Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-21-1067

Reviewer A

This research is very interesting because almost all nodules/masses found in IPF are cancers. The yield also good from bronchoscopy.

Comment 1: It will be very informative if there are separate yields from difference sample techniques done.

Reply 1: Thank you for your precious suggestion. We have clarified the diagnostic yeild for each sampling device and combined technique in an additional table (Table 1 . With this addition, the table numbers have been reassigned. Moreover, we have revised the following sentences.

Pages 15–16, lines 13–2 "The overall diagnostic yield was 82.6% (76/92 cases), and the details are summarized in Table 1. No other samplings, in addition to forceps biopsy which was conducted in all cases, were found to have a favorable effect on the diagnostic yield, whereas combined use of rapid on-site cytologic evaluation had a positive effect (diagnostic yield 86.7% vs. 64.7%, P=0.031). Meanwhile, the histopathological diagnoses are shown in Table 2. Two cases in which a definitive diagnosis could not be made (unknown) continue to remain under close follow-up."

We have also modified the following sentence.

Page 14, lines 10–12 : "After identifying the target, subsequent brushing, forceps biopsy, needle aspiration, and/or cryobiopsy were performed under X-ray fluoroscopic guidance (VersiFlex VISTA; Hitachi, Ltd., Tokyo, Japan)."

Comment 2: Also the association between lesion involved by UIP and position of US probe(within etc) to find out why nodules in UIP were difficult to diagnose.

Reply 2: Thank you for your precious suggestion. We reanalyzed the R-EBUS findings in terms of involved and not involved with UIP/probable UIP pattern, and have revised the renumbered Table 4. In contrast to the not involved cases, there was a significant difference between the location of the lesion as indicated by R-EBUS and the diagnostic yield in the involved cases. Therefore, we have added the following sentences.

Pages 18-19, lines 11–2: “In fact, when we examined the diagnostic yield of each R-EBUS finding, which was strongly related to the presence/absence of the bronchus sign, separately according to the location of the lesion relative to areas of the lung showing the UIP/probable UIP pattern, we found significant differences in the diagnostic yield depending on the R-EBUS findings in the involved cases, but not in the not involved cases (Table 4). This may be due to the fact that it was relatively difficult to identify the orientation of the bronchus towards the lesion by R-EBUS in the involved cases, as the boundary of the lesion with the background lung was obscured in these cases.”

With this addition, we have also modified the following sentence.

Page 20, lines 4–6: “Although the R-EBUS findings may vary somewhat, the sufficient detection of target PPLs (i.e., within the lesion) could improve the diagnostic yield, even in patients with IPF.”

Reviewer B

This manuscript describes the usefulness of bronchoscopy using R-EBUS for the diagnosis of PPLs in patients with IPF and the factors related to the diagnosis. The methodology is straightforward, well-written overall and contains sufficient interest and originality. However, I think several revisions are needed.

Major comments

Comment 1: In line 240

Please clarify whether the lesions involved with UIP/probable UIP pattern were actually negative for bronchial sign in many cases.

Reply 1: Thank you for your suggestion. Since the bronchus sign is a subjective assessment on CT, we validated it by replacing it with the R-EBUS finding, which strongly relates to it and is a more objective indicator. We reanalyzed the R-EBUS findings in terms of involved and not involved with UIP/probable UIP pattern, and have revised the renumbered Table 4. In contrast to the not involved cases, there was a significant difference between the location of the lesion as indicated by R-EBUS and the diagnostic yield in the involved cases. This may be due to the fact that it was relatively difficult to identify the orientation of the bronchus towards the lesion in the involved cases. To crarify this, we have added the following sentences.

Pages 18-19, lines 11–2: “In fact, when we examined the diagnostic yield of each R-EBUS finding, which was strongly related to the presence/absence of the bronchus sign, separately according to the

location of the lesion relative to areas of the lung showing the UIP/probable UIP pattern, we found significant differences in the diagnostic yield depending on the R-EBUS findings in the involved cases, but not in the not involved cases (Table 4). This may be due to the fact that it was relatively difficult to identify the orientation of the bronchus towards the lesion by R-EBUS in the involved cases, as the boundary of the lesion with the background lung was obscured in these cases."

Comment 2: In the lesions involved with severe emphysema in addition to fibrosis, was it difficult to detect the bronchus sign?
Reply 2: Thank you for your comment. We had classified the presence of emphysema into the following four categories: no, mild, moderate, and severe. When we sort the number of positive and negative bronchus sign cases according to the categories, they become 26 and 6 for no emphysema, 36 and 11 for mild, 10 and 1 for moderate, and 2 and 0 for severe, respectively. Since there is no significant difference in the positive rate for each category, the effect of emphysema on the bronchus sign is considered to be small. This study focuses on fibrosis, and in order to avoid confusion for the readers, we would like to limit our discussion to idiopathic pulmonary fibrosis in this paper.

Comment 3: Nevertheless, I think the diagnostic yield of this study is relatively high. Did you try to improve the reach of the lesion, for example, using a virtual bronchoscopy?
Reply 3: Thank you for your comment. We have clarified the diagnostic yeild for each sampling device and combined technique in an additional table (Table 1). With this addition, the table numbers have been reassigned. As you pointed out, the diagnostic yield was higher in cases with virtual bronchoscopy, although the number of cases without it was small and the difference was not significant. On the other hand, rapid on-site cytologic evaluation had a positive effect on the diagnostic yield. We also used a combination of various devices as shown in the table, which may have led to our relatively high diagnostic yield.
We have revised the following sentences.
Pages 15–16, lines 13–2 "The overall diagnostic yield was 82.6% (76/92 cases), and the details are summarized in Table 1. No other samplings, in addition to forceps biopsy which was conducted in all cases, were found to have a favorable effect on the diagnostic yield, whereas combined use of rapid on-site cytologic evaluation had a positive effect (diagnostic yield 86.7% vs. 64.7%, P=0.031). Meanwhile, the histopathological diagnoses are shown in Table 2. Two cases in which a definitive diagnosis could not be made (unknown) continue to remain under close follow-up."
We have also modified the following sentence.

Page 14, lines 10–12 : “After identifying the target, subsequent brushing, forceps biopsy, needle aspiration, and/or cryobiopsy were performed under X-ray fluoroscopic guidance (VersiFlex VISTA; Hitachi, Ltd., Tokyo, Japan).”

Comment 4: In line 243 and 266
Similarly, if there is a method to accurately approach the lesion invisible on X-ray fluoroscopy without causing a pneumothorax, please add it to Discussion.
Reply 4: Thank you for your comment. We have added the following sentences as advised.
Page 20, lines 9–13: “The possibility of sampling at the location of the lesion identified by R-EBUS is thought to account for the safety of the procedure. On the other hand, the diagnostic yield was low in cases where the lesions could not be identified clearly by R-EBUS or chest X-ray, which could possibly be related to the fact that sampling was not enforced in these cases.”

Comment 5: In Conclusions, it would be better to add and emphasize that bronchoscopy “using R-EBUS”...
Reply 5: Thank you for your advice. We have emphasized that our conclusions were based on using R-EBUS. Relatedly, we have also revised the description in the abstract.
Page 5, lines 10–11: “Bronchoscopy using R-EBUS was safe and showed an acceptable diagnostic yield for PPLs, even in patients with IPF.”
Page 21, lines 13–14: “Bronchoscopy using R-EBUS is safe and provides an acceptable diagnostic yield for PPLs, even in patients with IPF.”

Minor comments

Comment 6: In line 170
“local an aesthesia” is misspelled.
Reply 6: Thank you for pointing this out. We have corrected the spelling to “local anesthesia” (Page 14, line 4).

Comment 7: In line 384
The 9 in “right S9” should be in superscript.
Reply 7: Thank you for pointing this out. We have corrected “right S9” to “right S^{9}” (Page 30, line 1).

Comment 8: Table 3.
I suggest that “Lesion not visualizable” be replaced with “Invisible” in line 174.
Reply 8: Thank you for pointing this out. We have changed “Lesion not visualizable” to “Invisible” (Table 4).

Comment 9: In my opinion the description of the definition of idiopathic pulmonary fibrosis should be shortened a bit.
Reply 9: Thank you for your comment. The definition of idiopathic pulmonary fibrosis (IPF) was changed in 2018, and multidisciplinary discussion combining pathology and CT findings is increasing. Since IPF was defined only by CT findings in this study, we intentionally described the definition in detail to avoid its ambiguity, and we hope you understand the necessity of this.

Comment 10: Please be consistent in either British or American spelling. In particular, whether to unify tumor (4 locations) or tumour (Table 1).
Reply 10: Thank you for pointing this out. We have standardized all text into American English (Table 2).