Peer Review File

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Reviewer A

The authors retrospectively analyzed the factors associated with the success of EBUS-TBNA in patients with lung cancer. The data the authors mentioned in this manuscript has been reported and known by several articles and guidelines. Unfortunately, there was nothing novel in this article.

Reply: Thank you for taking the time to review our paper and for sharing your insights. Your feedback is valuable to us, and we appreciate your thoughtful consideration.

We acknowledge your observation that the factors associated with the success of EBUS-TBNA in our study align with those reported in several articles and guidelines. We understand your perspective that the content may not introduce novel elements, and we would like to express our gratitude for highlighting this point. However, while our findings may resonate with existing literature, our study is distinct in that it delves into the diagnostic yield by integrating CT and PET/CT interpretation results with EBUS-TBNA data. We believe this approach adds a unique dimension to the existing body of knowledge.

We genuinely value your feedback and assure you that we have addressed the specific concerns you raised in the revised manuscript. Your input is instrumental in helping us refine and strengthen our work. We eagerly anticipate your continued guidance to enhance the overall quality of our research. Thank you once again for your constructive input.

1. The inclusion criteria of this study are unclear.

1) Why did the authors exclude the failed EBUS-TBNA cases? Should the failed case be examined in this study?

Reply: Thank you for your thoughtful consideration and valuable feedback. I completely agree with your observation. There may have been a misunderstanding in the terminology we used. The term "failed EBUS-TBNA" does not mean cases of unsuccessful attempts to obtain results during EBUS-TBNA; those cases were, in fact, included in our analysis. We intended to convey situations in which EBUS-TBNA was prepared; however, the procedure could not be attempted at all due to factors such as severe patient respiratory distress.

The revised exclusion criteria now accurately reflect this clarification: Cases in which EBUS-TBNA was attempted but was not performed. (Page 7, Line 90)

We appreciate your keen attention to detail and are confident that this adjustment enhances the accuracy of the expressions in our manuscript. We look forward to any further insights you may have upon reviewing the revised manuscript.

2) How did the authors measure the “tissue diameter”?

Reply: Thank you for your insightful question. I appreciate the opportunity to clarify how we measured "tissue diameter." In our institution, clinical pathologists routinely measure the diameter, width, and height of the tissue whenever pathology slides are prepared, relying on the maximum values obtained. However, cases with severe tissue fragmentation that hinders accurate interpretation were excluded from the analysis.
To provide a clearer understanding, we have added the following sentence: The maximum diameter, representing the largest dimension of the acquired core tissue, was measured by a clinical pathologist when creating the slides. Tissue volume was estimated by multiplying the length, height, and width of the tissue. (Page 8, Lines 124-126)
Your feedback is highly valuable in refining the precision and comprehensibility of our research. We trust that this clarification enhances the transparency of our methodology. Please feel free to share any further suggestions or concerns.

3) What did "no interpretation of the imaging" mean?
Reply: Thank you for the insightful question and the opportunity to provide clarification. In our institution, the results of CT or PET/CT scans are interpreted by specialized experts. However, instances where we could not obtain the interpretation results had to be excluded from the subgroup analysis in this study.
To provide a clearer explanation, we made the following revision: no interpretation result from the imaging. (Page 7, Line 91)
We hope this adjustment helps to understand our methodology better. Please feel free to share any further suggestions or questions. Your input is invaluable in refining the precision and transparency of our research.

2. What was the purpose of EBUS-TBNA in this study for diagnosing nodal staging? Because only 1.5 lymph nodes per patient were examined in this study. If the meaning of EBUS-TBNA was for diagnosis, did the authors only sample the targeted lymph node?
Reply: Thank you for your insightful observation. We acknowledge and appreciate the clarity you seek regarding the purpose of EBUS-TBNA in our study. The objectives of EBUS-TBNA in our research can be categorized into two: first, diagnosis of lung cancer, and second, post-diagnosis staging of lymph nodes through alternative methods. When EBUS-TBNA is employed for initial diagnosis, it often focuses on sampling highly suspicious target lymph nodes, resulting in a lower count of nodes examined. Conversely, when used for staging, a higher number of lymph nodes would be expected to be sampled.
Due to the retrospective nature of our study, clearly distinguishing between these two objectives was challenging. The decision on the number of nodes sampled was influenced by the discretion and preferences of the performing physician. We appreciate your attention to this nuance in our methodology, and your insights contribute significantly to refining our research clarity. If you have further suggestions or inquiries, we welcome them to enhance the comprehensibility of our work.

3. The diagnostic yield of this study was 68.1%, which was lower than the previous report, even if only lung cancer patients were enrolled. It has been recommended that the four passes without tissue core or three passes with tissue core during EBUS-TBNA. Did the authors follow this recommendation?

Reply: Thank you for your insightful comments, and I believe these remarks have steered our research toward a more promising direction. We agree with the reviewer's observation that our diagnostic rate is lower than in previous reports. While the precise reasons for this discrepancy may not be fully understood, we have contemplated a few potential explanations.

Firstly, previous studies have indicated that rapid on-site evaluation (ROSE) can enhance the EBUS-TBNA diagnostic rate and reduce the number of sampling attempts. Unfortunately, ROSE was not feasible in our institution, and we believe this may have contributed to the lower diagnostic rate in our study compared to previous reports.

Secondly, our study included cases in which cancer was not suspected on either CT or PET/CT, or only one of these imaging modalities indicated a potential malignancy. In fact, the diagnostic rate in subgroups where malignancy was strongly suspected by either CT or PET/CT was 86.3%, which is quite reasonable. These two factors might have contributed to the lower diagnostic yield.

As mentioned earlier and consistent with the information provided in the manuscript (Page 8, Lines 112-114), our institution could not perform ROSE. Core tissue acquisition was primarily guided by the visual judgment of trained nurses, which had limitations. Regarding adherence to recommended practices, it is challenging to confirm this in a retrospective study, and the number of sampling attempts was determined at the discretion of the attending physician. However, we believe every effort was made to extract as much tissue as possible within the limited timeframe. Additionally, it is worth noting that in Korea, procedures like EBUS-TBNA are typically performed under moderate sedation with medications such as midazolam. In cases where patients did not cooperate well due to the effects of sedation, rapid sample acquisition within a single attempt was sometimes necessary. This aspect might have also influenced the lower diagnostic rate in our study.

4. There was no information about “cancer findings” of imaging.

Reply: Thank you for your valuable input. We acknowledge the importance of transparency in the interpretation of imaging data. In our study, the chest CT and PET/CT scans were independently reviewed by radiology and nuclear medicine specialists. These experts were unaware of the study's content, ensuring an unbiased assessment. To clarify the evaluation criteria for cancer findings in nodes, we have revised the wording as follows: The chest CT and PET/CT data were independently interpreted by radiology and nuclear medicine specialists. General principles of interpretation were applied for assessing cancer findings in nodes. Factors such as the increasing size of nodes, irregular shape, central necrosis, and compression of adjacent structures were considered for CT. The interpretation considered the results of the maximum standardized uptake value for PET/CT. (Page 7, Lines 92-96)

We hope this revision enhances the understanding of our methodology.

Reviewer B

I sincerely thank you for taking the time to review our paper despite your busy schedule. Your insightful comments have proven immensely valuable, guiding us to improve our work substantially. We truly appreciate your efforts and consider your feedback instrumental in steering our paper in a more refined and impactful direction. Thank you once again for your thoughtful review.

1. I have a few questions about the interpretation of sentence and the result of this study. The authors mentioned "The None group had no cancer findings on either CT or PET/CT imaging", and the meaning is focused on only lung area, I think the authors should mention about the difference of the diagnostic yields between the findings of mediastinal lymph nodes on PET/CT and CT imaging. And if the meaning of the sentence is including the findings of mediastinal lymph nodes, it seemed that the interpretation of the results of this study is that when the findings of CT and PET/CT imaging showed lung cancer we don't have to perform few number of passes and when it showed no findings of lung cancer we should increase the number of passes for diagnosis. And I think it dose not meant the diagnostic yields of EBUS-TBNA but meant just how to decide the stage of lung cancer. So, I think the conclusion is not suitable for the results of this study.

Reply: Thank you for your thorough examination of our paper. Your attention to detail is highly appreciated. There might be a potential for misunderstanding in our communication, and I appreciate your efforts in pointing that out. Your observations align with those of another reviewer, and in response, we have endeavored to provide additional clarity to our manuscript.

The term "cancer finding" in CT and PET/CT refers not to characteristics of the mass itself but rather to features related to the lymph nodes. We have addressed this by clarifying our intentions and adding the following sentence to the manuscript: The chest CT and PET/CT data were independently interpreted by specialists in radiology and nuclear medicine. General principles of interpretation were applied for assessing cancer findings in nodes. Factors such as the increasing size of nodes, irregular shape, central necrosis, and compression of adjacent structures were considered for CT. The interpretation considered the results of the maximum standardized uptake value for PET/CT. (Page 7, Line 92-96).

Considering your insights, we acknowledge the potential confusion in our study's conclusion. We intended to optimize the number of attempts in EBUS-TBNA by integrating CT and PET/CT results. This conclusion primarily focuses on evaluating the likelihood of cancer based on CT and PET/CT findings and enhancing the diagnostic process of EBUS-TBNA accordingly. Therefore, we will explicitly emphasize that our conclusion is not solely centered on the diagnostic accuracy of EBUS-TBNA but rather on an overall diagnostic strategy.

Your feedback has been instrumental in improving the accuracy and clarity of our paper, and we are grateful for your thoughtful review. We welcome further suggestions or inquiries to enhance the comprehensibility of our work.

2. So, I think authors clearly write the definition of “no cancer findings”.

Reply: Thank you for your astute observation. We acknowledge the importance of clarifying the term "no cancer findings." In response to this concern, we have revised the manuscript to provide a more detailed explanation: The chest CT and PET/CT data were independently interpreted by specialists in radiology and nuclear medicine. General principles of interpretation were applied for assessing cancer findings in nodes. Factors such as the increasing size of nodes, irregular shape, central necrosis, and compression of adjacent structures were considered for CT. The interpretation considered the results of the maximum standardized uptake value for PET/CT. (Page 7, Lines 92-96)

We trust that these modifications to our manuscript contribute to a clearer understanding. Your insights are crucial to the accuracy and clarity of our study. Should you have any additional suggestions or questions, kindly share them. We genuinely value your input and look forward to any further contributions you may offer to enhance the comprehensibility of our work.

3. In L277-279, authors mentioned about the number of passes for the diagnosis of sarcoidosis, I think there are many articles that mention about the number of passes for the diagnosis of lung cancer and the molecular analysis, it seems inappropriate to cite this paper.

Reply: Thank you for your meticulous review and valuable feedback. We genuinely appreciate your insights into the appropriateness of the citation in L277-279. Upon careful consideration, we agree with your perspective. As per your suggestion, we have decided to remove the mentioned portion for better logical coherence: Oki et al. prospectively investigated the cumulative yield of EBUS-TBNA needle passes in 109 patients suspected of having stage I/II sarcoidosis without ROSE based on their findings of increasing cumulative yield with the number of passes (29)."

4. In L285-286, authors wrote “Generally, a larger tissue sample size yields higher diagnostic accuracy and increases the risk of complications”, but there is no section mention to the complications of this study. So, please write the complications of this study.

Reply: Thank you for your observation, and we appreciate your recommendation to include information about the complications in our study. Your insights made us review our data comprehensively; after careful examination, we confirmed that no major complications posed significant threats to the patients in our study.

Post-procedure fever was the most common event, occurring in 15.4% of cases. Additionally, we documented minor bleeding, effectively managed through simple observation or local epinephrine injection, in 7.9% of cases. Desaturation requiring additional oxygen supply occurred in 2.2%, and a blood pressure drop that recovered with fluid resuscitation was noted in 1.8% of cases. However, only one case of major bleeding required endotracheal intubation for airway protection.

We have promptly incorporated this valuable information into Table 1 and addressed it in the text (Page 10, Lines 160-163): No significant adverse events related to EBUS-

TBNA were observed except for major bleeding that required endotracheal intubation for airway protection in one case. The most common complication was post-procedure fever, observed in 15.4%, followed by minor bleeding controlled with simple observation or local epinephrine use, which occurred in 7.9% (Table 1).
We welcome any further suggestions or questions to improve the overall clarity of our manuscript.

Table 1. Baseline characteristics

Complications	
Fever	35 (15.4%)
Minor bleeding*	18 (7.9%)
Desaturation	5 (2.2%)
Hypotension	4 (1.8%)
Major bleeding#	1 (0%)

* Minor bleeding is defined as cases where the bleeding stopped with simple observation or was controlled solely with topical epinephrine.
# Major bleeding refers to cases where massive hemorrhage occurred, necessitating endotracheal intubation for airway protection.