AJRCCM Articles in Press. Published on 03-June-2015 as 10.1164/rccm.201502-0205OC

Ultrathin Bronchoscopy with Multimodal Devices for Peripheral Pulmonary Lesions: A Randomized Trial

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Author Contributions: Conception and design: M.O., H.S., and M.A.
Collection, analysis and interpretation of data: M.O., H.S., M.A., F.A., N.K., and K.M
Drafting the article for important intellectual content: M.O., H.S., and M.A
Review and approval of the manuscript for submission: all authors

Support: The prototype ultrathin bronchoscopes were loaned to the authors by Olympus Medical Systems, Tokyo, Japan.

Running Head: Navigational endosonographic ultrathin bronchoscopy

Descripter Number: 9.24 - Interventional Pulmonology/Bronchoscopy

Word Count: 3,440

At a Glance Commentary

Scientific Knowledge on the Subject: The diagnostic yield of the combined bronchoscopic approach with endobronchial ultrasound and navigation for peripheral pulmonary lesions is higher than each technique alone, but the role of ultrathin bronchoscopes in such multimodality bronchoscopy is unknown.

What This Study Adds to the Field: The use of an ultrathin bronchoscope during navigational endosonographic bronchoscopy improves the diagnostic yield.

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Abstract

Rationale: The combination of an ultrathin bronchoscope, navigational technology and endobronchial ultrasound (EBUS) seems to combine the best of mutual abilities for evaluating peripheral pulmonary lesions, but ultrathin bronchoscopes which allow the use of EBUS have not been developed so far.

Objectives: To compare the diagnostic yield of transbronchial biopsy (TBB) under EBUS, fluoroscopy and virtual bronchoscopic navigation (VBN) guidance using a novel ultrathin bronchoscope with that using a thin bronchoscope with a guide sheath for peripheral pulmonary lesions.

Methods: In four centers, patients with suspected peripheral pulmonary lesions $\leq$ 30 mm in the longest diameter were included and randomized to undergo TBB with EBUS, fluoroscopy and VBN guidance using a 3.0-mm ultrathin bronchoscope (UTB group) or a 4.0-mm thin bronchoscope with a guide sheath (TB-GS group).

Measurements and Main Results: A total of 310 patients were enrolled and randomized, among whom 305 patients (150, UTB group; 155, TB-GS group) were analyzed. The ultrathin bronchoscope could reach more distal bronchi than the thin bronchoscope (median fifth- versus fourth-generation bronchi, $P < 0.001$). Diagnostic histologic specimens were obtained in 74% (42% for benign and 81% for malignant lesions) of UTB group and 59% (36% for benign and 70% for malignant lesions) of TB-GS group ($P = 0.044$, Mantel-Haenszel test). Complications including pneumothorax, bleeding, chest pain and pneumonia occurred in 3% and 5% in the respective groups.

Conclusions: The diagnostic yield of the UTB method is higher than that of the TB-GS method.

Clinical trial registered with www.umin.ac.jp/ctr/ (UMIN 000003177)

Word count for the Abstract: 241

Keywords: bronchoscopy, EBUS, lung cancer, navigation, solitary pulmonary nodule

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Recent modifications of bronchoscopy with ancillary techniques, such as the use of radial probe endobronchial ultrasound (EBUS) with or without a guide sheath (GS) (1, 2), navigation devices (3, 4), and thin/ultrathin bronchoscopes (5-8) have dramatically increased the diagnostic yield of bronchoscopy for small peripheral pulmonary lesions without compromising safety (9). Above all, the evidence on the usefulness of bronchoscopy with radial probe EBUS and/or navigation devices has increased and been well established. Thus, recent guidelines refer to the use of such bronchoscopic techniques as well as transthoracic needle aspiration (TTNA) as a first diagnostic procedure for peripheral sampling (10-12).

Although ultrathin bronchoscopy has not been mentioned in recent guidelines, its diagnostic performance seems comparable to that of other recommended bronchoscopic modalities such as EBUS and navigation devices (9). The good maneuverability, bronchial selectivity, and visibility of ultrathin bronchoscopes in the peripheral small bronchi seem to make for the effective use of navigation devices. The combination of EBUS and navigation provides higher diagnostic yield than each method alone (13, 14); thus, the combination of ultrathin bronchoscopes, navigation devices and EBUS seems to be promising. We conducted a comparative study to evaluate the diagnostic ability of bronchoscopic biopsy with a novel 3.0-mm ultrathin bronchoscope directed by a radial probe EBUS, virtual bronchoscopic navigation (VBN) and fluoroscopy. We used the bronchoscopic technique with a conventional 4.0-mm thin bronchoscope, radial probe EBUS with a guide sheath, VBN and fluoroscopy, as a reference arm in the present randomized comparative study, regarding which high diagnostic yields of the technique for small peripheral pulmonary lesions were reported by many studies (14-20).

Methods

Patients

We carried out a randomized study at 4 Japanese institutions (Nagoya Medical Center, Gifu Prefectural General Medical Center, St. Marianna University School of Medicine Hospital, Iwakuni Minami Hospital). From February 2010 to November 2012, patients with localized peripheral pulmonary lesions ≤ 30 mm, such as a solitary pulmonary nodule or a localized infiltrate, referred for diagnostic bronchoscopy were enrolled, and randomized for an ultrathin bronchoscopy (UTB) group, in which transbronchial biopsy (TBB) was performed using a 3.0-mm ultrathin bronchoscope under EBUS, VBN and fluoroscopic guidance (Figure 1); or for thin bronchoscopy with a guide sheath (TB-GS) group, in which TBB was performed using a 4.0-mm thin bronchoscope under EBUS with a guide sheath, VBN and fluoroscopic guidance (Figure 2). Patients with pure ground-glass nodules were excluded. Positron emission tomography/computed tomography (PET/CT) before bronchoscopy was not obligatory. Randomization was performed by the minimization method with stratification factors including lesion size in the longest diameter on chest computed tomography (CT) (> 20 mm vs ≤ 20 mm), lesion distance from hilum on CT (central vs intermediate vs peripheral, as classified by Baaklini et al. (21)) and examiner experience (staff pulmonologists vs pulmonary residents less than 6 years after receiving their M.D.). This study was approved by the institutional review board of the participating institution and registered with the UMIN-Clinical Trials Registry (identifier: UMIN000003177). All patients provided their written informed consent.

Procedures

Ultrathin Bronchoscopic Method. A prototype ultrathin hybrid-bronchofibervideoscope (Y-0025; Olympus Medical Systems; Tokyo, Japan, Figure 3A, 3B) with a charge-coupled device built into the control section was used. It has a 3.0-mm distal end diameter, a

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1.7-mm working channel diameter, 180° up and 130° down angulation, a 90° field of view and a 2−50-mm depth of field. EBUS procedures were performed with an endoscopic ultrasound center (EU-ME1; Olympus Medical Systems) and a 1.4-mm mechanical radial-type ultrasonic probe (UM-S20-17S; Olympus Medical Systems, Figure 3B). For TBB, a 1.5-mm biopsy forceps (FB-32D or FB-233D; Olympus Medical Systems) was used. Before bronchoscopy, a virtual bronchoscopic pathway which indicates the bronchial route to the lesion was made by a virtual bronchoscopic navigation system (Bf-NAVI; Cybernet Systems, Tokyo) from the helical CT data with 0.5−1.0 mm slice width.

Bronchoscopic procedures were performed using conscious sedation with bolus IV midazolam or the combined midazolam and fentanyl, and local anesthesia with lidocaine by staff pulmonologists or supervised pulmonary residents. Under EBUS, VBN and fluoroscopic guidance, TBBs for obtaining 10 visible specimens were performed followed by washing in a manner similar to what we previously described (7, 8). Other bronchoscopic procedures such as transbronchial needle aspiration, brushings, or bronchoalveolar lavage were not performed at the same setting. The bronchus level reached with the bronchoscope (subsegmental bronchi were regarded as third-generation bronchi and bronchial generation was calculated by adding the number of further branchings), the locational relation between the ultrasonic probe and the lesion on an EBUS image (within the lesion, adjacent to the lesion or invisible with EBUS, as classified by Kurimoto et al. (2)), and the duration of the procedure measured were recorded. A chest radiograph was obtained routinely to identify pneumothorax two hours after the procedures.

Thin Bronchoscopy with a Guide Sheath Method. A commercially available 4.0-mm hybrid-bronchofibervideoscope with a 2.0-mm working channel (P260F; Olympus Medical Systems, Figure 3A, 3B) and a guide sheath (SG-200C; Olympus Medical Systems, Figure 3B) was used for the TB-GS method. If the ultrasonic probe could not be advanced toward

the target lesion, a guiding device curette (CC-6DR-1; Olympus Medical Systems) was used. Other instruments including an ultrasonic probe and biopsy forceps used in the TB-GS method were the same type used with the UTB method.

The techniques were similar to the UTB method, except in the techniques for using a guide sheath, as previously described (8). The recorded items were similar to the UTB method.

Diagnosis

Each histologic and cytologic specimen was interpreted separately by an experienced pathologist. “Suspicious” findings were regarded as negative in our analysis. An inconclusive histological diagnosis of nonspecific fibrosis or inflammation was considered to be nondiagnostic. The final diagnoses were established by pathological evidence from biopsy including bronchoscopic or surgical procedures, microbiological analysis or clinical follow-up. Benign diagnoses, which could not be pathologically or microbiologically diagnosed, were confirmed by radiological size stability and clinical compatibility during the follow-up period for at least one year after bronchoscopy.

Endpoints

The primary endpoint was the histopathological diagnostic yield of TBB, while secondary endpoints were overall diagnostic yield, diagnostic yield according to benign or malignant, lesion size, lesion location, ultrasonic probe location on the EBUS image, level of bronchus reached with bronchoscopes, time of procedure and safety.

Data Analysis

This study was designed to prove non-inferiority of the histological diagnostic yield of the

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UTB method to that of the TB-GS method. If the non-inferiority was demonstrated, its superiority was then analyzed.

Based on the expected diagnostic yield of 80% using the TB-GS method (14) and 85% using the UTB method, demonstration of non-inferiority with a statistical power of 90% at a one-sided significance level of 0.025 would require 270 patients, and we arranged to enroll 300 patients with 150 in each group to account for dropouts. Non-inferiority of the ultrathin bronchoscopic method was to be concluded if the lower bound of the 90% confidence interval (CI) for the difference in the diagnostic yields exceeded the predetermined non-inferiority bound of -10%.

Means and percentages were presented as appropriate. Except for the non-inferiority analysis of the primary end point, categorical variables were analyzed using Pearson chi-square test or Mantel-Haenszel test. Continuous variables were analyzed using the Mann-Whitney *U* test or Kruskal Wallis test. Statistical analyses were performed using a statistical software program (PASW Statistics 18; SPSS Inc; Chicago, IL). Results were considered statistically significant when the *P* value was less than or equal to 0.05.

Results

Characteristics of Patients and Lesions

A total of 310 patients were enrolled in this study and 150 patients in the UTB group and 155 patients in the TB-GS group were finally analyzed (Figure 4). Characteristics of patients are summarized in Table 1. The median lesion size in the longest diameter on CT in the UTB group and the TB-GS group was 19.0 mm and 19.4 mm, respectively. There was no statistically significant difference in the baseline characteristics in both groups. The histopathological findings of TBB and the final diagnosis in each group are shown in Table 2.

Diagnostic Yields

The diagnostic yields in histological specimens sampled by TBB are shown in Table 3. The histological diagnostic yield in the UTB group and TB-GS group was 74% (111 of 150 patients) and 59% (92 of 155 patients), respectively. The difference in diagnostic yields was 14.6%, with a 95% CI from 5.8 to 23.4%. Non-inferiority of the UTB method was thus confirmed by the lower limit of the CI being more than the predetermined margin of -10%. In terms of the superiority, we confirmed that the UTB method gave a significantly higher diagnostic yield than the TB-GS method in total lesions ($P = 0.007$, Pearson chi-square test). As shown in Table 1, although the difference was not statistically significant, the prevalence of malignancy was higher in the UTB group. When divided based on the final histological diagnosis, the diagnostic yields of the UTB method and the TB-GS method were 42% and 36% *(*$P = 0.622$, Pearson chi-square test) in benign lesions and 81% and 70% ($P = 0.040$, Pearson chi-square test) in malignant lesions, respectively. Since the final histological diagnosis could be known only after randomization, we also compared the two diagnostic methods using Mantel-Haenszel test across strata for histological diagnosis (benign combined to unknown lesion vs malignant lesion) and again confirmed the diagnostic superiority of the UTB method ($P = 0.044$).

In each group, the diagnostic yield was associated with the lesion size (Table 3). In patients with negative TBB results, washing cytology and culture provided a diagnosis in 2 (1 lung cancer, 1 nontuberculous mycobacteriosis) in the UTB group and 3 (1 tuberculosis, 2 nontuberculous mycobacterioses) in the TB-GS group. Overall diagnostic yield in the UTB group and the TB-GS group was 75% (113 of 150 patients) and 61% (95 of 155 patients), respectively ($P = 0.008$, Pearson chi-square test).

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Other Outcomes

Other secondary outcomes are shown in Table 4. The ultrathin bronchoscope could reach more distal bronchi than the thin bronchoscope (median fifth-generation bronchi in UTB group and fourth-generation bronchi in TB-GS group, $P < 0.001$). Each method had bronchus levels reached with the bronchoscope or diagnostic yields that were independent of lobar location. In the analysis on the lesion location from the hilum and the presence of bronchus sign, each method had diagnostic yields, which were associated with the presence of bronchus sign, but not the lesion location from the hilum. Comparison of both groups revealed that the UTB method provided a higher diagnostic yield for lesions located within the outer third elliptical lung region ($P = 0.002$), and lesions with bronchus sign ($P = 0.001$) than the TB-GS method. For leading the guide sheath to the target lesion, a guiding device curette was used in 47 patients (30%) in the TB-GS group. There was no significant difference in the visibility on EBUS ($P = 0.080$), procedural time (median 27.5 minutes in UTB group and 28.5 minutes in TB-GS group, $P = 0.101$) and complication rate (3% of UTB group and 5% of TB-GS group, $P = 0.595$).

Discussion

To our knowledge, this is the first prospective study reported on the usefulness of combined techniques with an ultrathin bronchoscope, radial probe EBUS, VBN and fluoroscopy. Our study finally demonstrated that the histopathological diagnostic yield of TBB with the combination of a 3.0-mm ultrathin bronchoscope, EBUS, VBN and fluoroscopy was as high as 74%, which was significantly higher than that with the combination of a 4.0-mm thin bronchoscope, EBUS with a guide sheath, VBN and fluoroscopy.

Since the first report on the usefulness of a 3.5-mm thin bronchoscope for diagnosing peripheral pulmonary lesions in adult patients published in 1985 (22), many investigators

(4-8, 23-25) have reported the usefulness of various thin or ultrathin bronchoscopes for sampling from peripheral pulmonary lesions. Although thin bronchoscopy with even the traditional technique under fluoroscopic guidance seems to provide good results (5, 6), the potential ability seems to be demonstrated with ancillary techniques such as a radial probe EBUS (7, 8), CT fluoroscopy (24), and navigation (4, 25), which indicate the correct bronchial route to the lesion and its localization. Above all, the combination of a thinner bronchoscope and navigational technology seems quite reasonable, as the bronchial map provided by a navigation device ought to be less useful if the bronchoscope or a biopsy instrument can not follow the indicated route. In the current study, the UTB method provided a higher diagnostic yield for lesions with bronchus sign and lesions located within the outer third of the elliptical pulmonary region. Furthermore, although it was not statistically significant, an ultrasonic probe could be introduced into the lesion more frequently in the UTB group than in the TB-GS group. These findings suggested that the combination of an ultrathin bronchoscope and a navigational device can provide the best mutual abilities to introduce biopsy instruments correctly into the leading bronchus to the peripheral pulmonary lesion. In addition, the diagnostic yield of bronchoscopy with the combined EBUS and navigation guidance was reported to be higher than that of bronchoscopy with EBUS guidance alone or navigation guidance alone in the previous randomized studies (13, 14). Our study further demonstrated that incorporating ultrathin bronchoscopy into navigational endosonographic bronchoscopy improved the diagnostic yield for small peripheral pulmonary lesions.

Current commercially available ultrathin bronchoscopes $\leq$ 3.0 mm incorporate a working channel with a maximal inner diameter of 1.2 mm. It does not allow the use of an EBUS, and only a miniforceps less than 1.2 mm in diameter can be used. The novel ultrathin bronchoscope in the present study has a 1.7-mm working channel which allows the

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use of a radial probe EBUS and a 1.5-mm biopsy forceps. Nowadays, the diagnosis of lung cancer should include genotyping as well as subtype classification. Since the specimens obtained with the 1.5-mm biopsy forceps are relatively smaller than those sampled with a 1.8- or 1.9-mm standard size forceps, the question arises whether or not the specimens obtained with the 1.5-mm biopsy forceps are sufficient for molecular testing or immunohistochemistry. In the present study, we submitted sampled specimens for molecular testing in 68 patients, and epidermal growth factor receptor mutations were detected in 24 of them (exon 18 in 1 patients, exon 19 in 8 patients and L858R in 15 patients). Furthermore, special stains (e.g. for detecting mycobacterium or fungus) or immunohistochemistry were added to the routine hematoxylin and eosin stain in 86 patients (special stains in 15 patients and immunohistochemistry in 71 patients). The high frequency seems to suggest that the volume of specimens is sufficient for genotyping of lung cancer or immunohistochemistry for definitive diagnosis in our clinical practice. In fact, we demonstrated high feasibility and accuracy for molecular testing in specimens obtained with the 1.5-mm biopsy forceps in our recent study (26).

Although the overall diagnostic yield was higher in the UTB method in the present study, we do not regard it always as the preferred method. Radial probe EBUS-guided TBB has a potential methodological limitation that it is not “real-time” ultrasound guidance, because the ultrasonic probe must be removed from the bronchoscope to introduce biopsy instruments after the target lesion is localized. Hence, the biopsy instrument cannot often be re-inserted correctly along the same bronchi into which the ultrasonic probe was inserted. The novel 3.0-mm ultrathin bronchoscope, which can be advanced beyond the reach of conventional bronchoscopes, dramatically reduced the limitation; however, in some cases, repeated insertion of the biopsy instruments into the bronchi which was indicated by EBUS was difficult even using the ultrathin bronchoscope. In such cases, the thin guide sheath,

with its outer diameter of 1.95 mm, may facilitate the transfer of instruments for repeated biopsy correctly. In addition, the advantage of the 4.0-mm thin bronchoscope with a 2.0-mm working channel, which we employed in the present study, is the availability of various biopsy instruments. In the present comparison study, we used a 1.5-mm biopsy forceps in both groups. However, if the guide sheath is not used during the 4.0-mm thin bronchoscopic examination, a larger biopsy forceps and/or an aspiration needle, which reportedly increase the diagnostic yield (27), can be used. Besides thinner bronchoscopes and thinner biopsy forceps are more difficult to maneuver than the larger ones. The present study demonstrated that the UTB method is especially useful for lesions located within the outer third of the elliptical pulmonary region and lesion with bronchus sign. However, further study may be warranted to elucidate the appropriate bronchoscopic method for each individual lesion. In addition, we must further investigate the optimal way to refine the UTB method in terms of its accuracy, methodological simplicity, invasiveness, safety and cost-effectiveness.

The procedure of choice except for the present UTB method is TTNA or electromagnetic navigation bronchoscopy (ENB) which is recommended as a first diagnostic procedure for peripheral pulmonary lesions (10-12). The reported sensitivity of TTNA for peripheral lung cancer was 90% (10, 11), which seems to be better than that of bronchoscopy. However, the sensitivity of TTNA also depends on the lesion size, and there were limited data on the diagnostic sensitivity according to the lesion location (10). The risk of pneumothorax associated with TTNA was reportedly 15%, and 7% of the patients required a chest tube (10, 11), which seems to be higher than the risk associated with bronchoscopy. To our knowledge, only a small randomized study (28) comparing EBUS-guided TBB and CT-guided TTNA has been reported so far. The study found that the overall diagnostic accuracy of EBUS-guided TBB was non-inferior to CT-guided TTNA,

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and complications associated with EBUS-guided TBB were significantly fewer. ENB is another recommended procedure for diagnosing peripheral pulmonary lesions. In the now available two main types of navigational bronchoscopy, ENB rather than VBN bronchoscopy is becoming increasingly prevalent in the United States and Europe. In a meta-analysis (9), the diagnostic yields seem to be equivalent (VBN bronchoscopy 72%, ENB 67%). VBN bronchoscopy does not require expensive disposable instruments such as a location sensor and an extended working channel, so it is possible that the present UTB method is a cost-effective alternative to ENB. To determine whether or not the present UTB method is an adequate alternative to TTNA or ENB, randomized studies comparing diagnostic yields, cost-effectiveness and safety are required.

The current study has several limitations. The first is that it was carried out at expert centers on bronchoscopy. The current investigators have continuously studied to improve the accuracy of bronchoscopy for peripheral pulmonary lesions, and led the field of radial probe EBUS with a GS (2, 29), VBN (4, 16, 25) and ultrathin bronchoscopy (6-8). It is well-known that any bronchoscopic procedure involves an individual learning curve (30), so less experienced bronchoscopists may not always be able to make the most of the potential diagnostic abilities of new complex bronchoscopic procedures. To achieve satisfactory results with multimodality bronchoscopy, both didactic and hands-on training, as well as observation of the skilled examiner's procedures and the supervision of the skilled examiners may be necessary. The second limitation is the lack of the definitive diagnosis by gold standard diagnostics (e.g. pathological diagnosis with surgical procedures) in some patients categorized as having a benign diagnosis. We think simple observation with chest CT for patients with low probability of malignancy after non-diagnostic bronchoscopy is a reasonable approach in clinical practice. However, the lesions with a benign nature confirmed by stability or resolution on serial chest CT are not

always benign disease, so it is possible that some of the stable lesions categorized as benign are actually malignant lesions, although this does not affect overall diagnostic yield but the yield for malignant or benign lesions. The third limitation is heterogeneity in the benign diseases. Inconclusive histological results such as nonspecific fibrosis or inflammation were analyzed as nondiagnostic in the present study. The inflammatory lesions seem to be quite difficult to diagnose with bronchoscopy, even when we use a large biopsy forceps. Thus, the prevalence of inflammatory lesions influences the diagnostic yield. In fact, our study included a considerable number of cases with suspected inflammation that was diminished or had disappeared during the clinical follow-up period; as a result, the diagnostic yield for benign lesions, especially small ones, was low. Naturally, the prevalence of benign disease influences the overall diagnostic yield. However, even after controlling for a potential confounding effect from the final histological diagnosis, the difference of overall diagnostic yield remained significant across strata for benign and malignant disease.

In conclusion, the UTB method using a 3.0-mm ultrathin bronchoscope under EBUS, VBN, and fluoroscopic guidance provides a high diagnostic yield without sacrificing safety. The diagnostic yield was higher than that of the TB-GS method. Further studies may be needed to elucidate in more detail the most appropriate bronchoscopic approach for the individual case.

Acknowledgment

The prototype ultrathin bronchoscopes were generously loaned to the authors by Olympus Medical Systems, Tokyo, Japan.

References

1. Herth FJ, Ernst A, Becker HD. Endobronchial ultrasound-guided transbronchial lung

AJRCCM Articles in Press. Published on 03-June-2015 as 10.1164/rccm.201502-0205OC

biopsy in solitary pulmonary nodules and peripheral lesions. *Eur Respir J* 2002;20:972-974.

2. Kurimoto N, Miyazawa T, Okimasa S, Maeda A, Oiwa H, Miyazu Y, Murayama M. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. *Chest* 2004;126:959-965.
3. Gildea TR, Mazzone PJ, Karnak D, Meziane M, Mehta AC. Electromagnetic navigation diagnostic bronchoscopy: a prospective study. *Am J Respir Crit Care Med* 2006;174:982-989.
4. Asano F, Matsuno Y, Shinagawa N, Yamazaki K, Suzuki T, Ishida T, Moriya H. A virtual bronchoscopic navigation system for pulmonary peripheral lesions. *Chest* 2006;130:559-566.
5. Rooney CP, Wolf K, McLennan G. Ultrathin bronchoscopy as an adjunct to standard bronchoscopy in the diagnosis of peripheral lung lesions. A preliminary report. *Respiration* 2002;69:63-68.
6. Oki M, Saka H, Kitagawa C, Tanaka S, Shimokata T, Mori K, Kajikawa S. Novel thin bronchoscope with a 1.7-mm working channel for peripheral pulmonary lesions. *Eur Respir J* 2008;32:465-471.
7. Oki M, Saka H, Kitagawa C, Kogure Y, Mori K, Kajikawa S. Endobronchial ultrasound-guided transbronchial biopsy using novel thin bronchoscope for diagnosis of peripheral pulmonary lesions. *J Thorac Oncol* 2009;4:1274-1277.
8. Oki M, Saka H, Kitagawa C, Kogure Y, Murata N, Adachi T, Ando M. Randomized study of endobronchial ultrasound-guided transbronchial biopsy: thin bronchoscopic method versus guide sheath method. *J Thorac Oncol* 2012;7:535-541.
9. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for

the evaluation of the pulmonary nodule. *Chest* 2012;142:385-393.

10. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143(5 Suppl):e142S-65S.
11. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, Wiener RS. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143(5 Suppl):e93S-120S.
12. Vansteenkiste J, De Ruysscher D, Eberhardt WE, Lim E, Senan S, Felip E, Peters S; ESMO Guidelines Working Group. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi89-98.
13. Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. *Am J Respir Crit Care Med* 2007;176:36-41.
14. 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 2*011;66:1072-1077.
15. Asahina H, Yamazaki K, Onodera Y, Kikuchi E, Shinagawa N, Asano F, Nishimura M. Transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation. *Chest* 2005;128:1761-1765.
16. Asano F, Matsuno Y, Tsuzuku A, Anzai M, Shinagawa N, Yamazaki K, Ishida T,

AJRCCM Articles in Press. Published on 03-June-2015 as 10.1164/rccm.201502-0205OC

Moriya H. Diagnosis of peripheral pulmonary lesions using a bronchoscope insertion guidance system combined with endobronchial ultrasonography with a guide sheath. *Lung Cancer* 2008;60:366-373.

17. Omiya H, Kikuyama A, Kubo A, Okishio K, Kawaguchi T, Atagi S, Kawahara M, Takada M, Kusunoki Y. A feasibility and efficacy study on bronchoscopy with a virtual navigation system. *J Bronchology Interv Pulmonol* 2010;17:11-18.
18. Oshige M, Shirakawa T, Nakamura M, Mineshita M, Kurimoto N, Miyazawa T, Becker HD. Clinical application of virtual bronchoscopic navigation system for peripheral lung lesions. *J Bronchology Interv Pulmonol* 2011;18:196-202.
19. Tamiya M, Okamoto N, Sasada S, Shiroyama T, Morishita N, Suzuki H, Yoshida E, Hirashima T, Kawahara K, Kawase I. Diagnostic yield of combined bronchoscopy and endobronchial ultrasonography, under LungPoint guidance for small peripheral pulmonary lesions. *Respirology* 2013;18:834-839.
20. Umeda Y, Demura Y, Anzai M, Matsuoka H, Araya T, Nishitsuji M, Nishi K, Tsuchida T, Sumida Y, Morikawa M, Ameshima S, Ishizaki T, Kasahara K, Ishizuka T. ^{18}F-FDG uptake predicts diagnostic yield of transbronchial biopsy in peripheral lung cancer. *Lung Cancer* 2014;85:47-52.
21. Baaklini WA, Reinoso MA, Gorin AB, Sharafkaneh A, Manian P. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. *Chest* 2000;117:1049-1054.
22. Prakash UB. The use of the pediatric fiberoptic bronchoscope in adults. *Am Rev Respir Dis* 1985;132:715-717.
23. Tanaka M, Takizawa H, Satoh M, Okada Y, Yamasawa F, Umeda A. Assessment of an ultrathin bronchoscope that allows cytodiagnosis of small airways. *Chest* 1994;106:1443-1447.

24. Shinagawa N, Yamazaki K, Onodera Y, Miyasaka K, Kikuchi E, Dosaka-Akita H, Nishimura M. CT-guided transbronchial biopsy using an ultrathin bronchoscope with virtual bronchoscopic navigation. *Chest* 2004;125:1138-1143.

25. Asano F, Shinagawa N, Ishida T, Shindoh J, Anzai M, Tsuzuku A, Oizumi S, Morita S. Virtual bronchoscopic navigation combined with ultrathin bronchoscopy. A randomized clinical trial. *Am J Respir Crit Care Med* 2013;188:327-333.

26. Oki M, Yatabe Y, Saka H, Kitagawa C, Kogure Y, Ichihara S, Moritani S. Feasibility and accuracy of molecular testing in specimens obtained with small biopsy forceps: comparison with the results of surgical specimens. *Respiration* 2015;89:235-242.

27. Chao TY, Chien MT, Lie CH, Chung YH, Wang JL, Lin MC. Endobronchial ultrasonography-guided transbronchial needle aspiration increases the diagnostic yield of peripheral pulmonary lesions: a randomized trial. *Chest* 2009;136:229-236.

28. Steinfort DP, Vincent J, Heinze S, Antippa P, Irving LB. Comparative effectiveness of radial probe endobronchial ultrasound versus CT-guided needle biopsy for evaluation of peripheral pulmonary lesions: a randomized pragmatic trial. *Respir Med* 2011;105:1704-1711.

29. Kurimoto N, Murayama M, Yoshioka S, Nishisaka T. Analysis of the internal structure of peripheral pulmonary lesions using endobronchial ultrasonography. *Chest* 2002;122:1887-1894.

30. Lamb CR, Feller-Kopman D, Ernst A, Simoff MJ, Sterman DH, Wahidi MM, Kovitz KL. An approach to interventional pulmonary fellowship training. *Chest* 2010;137:195-199.

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Figure Legends

Figure 1. Computed tomographic image (A), ultrasonic image (B) and fluoroscopic image of transbronchial biopsy using an ultrathin bronchoscope (C) of a lung cancer (adenocarcinoma) examined and diagnosed with the ultrathin bronchoscopic method.

Figure 2. Computed tomographic image (A), ultrasonic image (B) and fluoroscopic image of transbronchial biopsy using a guide sheath (C) of a lung cancer (adenocarcinoma) examined and diagnosed by thin bronchoscopy with a guide sheath method.

Figure 3. A comparison of bronchoscopes. (A) The 4.0-mm thin bronchoscope with a 2.0-mm working channel (left), and the 3.0-mm ultrathin bronchoscope with a 1.7-mm working channel (right). (B) A 3.0-mm ultrathin bronchoscope with a 1.4-mm ultrasonic probe (left), and a 4.0-mm bronchoscope with a 1.95-mm guide sheath (arrow) and a 1.4-mm ultrasonic probe (right).

Figure 4. The flow of patients enrolled in the study. TB-GS = thin bronchoscopy with a guide sheath; UTB = ultrathin bronchoscopy.

Table 1. Characteristics of the Patients and Lesions

Characteristics	UTB Group (n = 150)		TB-GS Group (n = 155)		P Value*
Gender					
Male	87	(58)	91	(59)	0.900
Female	63	(42)	64	(41)	
Age, median, year (range)	70	(35-93)	71	(31-88)	0.947
Smoking history					
Never	42	(28)	46	(30)	
Former	56	(37)	59	(38)	0.897
Current	52	(35)	50	(32)	
Lesion size in the longest diameter on CT					
Median, mm (range)	19.0	(8.8-30.0)	19.4	(7.0-30.0)	0.726
≤ 20 mm	80	(53)	82	(53)	0.940
> 20 mm to ≤ 30 mm	70	(47)	73	(47)	
Lesion located in bronchopulmonary segment					
Right upper lobe	45	(30)	57	(37)	
Right middle lobe	17	(11)	8	(5)	
Right lower lobe	36	(24)	30	(19)	0.251
Left upper lobe	23	(15)	32	(21)	
Lingula	6	(4)	6	(4)	

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Left lower lobe	23	(15)	22	(14)	
Lesion location from the hilum					
Central	1	(1)	0	(0)	
Intermediate	36	(24)	44	(28)	0.420
Peripheral	113	(75)	111	(72)	
Bronchus sign					
Present	115	(77)	127	(82)	0.256
Absent	35	(23)	28	(18)	
Appearance on CT					
Solid	116	(77)	125	(81)	0.478
Others[†]	34	(23)	30	(19)	
Preprocedural PET/CT					
Examined	30	(20)	19	(12)	0.066
Not examined	120	(80)	136	(88)	
Final diagnosis					
Malignant	123	(82)	109	(70)	
Benign	26	(17)	44	(28)	0.057
Unknown	1	(1)	2	(1)	
Examiner					
Staff pulmonologist	143	(95)	146	(94)	0.655
Resident	7	(5)	9	(6)	

Definition of abbreviations: CT = computed tomography; PET = Positron emission tomography; TB-GS = thin bronchoscopy with a guide sheath; UTB = ultrathin bronchoscopy.

Data are presented as N (%) unless otherwise noted.

*Pearson chi-square test or Mann-Whitney *U* test.

†Part solid nodule and cavity.

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Table 2. Histological Findings of Transbronchial Biopsy and Final Diagnosis

	Number of Patients and Final Outcomes			
Histological Findings of Transbronchial Biopsy	**UTB Group (n =150)**		**TB-GS Group (n =155)**	
Diagnostic				
Benign				
Epithelioid cell granuloma with/without necrosis	8	2 TB	11	5 TB
		3 NTM		3 NTM
		3 Unspecified		3 Unspecified
Organizing pneumonia	3		3	
Fungal infection			1	1 Aspergillosis
Sclerosing hemangioma			1	
Malignant				
Adenocarcinoma	63		42	
Squamous cell carcinoma	22		16	
Squamous cell carcinoma + Adenocarcinoma			1	
Large cell carcinoma	1			
Non-small cell carcinoma	2		5	
Small cell carcinoma	4		3	
Small cell carcinoma + Adenocarcinoma			1	
Metastatic carcinoma	8	2 Colon	6	3 Colon

		1 Rectum		1 Rectum	
		1 Pharynx		1 Kidney	
		1 Pancreas		1 Breast	
		1 Breast			
		1 Orbit			
		1 Uterus			
MALT lymphoma			1		
Undifferentiated carcinoma (unknown origin)			1		
Nondiagnostic					
Suspected lung cancer	2	2 Lung cancer	5	5 Lung cancer	
Nonrepresentative samples	37	15 Benign	58	28 Benign	
		1 NTM		5 TB	
		1 Unspecified granuloma		1 NTM	
		7 Improved		1 Hamartoma	
		6 Unchanged with 15−38-mo follow-up		1 Organizing pneumonia	
		21 Malignant		16 Improved	
		17 Pathologically proven lung cancer		4 Unchanged with 16−46-mo follow-up	
		1 Metastatic carcinoma		28 Malignant	
		3 Suspected malignancy		21 Pathologically proven lung cancer	
		1 No follow-up		2 Metastatic carcinoma	
				5 Suspected malignancy	

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		2 No follow-up

Definition of abbreviations: CT = computed tomography; MALT = mucosa-associated lymphoid tissue; NTM = nontuberculous mycobacteriosis; TB = tuberculosis; TB-GS = thin bronchoscopy with a guide sheath; UTB = ultrathin bronchoscopy.

Table 3. Histopathological Diagnostic Yield

	UTB Group (n = 150)				TB-GS Group (n = 155)				
Variables	**N/Total (%)**		**95% CI**		**N/Total (%)**		**95% CI**		**P Value**
Benign									
≤ 20 mm	5/17	(29)	10-56	*P* = 0.067	5/24	(21)	7-42	*P* = 0.019	0.529
> 20 mm to ≤ 30 mm	6/9	(67)	30-93		11/20	(55)	32-77		0.555
Total	11/26	(42)	23-63		16/44	(36)	22-52		0.622
Malignant									
≤ 20 mm	47/62	(76)	63-86	*P* = 0.115	35/57	(61)	48-74	*P* = 0.048	0.090
> 20 mm to ≤ 30 mm	53/61	(87)	76-94		41/52	(79)	65-89		0.255
Total	100/123	(81)	73-88		76/109	(70)	60-78		0.040
Unknown*									
≤ 20 mm	0/1	(0)			0/1	(0)			
> 20 mm to ≤ 30 mm	0				0/1	(0)			
All									
≤ 20 mm	52/80	(65)	54-75	*P* = 0.007	40/82	(49)	38-60	*P* = 0.005	0.037
> 20 mm to ≤ 30 mm	59/70	(84)	74-92		52/73	(71)	59-81		0.061
Total	111/150	(74)	66-81		92/155	(59)	51-67		0.044†

Definition of abbreviations: CI = confidence interval; TB-GS = thin bronchoscopy with a guide sheath; UTB = ultrathin bronchoscopy.

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*Patients who did not return to follow-up.

†Mantel-Haenszel test. Other variables were calculated with Pearson chi-square test.

Table 4. Secondary Outcomes

Variables	UTB Group (n = 150)		TB-GS Group (n = 155)		P Value[†]
Bronchus level reached with the bronchoscope, median, generation (range), all	5 (3-12)		4 (2-7)		<0.001
Right upper lobe	5 (4-9)		4 (2-7)		<0.001
Right middle lobe	6 (4-12)		4 (3-7)		0.031
Right lower lobe	5 (3-9)	$P = 0.084$	4 (3-6)	$P = 0.385$	<0.001
Left upper lobe	5 (4-7)		4 (3-7)		0.002
Lingula	5 (3-7)		4 (3-5)		0.186
Left lower lobe	4 (3-8)		4 (3-7)		0.173
Histopathological diagnostic yield by lobar location					
Right upper lobe	32/45 (71)		36/57 (63)		0.398
Right middle lobe	13/17 (64)		4/8 (50)		0.186
Right lower lobe	23/36 (76)	$P = 0.389$	18/30 (60)	$P = 0.380$	0.745
Left upper lobe	20/23 (87)		20/32 (63)		0.045[‡]
Lingula	4/6 (67)		5/6 (83)		0.505
Left lower lobe	19/23 (83)		9/22 (41)		0.004[§]
Histopathological diagnostic yield by lesion location from the hilum					
Central or intermediate	24/37 (65)	$P = 0.144$	28/44 (64)	$P = 0.494$	0.909

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Peripheral	87/113	(77)		64/111	(58)		0.002[ll]
Histopathological diagnostic yield by bronchus sign							
Present	94/115	(82)	$P < 0.001$	80/127	(63)	$P = 0.050$	0.001[**]
Absent	17/35	(49)		12/28	(43)		0.651
Location of probe in relation to lesion confirmed by EBUS							
Within the lesion	117	(78)		103	(66)		
Adjacent to the lesion	26	(17)		41	(26)		0.080
Invisible with EBUS	7	(5)		11	(7)		
Procedural time, median, min (range)	27.5	(12-77)		28.5	(15-81)		0.101
Complications, all	5	(3)		7	(5)		0.595
Pneumothorax	3	(2)		5[*]	(3)		
Pneumonia	1	(1)		0	(0)		
Bleeding	0	(0)		2	(1)		
Chest pain	1	(1)		0	(0)		

Definition of abbreviations: EBUS = endobronchial ultrasound; TB-GS = thin bronchoscopy with a guide sheath; UTB = ultrathin bronchoscopy.

Data shown are N (%) unless otherwise stated.

[*]Three patients required chest tube placement.

[†]Pearson chi-square test, Mann-Whitney *U* test or Kruskal Wallis test.

[‡]$P = 0.329$, [§]$P = 0.167$, [ll]$P = 0.017$ and [**]$P = 0.009$, Mantel-Haenszel test for histological diagnosis (benign and unknown lesion vs malignant lesion).

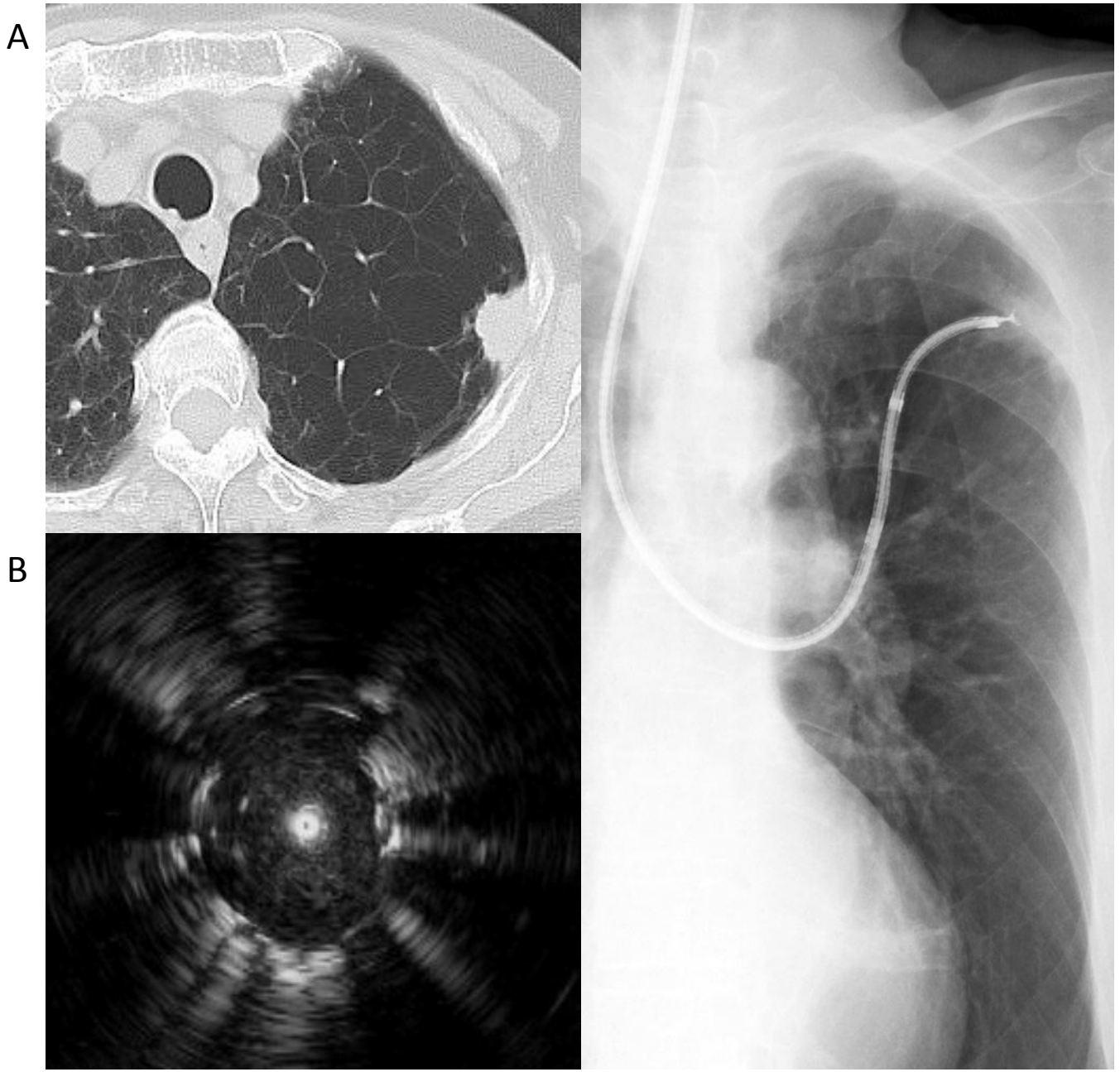

Figure 1.

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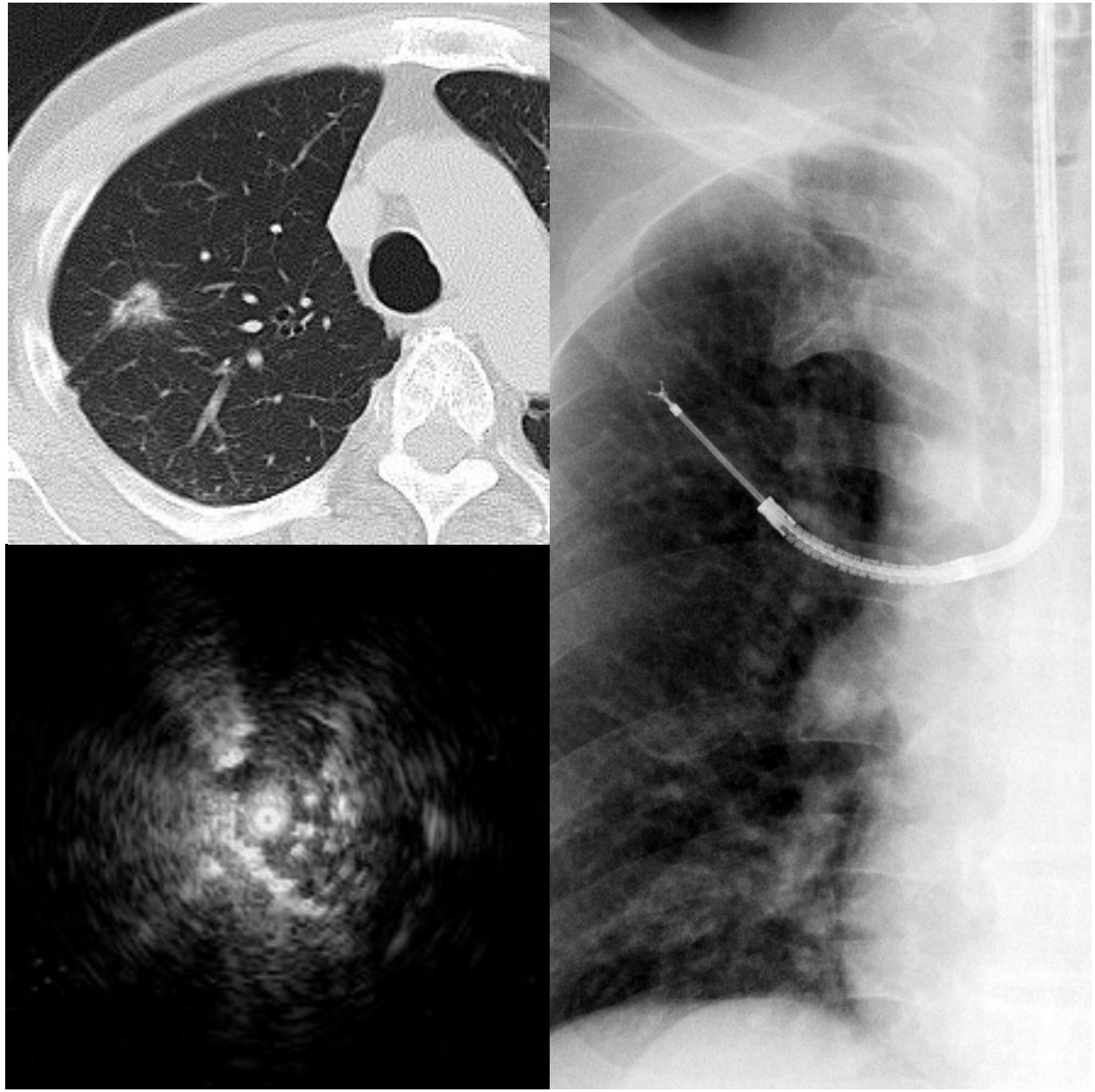

Figure 2.

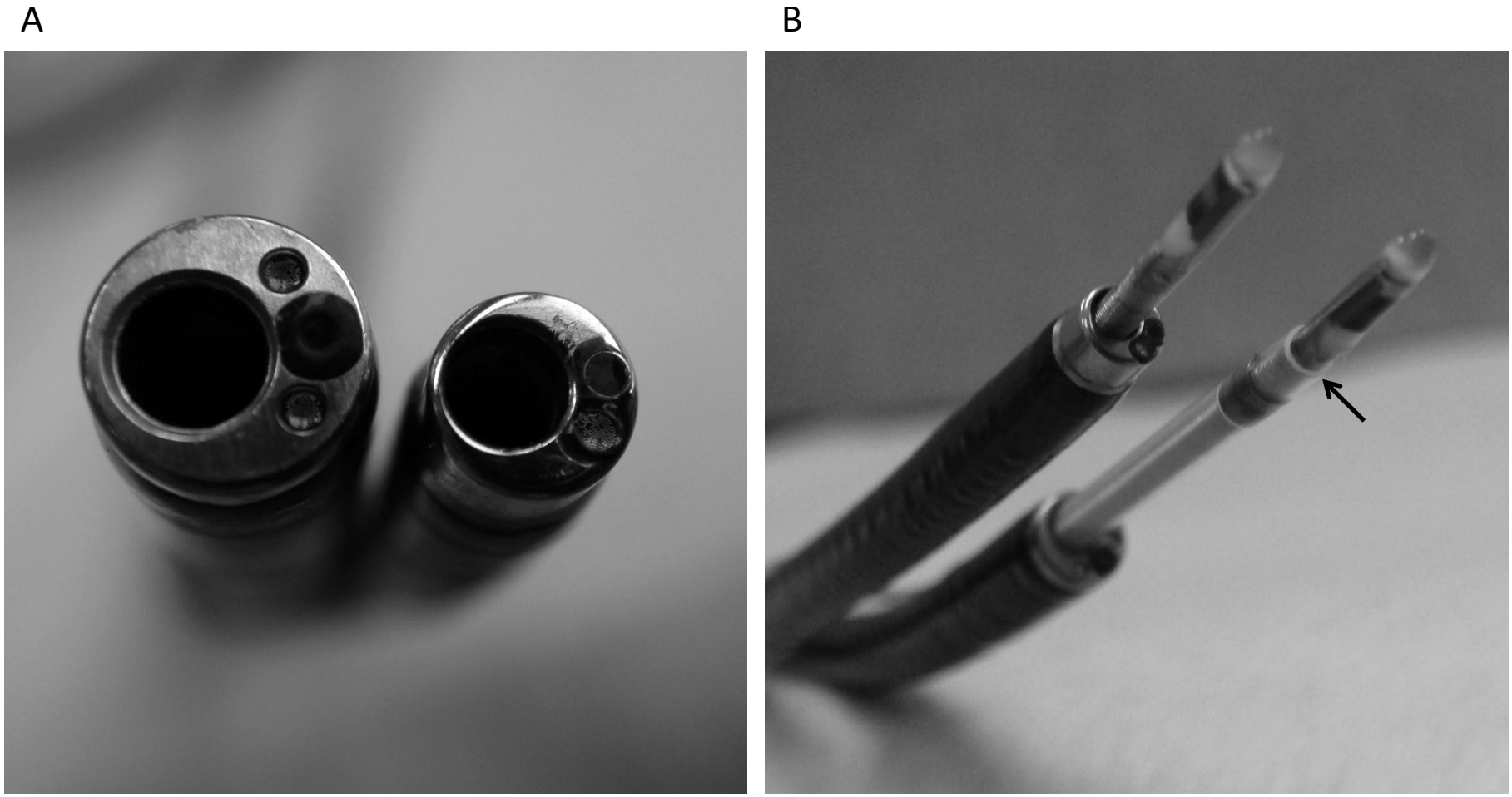

Figure 3.

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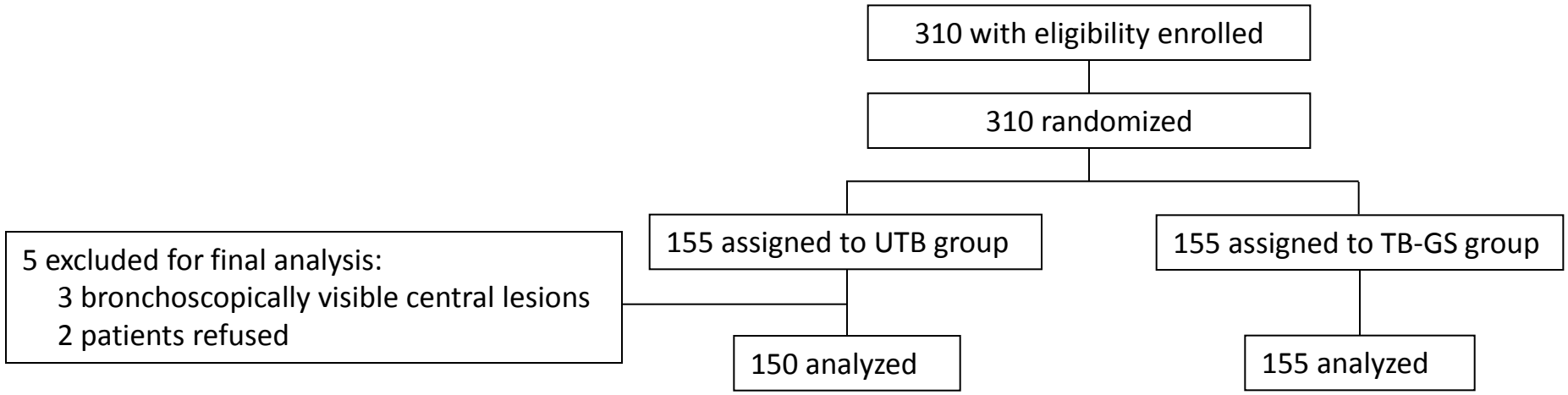

Figure 4.