Peer Review File
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Reviewer A

Comment 1. Abstract, Line 29-30: the background is thin within the abstract and does not mention the use of intraprocedural confirmational imaging techniques which is essential to this manuscript. Please use 2 sentences to describe what is currently known benefit of radial EBUS or CBCT in improving diagnostic yields.

Reply 1. We added the requisite sentences in the abstract.

Changes in text: We included "Radial endobronchial ultrasound provides real-time imaging and confirmation of the location of the lesions. Cone-beam computed tomography can confirm that the forceps tip has reached the lesion before biopsy." (Lines 42-44)

Comment 2. Results, Lines 142-153 and Table 2: I would recommend reporting sensitivity and specificity for malignancy, rather than diagnostic yield. This is already reported as such in the Discussion, line 181.

Reply 2. We apologize, but we did not understand the intent of your recommendation. Sensitivity for malignancy was considered synonymous with diagnostic yield for malignancy. The specificity for malignancy was considered to be 100%.

Comment 3. Methods, Lines 103-105: The authors mention that navigation was performed with virtual bronchoscopy and fluoroscopy. As this technique is heavily reliant on the experience of the bronchoscopist and can be challenging, it would be helpful to describe how many bronchial divisions were visibly identified during navigation as compared to the virtual map (or any other specifics that the authors feel is relevant to the success of navigation using this approach), and how many lesions were fluoroscopically visible.

Reply 3. This is a valid opinion. However, in this study, we did not analyze how many bronchial divisions were visibly identified during navigation as compared to the virtual map. There were many cases in which the EBUS probe was inserted under fluoroscopy because the lumens of the peripheral bronchi could not be fully visualized. Also, successful navigation was not defined and could not be reported. Primary EBUS type 2 and Primary CBCT type 1 cases were biopsied without re-navigation, but it was unclear whether this was considered successful navigation.

Eleven lesions (55%) were fluoroscopically visible. The diagnostic yield for those lesions was 90.9% (10/11). On the other hand, the diagnostic rate for 9 cases of fluoroscopically invisible lesions was 77.8% (2/9). There was no statistically significant difference in this diagnostic yield (p=0.421).

Changes in the text: We added "Eleven lesions (55%) were fluoroscopically visible" to the Results section (Lines 168-169). We also added this information to Tables 1 and 2.

Comment 4. Discussion, Lines 246-252: this particular section is difficult to follow, especially the sentences "CBCT was useful in three cases with type 2 primary CBCT images out of 12 cases with type 1 primary EBUS images; however primary CBCT could be omitted in nine cases with type 1 primary CBCT images." I recommend rewording this if possible.

Reply 4. As you pointed out, the expression was difficult to understand, so we rephrased it as follows:

Changes in the text: Lines 267-270 "Of the 12 cases with type 1 primary EBUS images, 3 cases with type 2 primary CBCT images required re-navigation based on primary CBCT images. In 9 cases with type 1 primary EBUS images and type 1 primary CBCT images, it was possible that primary CBCT imaging could have been omitted."

Comment 5. Discussion, Line 256: I would add an additional sentence on the value of a larger study aimed at identifying patients in whom CBCT confirmation after navigation with UTB could be omitted, or as compared to no rEBUS use.

Reply 5. In CBCT-guided TBB using a UTB, the combined use of R-EBUS can be expected to reduce the number of CBCT imaging. If it is possible to identify in advance cases in which image discrepancies are not expected, CBCT can be omitted, which is expected to further reduce radiation exposure and shorten examination time.

Changes in the text: As mentioned above, by using an R-EBUS combination with CBCT-guided TBB using a UTB, there is a possibility that the number of CBCT imaging can be reduced. For further radiation exposure reduction, it would be necessary to analyze cases in which primary EBUS and CBCT images do not match. Thereby, in the future, patients' exposure to radiation can be further reduced by identifying those in whom primary CBCT imaging is not essential. Also, in patients for whom CBCT can be omitted, it is expected that the current average examination time of 44 minutes will be further shortened.

Comment 6. Discussion, Lines 187-188: I would add some additional detail regarding the

fact that the forceps may take a different trajectory than the radial EBUS probe when the thin flexible scope is significantly flexed/retroflexed which could explain some of the discrepant EBUS vs. CBCT types.

Reply 6. Thank you for your thought-provoking comment. We have added a point regarding your comment to the text.

Changes in the text: Lines 205-207 “This may be due to the fact that the forceps may take a different trajectory compared to that of the radial EBUS probe when the thin flexible scope is significantly flexed/retroflexed.”

Comment 7. Discussion: can the authors comment on why TBNA samples were not obtained? This biopsy modality is in common usage for peripheral lesions at many centers.

Reply 7. In the past, we performed CT-guided TBB using a UTB with a small channel diameter and then CBCT-guided TBB using a UTB with a small channel diameter. Both methods had a channel diameter of 1.2 mm, making TBNA infeasible. After that, we used a bronchoscope with a channel diameter of 1.7 mm in this study, but we have not used it in this pilot study because we have little experience with TBNA. Since the effectiveness of this study was confirmed, we plan to introduce TBNA in the future.

Comment 8. Line 144: “patients”

Reply 8. Thank you. We fixed the spell error.

Comment 9. Line 144-146: to be clear, was the diagnostic yield based on the initial biopsy results or based on initial biopsy results as well as imaging follow up at 6 months?

Reply 9. These are the diagnostic criteria that have been used in previous papers. Cases diagnosed with organizing pneumonia by TBB were sometimes judged to be correctly diagnosed after 6 months of follow-up. There were 4 benign lesions in the patients in this study. Two cases were culture-proven to be of *Mycobacterium tuberculosis* and nontuberculous mycobacterial disease. The remaining two cases had no specific histological findings by TBB and were classified as “undiagnosed”, with subsequent surgical biopsies revealing nonspecific inflammation. Therefore, there were no cases diagnosed as benign lesions at 6-month follow-up during this study. This sentence has been deleted.

Comment 10. Line 237: Short interval imaging followup should also be cited as a limitation for diagnostic yield calculations, though it would not have a significant effect on the results as described.

Reply 10. You are right. In this study, which included a small number of cases, there were no cases in which the diagnostic results differed even if the image follow-up period was extended.

Reviewer B

Comment 11. How did patients tolerate these bronchoscopy procedures with only moderate sedation, especially if they are on average 44 minutes? Standard practice for peripheral bronchoscopy in many areas includes general anesthesia with neuromuscular blockade, which contrasts heavily with the practice in this study. Discussion of the anesthetic approach may add to the novelty of the study.

Reply 11. All procedures were completed with sedation with midazolam as described in the British Thoracic Society guideline (1). No opioids were used. At our institution, we do not use neuromuscular blockade that requires the involvement of an anesthesiologist in performing TBB. Sedation with midazolam is considered standard in Japan, as has been the case with RCTs in Japan (2,3).

1. Du Rand IA, Blaikley J, Booton R, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax 2013;68 Suppl 1:i1-44.
2. Oki M, Saka H, Asano F, et al. Use of an ultrathin vs thin bronchoscope for peripheral pulmonary lesions: a randomized trial. Chest 2019;156:954-64.
3. Oki M, Saka H, Ando M, et al. Ultrathin bronchoscopy with multimodal devices for peripheral pulmonary lesions. a randomized trial. Am J Respir Crit Care Med 2015;192:468-76.

Comment 12. Is it possible to further describe your algorithm for re-navigation? This is an interesting and largely unexplored area in peripheral bronchoscopy.

Reply 12. Re-navigation techniques are certainly important, but they are very difficult to explain. Based on the CBCT image, we confirmed whether the tip of the bronchoscope was inserted into the target bronchi and the direction of the target bronchi (ventral or dorsal, lateral, or medial). (See below schema)

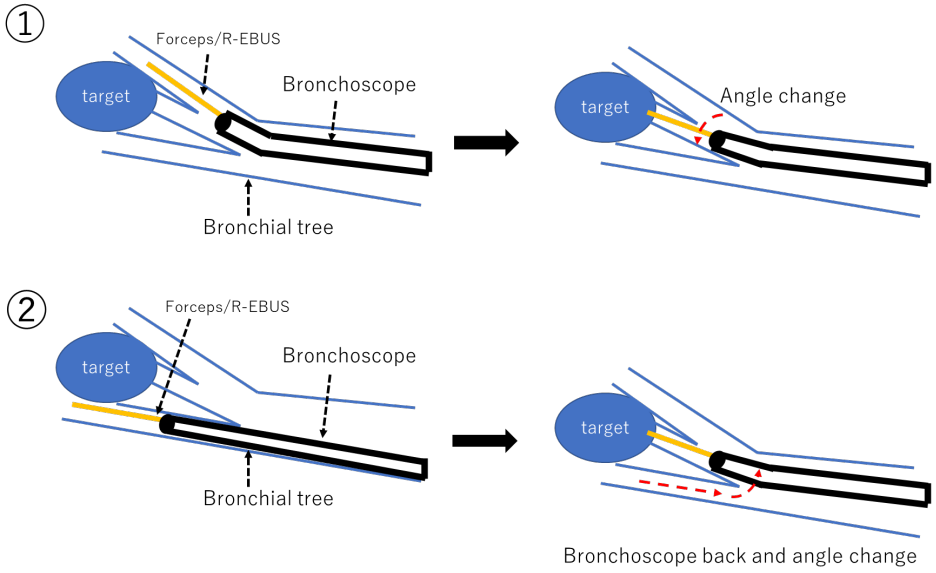
①When the bronchoscope is inserted into the target bronchus but is mistaken for a more distal bifurcation.

→Insert the R-EBUS while correcting the angle of the tip of the bronchoscope with 2D fluoroscopy.

②If the bronchoscope is not inserted into the target bronchus.

→Back the bronchoscope and insert the R-EBUS while correcting the angle of the tip with 2D fluoroscopy.

Changes in the text: Page 5, Line 139-145 "In the re-navigation procedure, first, based on the multi-planar reconstruction image obtained from the CBCT image, it was determined whether the target bronchus was ventral or dorsal and lateral or medial to the current forceps tip position. It was also determined if the position of the bronchoscope tip needed to be adjusted. Next, while viewing the 2D fluoroscopic image of the front or side, the position and direction of the tip of the bronchoscope were adjusted, and the R-EBUS probe was advanced in the direction of the target bronchus."



Reviewer C

Comment 13. It would be good to clearly define each type of EBUS image more explicitly, and perhaps include a a figure with examples of each definition. This would be particularly useful to clinicians not familiar with bronchoscopy.

Similarly images to accompany definitions of CT images would be helpful to elucidate the methodology to those un-initiated in bronchoscopy and EBUS.

Reply 13. The definition images of the EBUS image type and CBCT image type were added independently as Figure 2.