Introduction

The diagnostic rate of peripheral pulmonary lesions larger and smaller than 2 cm using traditional bronchoscop- 
copy were 63 and 34%, respectively. The transbronchial approach of the forceps to the target lesions depends on 
the bronchial structure, which is not always in direct contact with the peripheral small lesions, and recognizing 
these small lesions is sometimes quite difficult under fluoroscopy. To improve the diagnostic rate of the 
endobronchial approach, direct visualization of target lesions by the radial probe endobronchial ultrasonogra-
phy (EBUS) has been introduced for better recognition of the forceps’ location relative to the lesions; however, 
it is not always available in all facilities. As another method for real-time confirmation, we attempted to 
combine bronchoscopy and body-surface ultrasound for detecting peripheral lung lesions in contact with the 
thoracic wall. This study was performed to evaluate the usefulness of the body-surface ultrasound-guided bron-
choscopy (BSUS-BF) in diagnosing peripheral lung lesions.

Patients and methods

Patients

Among patients who underwent bronchofiberscopy between August 1997 and March 2003 at the National 
Center for Global Health and Medicine, those with peripheral lung lesions ≤5 cm in the longer axis in com-
puted tomography (CT) scan and visible in body-surface ultrasound were selected for the study. This study was 
approved by the ethics committee of the National Center for Global Health and Medicine (Registration number 
77) and informed consent was obtained from all participants in the study.

Methods

Each patient was premedicated with 0.5 mg of atro-
pine sulfate and 50 mg of hydroxyzine hydrochloride. Continuous pulse oximetry was monitored during the procedure, and blood pressure was measured every 5 min. Oxygen was administered via a nasal cannula to maintain the pulse oximetric saturation above 93%. Flexible fiberoptic bronchoscopes BF Type200, IT200, Type240, and IT240 (Olympus) were used. After observation of all segments of the airway, the forceps were introduced into the bronchus of interest and controlled by fluoroscopy in both groups. Curettage forceps were tried first, and biopsy or brushing forceps were added if possible. Fluoroscopy was turned off when the curettage forceps were settled down, and the lesions were checked by ultrasound for the real-time visualization of the forceps. Recognition of the forceps in the lesions was confirmed by the simultaneous handling of the forceps, such as opening and closing of the cup of biopsy forceps or bending and stretching or pushing and pulling of the curettage forceps. When the forceps were not recognized in the lesions, then the forceps were re-positioned to be visualized using fluoroscopy and BSUS at the same time. Re-positioning was repeated at most 5 times, depending on the patients’ condition. The hand controlling the probe under fluoroscopy was protected by a glove-type lead shield. Visualization of the forceps in the lesions was confirmed by all staff (usually, four or five) involved in the procedures. The ultrasonographs used in the study were RT-fino (GE-Yokogawa) and SSD-1200 (Aloka) with the convex type 3.5 MHz probes.

When the result was negative for suspected malignant lesions, further examination was made by the re-study of bronchofiberscopy, CT-guided transcutaneous needle biopsy, or open lung biopsy. A positive smear result for acid fast bacilli was interpreted as mycobacterium infection and divided into tuberculosis and atypical mycobacterium infection based on culture results. A diagnosis of pneumonia and inflammation was made when the lesion disappeared or shrank with or without antibiotics or steroid therapy.

Statistical Analysis

Pearson’s chi-squared test was employed, and calculations were performed using the JMP for Windows version 10. All P-values are two-tailed, and a P-value < 0.05 is considered statistically significant.

Results

The patients’ profiles are shown in Table 1; 115 patients were enrolled in the study. Malignancy was the most frequent diagnosis and followed by pneumonia and inflammation, tuberculosis, and atypical mycobacterium.

Visualization of the forceps was demonstrated by the recognition of the high echoic linear or dot markings in the lesions. Fig. 1 shows how the biopsy forceps were demonstrated in the mass (see Video, Supplemental Digital Content 1, demonstrating the forceps in the lesion). Fig. 2 shows small lesions that only curettage forceps could reach, and the linear structures were recognized in the shadows (see Video, Supplemental Digital Content 2–4, demonstrating the forceps in the lesions). The forceps did not always hit the center of the lesions and often only scratched the marginal zone, even after several trials (Fig. 3; see Video, Supplemental Digital Content 5, demonstrating the forceps scratching on the surface of the lesion). BSUS-BF was particularly useful when the target lesions were difficult to recognize by fluoroscopy alone (for example, when they were too small or were surrounded by pre-existing shadows due to past tuberculosis) because the echo probe itself showing the lesions under fluoroscopy could also be a target for the forceps. Fig. 4(a) shows a 1.4 x 1.3 cm lesion surrounded by old shadows from past tuberculosis and behind the pacemaker in the frontal view. Fig. 4(b) shows that the lesion is visible in the frontal view, but unrecognized in the lateral view. In both cases the exact location of the lesions could not be clarified without BSUS guidance.

The forceps were visualized in 79 out of 115 (visualization rate 68.7%) for all lesions, and in 42 out of 62 (67.7%) for malignant lesions (Table 2). The visualization rate of the large size group (≥3–≤5 cm) was 68.6% (35/51) for all lesions and 69.7% (23/33) for malignant lesions, whereas for the small size group (≤3 cm), the visualization rates were 68.8% (44/64) and 65.5% (19/29) for all and malignant lesions, respectively. There was no significant difference in the visualization rate between all and malignant lesions or between different size groups.

### Table 1 Characteristics of study population (n = 115)

| Age (years, median; range) | 61 (21–88) |
| Male, n (%) | 72 (62.6) |
| Lesion size (cm, median; range) | 3.0 (1.0–5.0) |
| ≤3 cm, n (%) | 64 (55.7) |
| ≥3–≤5 cm, n (%) | 5 (44.3) |
| Non-malignancy, n (%) | 79/115 (68.7) |
| Malignancy, n (%) | 36/115 (31.3) |
| Pulmonary thromboembolism, n (%) | 5 (4.3) |
| Round atelectasis, n (%) | 2 (1.7) |
| Rheumatoid nodule, n (%) | 1 (0.9) |
| Cryptococcosis, n (%) | 3 (2.6) |
| Tuberculosis, n (%) | 14 (12.2) |
| Non-malignancy, n (%) | 53 (46.1) |
| Malignancy, n (%) | 25 (21.7) |
| Malignancy, n (%) | 62 (53.9) |

### Table 2 Visualization of the forceps in the lesions

| Lesion size (cm, median; range) | all | malignancy |
|-------------------------------|-----|-----------|
| ≤3 cm | 44/64 (68.8) | 19/29 (65.5) |
| >3–≤5 cm | 35/51 (68.6) | 23/33 (69.7) |

Total | 79/115 (68.7) | 42/62 (67.7) |

Data are presented as n/total n (%)
**Fig. 1** Visualization of the biopsy forceps in the lesion by BSUS-BF. 
(a) 3.6 x 1.8 cm tuberculoma. a-1) and a-2) shows opened and closed cup of biopsy forceps respectively. (b) 3.7 x 4.6 cm bronchioloalveolar carcinoma. (see Video, Supplemental Digital Content 1) 
BSUS-BF: body-surface ultrasound-guided bronchofiberscope

**Fig. 2** Visualization of the curetage forceps in the lesions.
(a) 3.3 x 2.2 cm adenocarcinoma. (see Video, Supplemental Digital Content 2) (b) 3.0 x 2.3 cm adenocarcinoma. (see Video, Supplemental Digital Content 3) (c) 2.4 x 2.2 cm adenocarcinoma. (see Video, Supplemental Digital Content 4). All diagnosed by BSUS-BF. 
BSUS-BF: body-surface ultrasound-guided bronchofiberscope

**Fig. 3** Visualization of the curetage forceps in marginal zone of the lesions.
(a) 3.3 x 2.2 cm adenocarcinoma. Negative by BSUS-BF, diagnosed by transthoracic needle aspiration. (b) 1.7 x 1.4 cm squamous cell carcinoma diagnosed by BSUS-BF. (c) 1.5 x 1.5 cm tuberculosis diagnosed by BSUS-BF. (see Video, Supplemental Digital Content 5) 
BSUS-BF: body-surface ultrasound-guided bronchofiberscope
Table 3  Size and diagnostic rate of all lesions

| Visualization of the forceps | Total (+) | Total (−) |
|-----------------------------|-----------|-----------|
| ≤3 cm                       | 24/44 (54.5) | 7/20 (35.0) |
| >3–≤5 cm                    | 29/35 (82.9) | 10/16 (62.5) |
| Total                       | 53/79 (67.1) | 17/36 (47.2) |

Data are presented as n/total n (%)

Table 4  Size and diagnostic rate of malignant lesions

| Visualization of the forceps | Total (+) | Total (−) |
|-----------------------------|-----------|-----------|
| ≤3 cm                       | 14/19 (73.7) | 4/10 (40.0) |
| >3–≤5 cm                    | 19/23 (82.6) | 8/10 (80.0) |
| Total                       | 33/42 (78.6) | 12/20 (60.0) |

Data are presented as n/total n (%)

Table 5  Effect of the forceps location in the lesions to diagnostic rate

| Malignant      | Non-malignant* | Total † |
|----------------|----------------|---------|
| Within         | 23/28 (82.1)   | 14/22 (63.6) |
| Adjacent       | 10/14 (71.4)   | 4/15 (26.7) |
| Total          | 33/42 (78.6)   | 18/37 (48.6) |

Data are presented as n/total n (%)

* p = 0.0272, χ² "within" vs "adjacent"
† p = 0.0221, χ² "within" vs "adjacent"

Fig. 4  BSUS-BF in the lesions that could not be recognized by fluoroscopy.
(a) Small lesion surrounded by old inflammatory changes and disturbed visualization in frontal view due to a pacemaker. Past history of lung cancer and metastasis was suspected. (1.4 × 1.3 cm, inflammation, negative by BSUS-BF, judged by clinical course) (b) Visualized only in frontal view. (3.2 × 1.8 cm, tuberculosis, diagnosed by BSUS-BF)
BSUS-BF: body-surface ultrasound guided bronchofiberscope
For all lesions, the overall diagnostic rate for the BSUS-BF group was 59.1% (Table 3). The positive visualization subgroup had a 67.1% diagnostic rate and tended to be higher than the negative visualization subgroup (47.2%, p = 0.08, $\chi^2$-test). In the large size group, the diagnostic rate of positive visualization subgroup was 82.9% and tended to be higher than that of negative visualization subgroup (62.5%, p = 0.12, $\chi^2$-test). In the small size group, the diagnostic rate of the positive visualization subgroup was 54.5% and tended to be higher than that of the negative visualization subgroup (35.0%, p = 0.26, $\chi^2$-test). For malignant diseases, the diagnostic rate of the positive visualization subgroup was 78.6% and tended to be higher than that of the negative visualization subgroup (60.0%, p = 0.13, $\chi^2$-test; Table 4). For the small size group, the positive visualization subgroup had a 73.7% diagnostic rate that tended to be higher than that of the negative visualization subgroup (40.0%, p = 0.08, $\chi^2$-test). In the large size group, the rate was almost equal for the subgroups, approximately 80% for each.

The effect of forceps location in the lesions is shown in Table 5. The position of the visualized forceps in the lesions was classified into two types: “within,” in which the forceps were deeper than 2 mm from the surface of the lesions, and “adjacent to,” ≤2 mm, which is based on the forceps’ diameter of 1.9 mm. In all lesions and non-malignant lesions, the “within” group had a significantly higher diagnostic rate compared to the “adjacent” group (p = 0.02, p = 0.03, respectively, $\chi^2$-test). For malignant lesions, there was no statistical difference in diagnostic rate between the two groups (p = 0.43, $\chi^2$-test).

Discussion

Interpretations

Guidance by body-surface ultrasound has so far been limited to transcutaneous biopsy or aspiration cytology.

For all lesions, the overall diagnostic rate for the BSUS-BF group was 59.1% (Table 3). The positive visualization subgroup had a 67.1% diagnostic rate and tended to be higher than the negative visualization subgroup (47.2%, p = 0.08, $\chi^2$-test). In the large size group, the diagnostic rate of positive visualization subgroup was 82.9% and tended to be higher than that of negative visualization subgroup (62.5%, p = 0.12, $\chi^2$-test). In the small size group, the diagnostic rate of the positive visualization subgroup was 54.5% and tended to be higher than that of the negative visualization subgroup (35.0%, p = 0.26, $\chi^2$-test). For malignant diseases, the diagnostic rate of the positive visualization subgroup was 78.6% and tended to be higher than that of the negative visualization subgroup (60.0%, p = 0.13, $\chi^2$-test; Table 4). For the small size group, the positive visualization subgroup had a 73.7% diagnostic rate that tended to be higher than that of the negative visualization subgroup (40.0%, p = 0.08, $\chi^2$-test). In the large size group, the rate was almost equal for the subgroups, approximately 80% for each.

The effect of forceps location in the lesions is shown in Table 5. The position of the visualized forceps in the lesions was classified into two types: “within,” in which the forceps were deeper than 2 mm from the surface of the lesions, and “adjacent to,” ≤2 mm, which is based on the forceps’ diameter of 1.9 mm. In all lesions and non-malignant lesions, the “within” group had a significantly higher diagnostic rate compared to the “adjacent” group (p = 0.02, p = 0.03, respectively, $\chi^2$-test). For malignant lesions, there was no statistical difference in diagnostic rate between the two groups (p = 0.43, $\chi^2$-test).

The diagnostic rate for all lesions was relatively low compared to that for malignant lesions; this is due to the non-specific results in the small inflammatory lesions that only curettage forceps can reach and for which histology was not available, while a positive cytology result is enough to diagnose a malignant lesion. In the large size group of malignant lesions, the diagnostic rates were around 80% regardless of visualization of the forceps; for the small size group, the positive visualization subgroup showed a diagnostic rate of 73.7%, and this tended to be higher than the rates for the negative visualization subgroup. Although the diagnostic rate did not reach statistical difference, the results suggested that BSUS-BF is useful for small lesions ≤3 cm in diameter. The diagnostic rate for the negative visualization subgroup was as low as 40%, suggesting that when we get a negative result in the negative visualization subgroup, other methods such as the transcutaneous approach should be applied rather than a re-study with a bronchofiberscope.

The diagnostic rate of EBUS with guide sheath (GS) in lesions ≤3 cm was 73% (91/124) in all lesions in the study by Kurimoto et al, 67% (106/155) in all lesions and 70% (90/128) in malignant lesions in the study by Yamada et al, 58.3% (14/24) in all lesions and 66.7% (12/18) in malignant lesions in the study by Kikuchi et al, and 67.4% (64/95) in all lesions including 76 malignant cases in the study by Ishida et al. In BSUS-BF of the same size, the diagnostic rate was 48.4% (31/64) in all lesions and 62.7% (18/29) in malignant lesions. Compared to the past studies, the diagnostic rate of BSUS-BF was lower, particularly in all lesions, possibly due to the absence of GS use. Yet, the diagnostic rate was higher when the forceps were visualized in the lesions (54.4% in all lesions and 73.7% in malignant lesions), and BSUS-BF is expected to be beneficial as an alternative navigation method.

Trans-thoracic needle biopsy has higher diagnostic rate for the peripheral lung lesions, but it has higher complication rate for pneumothorax and rare but serious complication such as needle tract implantation of malignant cells or air embolism can occur, with the rate ranging from 0.061% to 0.56%, and from 0.061% to 0.21% for the air embolism. When the lesions are abutting the pleural surface, the chance of pneumothorax and air embolism would be lower, and our study population would be best candidates for the trans-thoracic approach, but still needle tract implantation remains great concern specially in the case whom the complete resection can be expected. Thus, transbronchial approach should be kept for the alternative for the diagnosis of peripheral lung lesions.

Limitations

The limitation of BSUS-BF is that the total mass of the lesions is not always covered by ultrasound, mainly due to their partial attachment to the thoracic wall, aerated marginal zone, cavitation in the lesions, and skeletal structures. The diagnostic rates based on forceps location in the lesions were not significantly different between “within” and “adjacent” in malignant lesions. In EBUS, the diagnostic rate was much higher in the “within” group than the “adjacent” group. This discrepancy may be due to better visualization of the whole lesion by the EBUS probe, which is 20 MHz (3.5 MHz in this study), and the limited echo window in BSUS-BF. Thus, some “adjacent” cases in BSUS-BF might have been “within”
cases in the application of EBUS. The ultrasound probe with higher frequency or GS was not available in our institute when this study was conducted, and these should be applied in future studies. Further, when the lesions are located in dorsal side, the patients have to change their position from supine to decubitus for the ultrasound image, and this might cause additional burden to both patients and clinicians.

Conclusions
BSUS-BF, a novel combination of bronchofiberscope and body-surface ultrasound, was used for real-time confirmation of the positioning of forceps in lesions in direct contact with the thoracic wall. It is useful particularly when the lesions are small and difficult to recognize by fluoroscopy due to surrounding infiltrates or cicatrices. Though the diagnostic rate might be lower compared to EBUS with GS, the procedure is easy to perform and should be considered as an alternative method for forceps guidance in settings where the guide bronchofiberscopic technologies are not available.

Abbreviations
BSUS-BF: body-surface ultrasound-guided bronchofiberscope
CT: computed tomography
EBUS: Endobronchial ultrasonography
GS: guide sheath

Competing interests
The authors have no financial support or conflict of interest to declare in association with this work.

Acknowledgment
We thank Dr. Yuya Kobayashi for editing Video supplementations.

References
1) Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, ed 3. American College of Chest Physicians evidence-based clinical practice guidelines. Chest, vol. 143, no. 5 Suppl. e142S-e165S, 2013.
2) Deng C, Cao X, Wu D, Ding H, You R, Chen Q, Chen L, Zhang X, Zhang Q, Wu Y. Small lung lesions invisible under fluoroscopy are located accurately by three-dimensional localization technique on chest wall surface and performed bronchoscopy procedures to increase diagnostic yields. BMC Pulm Med. Nov 29;16(1):166, 2016.
3) Kurimoto N, Miyazawa T, Okimasa S, Maeda A, Oiwa H, Miyazu Y, Murayama M. Endobronchial ultrasoundography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest, vol. 126, no. 3, pp. 959–965, 2004.
4) Meena N, Barter T. Ultrasound-guided Percutaneous Needle Aspiration by Pulmonologists: A Study of Factors with Impact on Procedural Yield and Complications. Journal of Bronchology & Interventional Pulmonology, vol. 22, no. 3, pp. 204–208, 2015.
5) Sigt JA, Groen HJ. Percutaneous ultrasonography as imaging modality and sampling guide for pulmonologists. Respiration, vol. 87, no. 6, pp. 441–451, 2014.
6) Yamada N, Yamazaki K, Kurimoto N, Asahina H, Kikuchi E, Shinagawa N, Oizumi S, Nishimura M. Factors related to diagnostic yield of transbronchial biopsy using endobronchial ultrasonography with a guide sheath in small peripheral pulmonary lesions. Chest, vol. 132, no. 2, pp. 603–608, 2007.
7) Kikuchi E, Yamazaki K, Sukoh N, Kikuchi J, Asahina H, Imura M, Onodera Y, Kurimoto N, Kinoshita I, Nishimura M. Endobronchial ultrasoundography with guide-sheath for peripheral pulmonary lesions. European Respiratory Journal, vol. 24, no. 4, pp. 533–537, 2004.
8) Ishida T, Asano F, Yamazaki K, Shinagawa N, Oizumi S, Moriya H, Munakata M, Nishimura M. Virtual Navigation in Japan Trial Group. Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomised trial. Thorax, vol. 66, no. 12, pp. 1072–1077, 2011.
9) DiBardino DM, Yarmus LB, Semaan RW. Transthoracic needle biopsy of the lung. J Thorac Dis, Dec;7(Suppl 4):S304-16, 2015.
10) Tomiyama N, Yasuhara Y, Nakajima Y, Adachi S, Arai Y, Kusumoto M, Eguchi K, Kuriyama K, Sakai F, Noguchi M, Murata K, Murayama S, Mochizuki T, Mori K, Yamada K. CT-guided needle biopsy of lung lesions: a survey of severe complication based on 9783 biopsies in Japan. Eur J Radiol, vol. 59, no. 1, pp. 60–64, 2006.
11) Ibukuro K, Tanaka R, Takeguchi T, Fukuda H, Abe S, Tobe K. Air embolism and needle track implantation complicating CT-guided percutaneous thoracic biopsy: single-institution experience. Am J Roentgenol, vol. 193, no. 5, pp. W430–436, 2009.