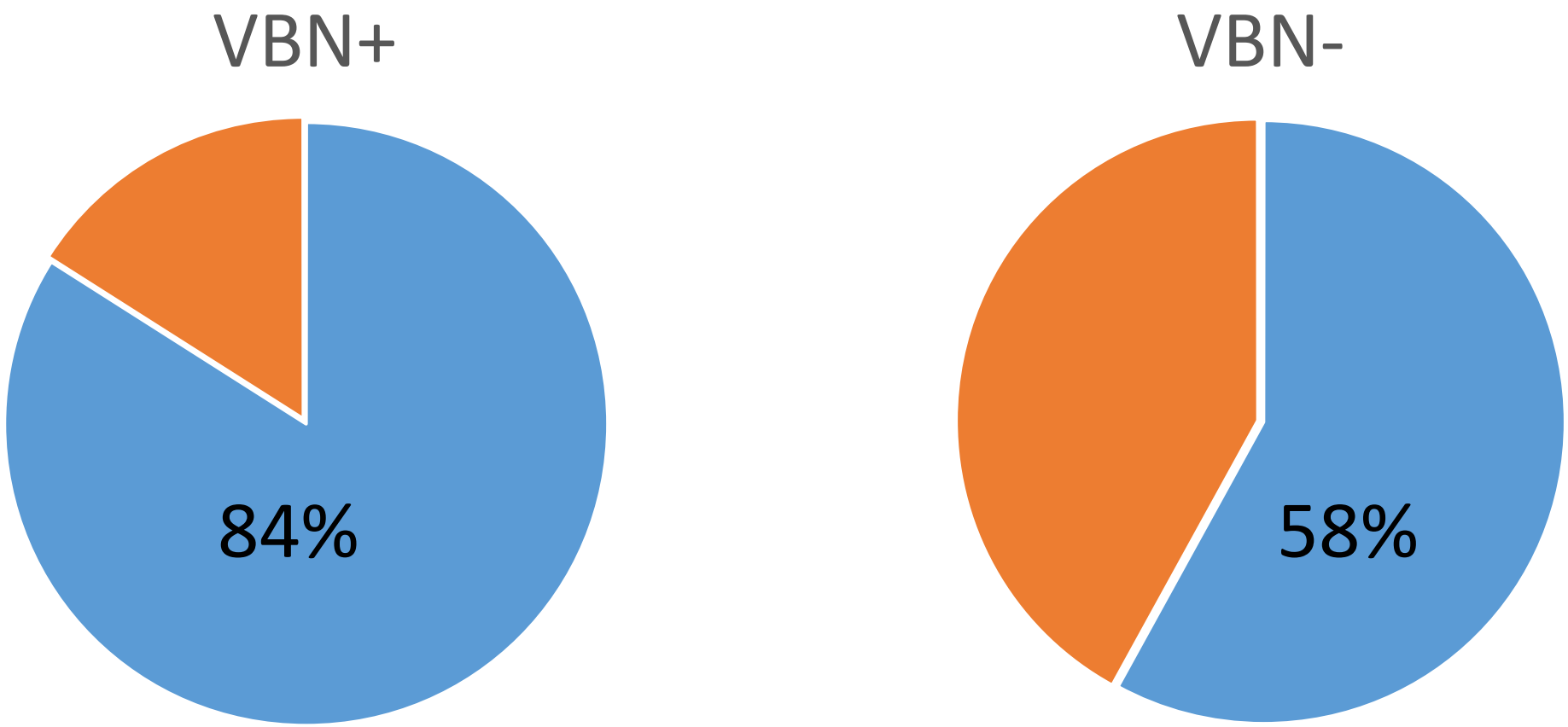
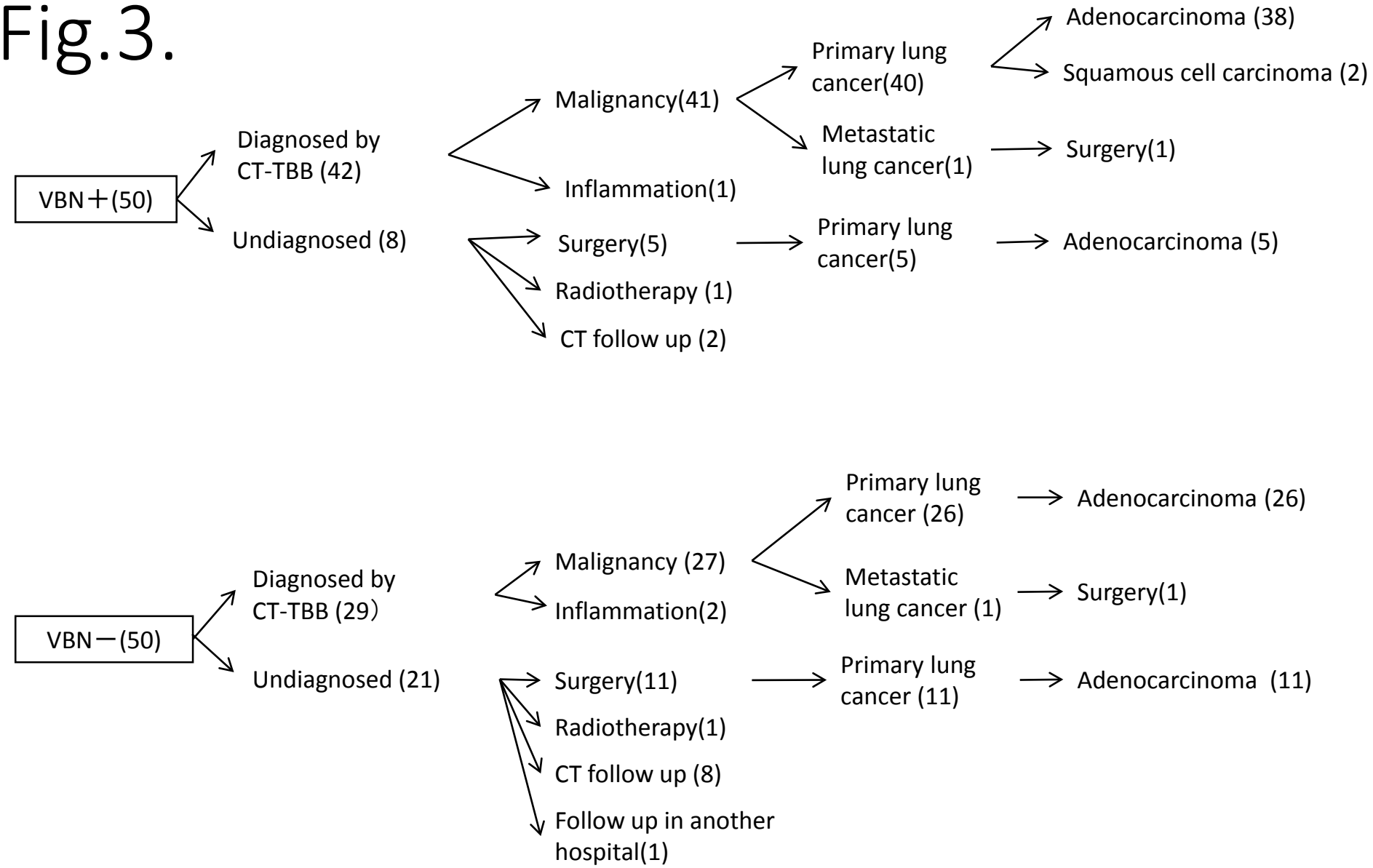


Fig.3.


VBN＋(50)
Diagnosed by CT-TBB (42)
Undiagnosed (8)
Malignancy(41)
Inflammation(1)
Surgery(5)
Radiotherapy (1)
CT follow up (2)
Primary lung cancer(40)
Metastatic lung cancer(1)
Primary lung cancer(5)
Adenocarcinoma (38)
Squamous cell carcinoma (2)
Surgery(1)
Adenocarcinoma (5)
VBN－(50)
Diagnosed by CT-TBB (29）
Undiagnosed (21)
Malignancy (27)
Inflammation(2)
Surgery(11)
Radiotherapy(1)
CT follow up (8)
Follow up in another hospital(1)
Primary lung cancer (26)
Metastatic lung cancer (1)
Primary lung cancer (11)
Adenocarcinoma (26)
Surgery(1)
Adenocarcinoma (11)

Online supplemental material

Virtual bronchoscopic navigation as an aid to computed tomography-guided transbronchial biopsy improves the diagnostic yield for small peripheral pulmonary lesions

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Patients and Methods

How to examine the CT-guided transbronchial biopsy

In the examination room, the VBN system (LungPoint®) was installed next to the bronchoscopist to facilitate visualization of the route to the target PPL. The VB image was rotated such that it matched the actual image, and was then advanced to the forward bronchial branch; the bronchoscope was moved in the same manner. Whenever rotation of the bronchoscope (through forward motion) resulted in any discrepancy between the real and virtual image, the VB image was re-aligned to match the actual image. Using VB imaging as a navigation tool, the bronchoscope was advanced as far as possible under direct vision[1].

Diagnostic criteria

A definitive diagnosis of malignant or benign PPL was based on an evaluation of the histopathology by two pathologists. In addition, any malignancy was confirmed by the presence of malignant cells as identified by cytology. All benign lesions were diagnosed

based on tissue pathology. In the absence of such evidence, lesions were described as undiagnosed. In all other cases (e.g. the collection of inflammatory cells, bronchial epithelium without microbial detection), PPLs were also described as undiagnosed.

Statistical analysis

Statistical analyses were with SPSS 14.0 (SPSS Inc., Chicago, IL, USA) for Windows (Microsoft Inc., Redmond, WA, USA). Quantitative data were presented as means ± standard deviation. Qualitative data were counted and analysed using Pearson's chi-squared test, which was substituted with Fisher's exact test for the evaluation of low numbers of cases (less than 5). Logistic regression was used to analyse factors that affect diagnostic yield. If univariate analysis demonstrated significance for a factor in terms of diagnostic yield, then multivariate analysis was performed using multiple logistic regression. A p-value of <0.05 was considered to be statistically significant.

Results

Complication and adverse events

Complications were observed in 7 (14%) of the VBN+ group and 4 (8%) of the VBN- group (P=0.34) including moderate bleeding of 6 cases (12%) in VBN+ and 4 cases (8%) in VBN- groups; and vasovagal reflex or orthostatic hypotension* of one case (2%) in VBN+ group. The complication of moderate bleeding indicated that the bleeding had flowed into the other side of the bronchus. There was no pneumothorax nor pneumonia complicated in both groups. There was no serious adverse event in both groups.

*: One patient had vasovagal reflex or orthostatic hypotension after 4 hours of the CT-TBB. The patient was given an information about the results of the CT-TBB (Adenocarcinoma was diagnosed by cytology at that time) in sitting position. Immediately after the explanation, the patient stood up and felt dizzy. Although his consciousness did not lose, he hit his head to the entrance door of the patient's room. His blood pressure was 102/56 mmHg, heart rate was 67 bpm, oxygen saturation was 93% in room air in that time. The ECG, brain CT was normal. We assessed his symptoms as temporally vasovagal reflex or orthostatic hypotension. He recovered soon and did not show these symptoms thereafter.

Reference of Supplemental data

1. Yasuo M, Kobayashi T, Hama M, Ichiyama T, Horiuchi T, Yamamoto H, Kawakami S, Hamanaka K, Honda T, Hanaoka M. Combination of virtual bronchoscopic navigation with conventional transbronchial needle aspiration in the diagnosis of peribronchial pulmonary lesions located in the middle third of the lungs. Respir Investig 2016; 54: 355-63.