Reviewer A

Thank you for the opportunity to review your intriguing paper.
I have several questions that I hope can be addressed to further enhance the impact of your work.

1. Can you provide more details on the nodule appearances in your study (solid, part-solid, pure GGN)?
It seems to be potentially difficult to measure the adjacent angle in GGNs.

Reply 1:
We would like to thank the reviewer for their constructive critique to improve the manuscript. We have made every effort to address the issues raised and to respond to all comments. The revisions are indicated in red font in the revised manuscript.
Please, find next a detailed, point-by-point response to the reviewer's comments. We hope that our revisions will meet the reviewer's expectations.
Of the 179 cases, 171 were solid, 7 were part-solid, and 1 was pure GGN. We have added this information to Table 1 and the Results section. One pure GGN case had blizzard findings, and we measured the adjacent angle of the blizzard range. We have provided this information in the Methods section. Measuring the adjacent angle is difficult in pure GGN, but as there was only one case of pure GGN in this study, the overall impact was expected to be small.

Changes in the text:
In the Methods section, we have added the following sentence: "In a patient with pure ground glass nodule, we measured the adjacent angle of the blizzard range. We measured the angles in 10° increments. We used images taken prior to biopsy EBUS to determine the shortest diameter and adjacent angle." (see Page 8, line 123)
In the Results, we have added the following sentence: "The lesion structure was as follows: 171 lesions (96%) were solid nodules, 7 (4%) were part-solid nodules, and 1 (1%) was a pure ground glass nodule." (see Page 9, line 145)

2. Could you specify if any additional procedures were conducted in your cohort, such as cryobiopsy, TBNA via Peliview-flex, or conventional forceps biopsy in the case of K201, or was the cohort limited to TBB under GS?

Reply 2:
We would like to thank the reviewer for this valuable comment.
Additional procedures were performed in 0 cases for cryobiopsy, 34 cases for TBNA, and 26 cases for conventional forceps biopsy. In this study, the pathology results from each specimen were confirmed separately, and the diagnostic yield of GS-TBB was

defined by the presence of malignant findings in the histology of the GS-TBB specimens.

Changes in the text:
In the Methods, we have added the following sentence: "Even in cases where additional procedures, such as EBUS-guided transbronchial needle aspiration (TBNA) and conventional forceps biopsy, were performed, the pathology of each specimen was confirmed separately, and a positive diagnosis by EBUS-GS-TBB was defined as a malignant finding in the EBUS-GS-TBB tissue specimen." (see Page 7, line 113)

3. In the case of adjacent, I assume that the adjacent angle may change after several EBUS checks throughout the examination, but would it be correct to say that the best (maximum) angle was evaluated during the examination? Or is it evaluated based on the EBUS findings before starting the biopsy?

Reply 3:
We would like to thank the reviewer for this valuable comment.
We have employed EBUS findings before biopsy initiation.

Changes in the text:
In the Methods, we have added the following sentence: "We used images taken prior to biopsy EBUS to determine the shortest diameter and adjacent angle." (see Page 8, line 125)

These inquiries stem from a desire to fully understand the depth and implications of your study. I look forward to your responses and any resulting improvements in the manuscript

Reviewer B

I read with interest the report on the usefulness of adjacent angle size in EBUS-GS.

1.Numerous reports have been published on transbronchial biopsies. As far as I know, most reports use "diagnostic yield" instead of "diagnostic rate". I recommend using "diagnostic yield" unless you have a particular reason to do so.

Reply 1:
We would like to thank the reviewer for their constructive critique to improve the manuscript. We have made every effort to address the issues raised and to respond to all comments. The revisions are indicated in red font in the revised manuscript. Please, find next a detailed, point-by-point response to the reviewer's comments. We hope that our revisions will meet the reviewer's expectations.
We have changed the wording from "diagnostic rate" to "diagnostic yield."

2.The definition of a positive diagnosis is stated as when malignancy is obtained histologically. Were the malignant findings on cytology not included in the positive diagnosis? The tissue diagnosis yield of 91.6% within image is very high, but what is the diagnosis yield if cytology is included?

Reply 2:
We would like to thank the reviewer for this valuable comment.
We did not include the malignant findings on cytology. As the reviewer noted, the diagnostic yield of within lesions in previous papers is 78.7–83%. Therefore, in this work, the diagnostic yield of 91.6% was higher. The high diagnostic yield may be attributed to the fact that previous papers were limited to smaller lesion sizes or peripheral lesions, whereas this study had no such limitation.

3.Question regarding patient selection, were the 29 excluded unknown diagnosed patients followed up? Is it possible that some of these patients have primary lung cancer?

Reply 3:
We would like to thank the reviewer for this valuable comment.
Cases with no diagnosis after medical record follow-up through December 31, 2022, were defined as unknown. We have provided this information in the Methods section

Changes in the text:
In the Method section, we have added the following sentence: "The cutoff for follow-up on whether a diagnosis was made was December 31, 2022." (see Page 6, line 82)

What are the significant digits of the adjacent angle size? 1° unit or 10° unit?

Reply:

We would like to thank the reviewer for this valuable comment.

We measured this value in 10° increments. We have provided this information in the Methods section as follows:

Changes in the text:

In the Method section, we added the sentence "We measured the angles in 10° increments." (see Page 8, line 124)

4.Page 8, line 183-188. You discussed the short diameter of the within image, but what do you mean by 19mm? Table 3 shows that the range of short diameters is 2-18 mm, and there is no such patient with a short diameter of 19 mm.

Reply 4:

We would like to thank the reviewer for this valuable comment.

Please note that the correct cutoff for a short diameter was 9 mm. We apologize for this error. We have corrected it in the Discussion section as follows:

Changes in the text:

In the Discussion section, we have changed the corresponding part as follows: "According to the ROC curve, the most appropriate cut-off for a short diameter was 9 mm. In our study, the diagnostic yield of EBUS-GS-TBB was 100% for lesions ≥9 mm and 88.2% for lesions <9 mm. From these results, we suggested that the classification of within lesions by more detailed EBUS findings is only slightly significant in clinical practice." (see Page 11, line 203)

5.Lesion size is generally a contributing factor to a positive diagnosis. Although lesion size was not a significant univariate factor in Table 2, please consider including lesion size in multivariate analysis based on previous reports.

Reply 5:

We would like to thank the reviewer for this valuable comment.

We performed a multivariate analysis of the following four items: EBUS findings, CT bronchus sign, lesion location plus lesion size, with P-values of <0.0001, 0.0670, 0.1426, and 0.0794, respectively, with only EBUS findings being significantly different. In the multivariate analysis of the original three items, only the EBUS findings showed significant differences, and the results were the same when the lesion size was added. We selected items that showed significant differences in univariable analysis as items for multivariable analysis. Thus, we will continue to analyze these three items. We have presented the criteria for variable selection for multivariable analysis in the Methods section.

Changes in the text:

In the Methods section, we have added the following sentence: "If more than one

factor was statistically significant in univariable analysis, multivariable analysis with logistic regression models was performed on those factors." (see Page 8, line 130)

6. I suspect that there is a correlation between adjacent angle and lesion size. Is there a correlation between the two factors?

Reply 6:
We would like to thank the reviewer for the valuable comment.
Analysis of the correlation between adjacent angle and lesion size showed no significant difference ($P>0.05$). As shown in Table 4, the lesion size did not significantly contribute to the adjacent lesion diagnostic yield. Thus, we believe that the adjacent angle was the only factor that affected the diagnostic yield with a significant difference.

7.This study targets very large lesions with a median lesion size exceeding 3 cm. I think that there are many facilities where EBUS-GS is not indicated for central lesions with large lesion sizes. Please comment on the indications for EBUS-GS.

Reply 7:
We would like to thank the reviewer for this valuable comment.
In our hospital, we performed EBUS-GS-TBB regardless of lesion size except for lesions that can be detected under direct visualization when observing the bronchial lumen.

Changes in the text:
In the Methods section, we have added the following sentence: "In our clinical practice, EBUS-GS-TBB was performed regardless of the lesion size except for lesions that could be directly visualized by bronchial lumen observation." (see Page 6, line 83)

Reviewer C
The reviewer is honored to review an article about the diagnostic factor of EBUS-GS-TBB method. This study was retrospectively conducted in a single institution in Japan. The paper is concise, but well written. And it is easy to understand. Successful diagnosis is obtained when the EBUS finding is "within". When EBUS finding is "adjacent to", it is recommended that the operator should identify the branch of the bronchus with a greater adjacent angle.

Minor points:
Regarding Table 3 and 4, "Univariate" should be written s "Univariate analysis".

Reply:
We would like to thank the reviewer for evaluating our manuscript and for the insightful comment.

We have also integrated the suggestions from Reviewer F and changed "Univariate" to "Univariable analysis."

Reviewer D

This is a retrospective single center cohort study of consecutive lung cancer patients who underwent transbronchial biopsy with endobronchial ultrasonography with a guide sheath to determine predictive factors affecting diagnostic rates of lung cancer. 78.2% of lesions in their cohort were diagnosed using this technique, with significantly higher diagnostic rate if within vs adjacent to the lesion. Notably, they found diagnostic rates different among the cohort of adjacent lesions depending on angle (either greater than or equal to 180 degrees or less than 180 degrees) from midpoint of the probe and the two points where the edge of the probe and shadow of tumor intersected.

Well written paper summarizing current literature and how their retrospective study (noting limitations) adds to the literature, particularly factors for procedures to potentially use in setting of r-EBUS findings with adjacent lesions to potentially increase angle and yield.

Reply:
We would like to thank the reviewer for the positive evaluation of our work.

Reviewer E

The authors offer a more profound exploration of the concept of "adjacent to" in EBUS-GS-TBB. I have a few inquiries to obtain a deeper comprehension of the contextual backdrop in which this study was executed.

1: Was the implementation of Rapid On-Site Cytologic Evaluation (ROSE) a regular practice during the study duration to augment the diagnostic yield?

Reply 1:
We would like to thank the reviewer for their constructive critique to improve the manuscript. We have made every effort to address the issues raised and to respond to all comments. The revisions are indicated in red font in the revised manuscript. Please, find next a detailed, point-by-point response to the reviewer's comments. We hope that our revisions will meet the reviewer's expectations.
ROSE is not conducted in regular practice and is expected to have a little impact on our study.

2: Was the selection of bronchial branches routinely conducted using curette during the period encompassing this study to enhance the diagnostic rate?

Reply 2:
We would like to thank the reviewer for the valuable comment.
As a rule, we do not use curette. Thus, we do not know their contribution.

3: Considering the inclusion of Stage 1 lung cancer, it is anticipated that certain cases might have exhibited a ground-glass nodule on CT scans. In such instances, how were the lung cancers demonstrating a blizzard sign managed within the scope of this study?

Reply 3:
We would like to thank the reviewer for the valuable comment.
Of the 179 cases, 171 were solid, seven were part-solid, and one was pure GGN. We have added this result to Table 1 and the Results section. One pure GGN case had blizzard findings, and we measured the adjacent angle of the blizzard range. We have provided this information in the Methods section. Measuring the adjacent angle is difficult in pure GGN, but as there was only one case of pure GGN in this study, the overall impact is expected to be small.

Changes in the text:
In the Methods section, we have added the following sentence: "In a patient with pure ground glass nodule, we measured the adjacent angle of the blizzard range." (see Page 8, line 123)
In the Results, we have added the following sentence: "The lesion structure was as

follows: 171 lesions (96%) were solid nodules, 7 (4%) were part-solid nodules, and 1 (1%) was a pure ground glass nodule." (see Page 9, line 145)

4: The rightmost column on the horizontal axis of Figure 3 ought to be labeled as "within," yet it currently lacks any content. Kindly provide the necessary information to complete this column.

Reply 4:
We would like to thank the reviewer for the valuable comment.
We have added a "within" label to Figure 3.

5: Within Table 4, within the column denoting the "Location of lesion," it is presumed that the figures in parentheses represent percentages, although no explicit explanation is provided. Furthermore, the cumulative total does not add up to 100%; therefore, please verify the accuracy of the numerical values.

Reply 5:
We would like to thank the reviewer for the valuable comment.
We apologize for the mistake. The correct percentage for "Location of lesion" in Table 4 was 61%. We have corrected the corresponding part in Table 4.

Reviewer F

This manuscript aimed to determine whether detailed ultrasonographic findings during radial EBUS-guided transbronchial biopsy were associated with lung cancer diagnosis. This article includes novel and interesting results and is generally well-written and easy to follow. I have a few comments to be addressed to improve the manuscript.

Remarks:

General:
-Throughout the manuscript, the authors use the term 'diagnostic rates,' which is not commonly used in diagnostic studies. The primary outcome that the authors investigated would be 'sensitivity' for diagnosing lung cancer. I suggest changing the term to 'sensitivity for lung cancer.'

Reply 1:
We would like to thank the reviewer for their constructive critique to improve the manuscript. We have made every effort to address the issues raised and to respond to all comments. The revisions are indicated in red font in the revised manuscript. Please, find next a detailed, point-by-point response to the reviewer's comments. We hope that our revisions will meet the reviewer's expectations.
Reviewer B also pointed out that we should change "diagnostic rates" to "diagnostic yield." Thus, we have made this change.

Methods
-In the study design, please provide more specific information on how the authors defined lung cancer cases and the length of follow-up. For initially cancer-negative cases by EBUS-guided biopsy, was there a pre-defined protocol for lesion follow-up or performing additional diagnostic procedures? How long was an initial negative lesion followed up clinically to preclude lung cancer as the final diagnosis?

Reply 2:
We thank you for this valuable comment.
Patients with a diagnosis of lung cancer with medical record follow-up through December 31, 2022, were included in the analysis. We have added this point to the Methods section. There were no protocols for follow-up or additional diagnostic procedures for patients with initial negative EBUS-GS-TBB results, and this was left to the discretion of the individual clinician. We have added this point in the Limitation part of the Discussion section. The median observation period from bronchoscopy to the end of follow-up was 856 days (range: 659–1,058) for patients without a diagnosis of lung cancer.
Changes in the text:
In the revised manuscript, we have added the following parts: "The cutoff for follow-

up on whether a diagnosis was made was December 31, 2022. In our clinical practice, EBUS-GS-TBB was performed regardless of the lesion size except for lesions that could be directly visualized by bronchial lumen observation. (see Page 6, line 82)

In the Result section, we have added the following sentence: "The median observation period from bronchoscopy to the end of follow-up in unknown cases was 856 days (range 659–1,058 days). (see Page 8, line 139)

In the Discussion section, we have added the following sentence "No protocols for follow-up or additional diagnostic procedures for patients with initial negative EBUS-GS-TBB results were set, and further testing was left to the discretion of the individual clinician. (see Page 12, line 208)

-Please provide the IRB approval number in the study design session

Reply 3:
We would like to thank the reviewer for this suggestion.
Changes in the text:
In the Methods section, we have added the following sentence:
"This study was approved by the ethics review board or institutional review board of the Wakayama Medical University Ethics Committee (approval number: 3413) and was conducted in accordance with the principles of the Declaration of Helsinki." (see Page 6, line 89)

-More detailed information on the EBUS-GS-TBB procedure would be helpful. What kind of anesthesia methods (e.g., general anesthesia, moderate sedation, etc.) were used for the procedures? How many pulmonologists performed the procedures? Was there a routine procedure protocol for biopsy tool selection and attempts of biopsy? Were any other guidance techniques (e.g., fluoroscopy, ROSE) used? If TBB using forceps were the only tool that was used for biopsy, it would be more apparent to state that all biopsies were performed using a single uniform tool, and no additional needle aspiration was attempted.

Reply 4:
We would like to thank the reviewer for this suggestion.
EBUS-GS-TBB was performed by at least two pulmonologists under sedation with pentazocine and midazolam. It was performed for lesions that could not be biopsied under direct visualization by observation of the bronchial lumen. Guidance techniques, such as fluoroscopy and ROSE, are not used in regular practice.
Needle aspiration was not routinely performed, but even when it was performed, the pathology of each specimen was confirmed separately, and a positive diagnosis by EBUS-GS-TBB was defined as a malignant finding in the EBUS-GS-TBB tissue specimen.
Changes in the text:
We have provided this information in the Methods section as follows:
"EBUS-GS-TBB was performed by at least two pulmonologists under sedation with

pentazocine and midazolam. EBUS-GS-TBB was performed for lesions that could not be biopsied under direct visualization by observation of the bronchial lumen." (see Page 6, line 96)

In the Methods section, we have also added the following sentence:

" Even in cases where additional procedures, such as EBUS-guided transbronchial needle aspiration (TBNA) and conventional forceps biopsy, were performed, the pathology of each specimen was confirmed separately, and a positive diagnosis by EBUS-GS-TBB was defined as a malignant finding in the EBUS-GS-TBB tissue specimen." (see Page 7, line 113)

Page 5, Line 102
- Recent guidelines on diagnostic procedures for lung cancer diagnosis suggest classifying central or peripheral by lesion location, assessing whether the lesion is located within the inner one-third of the hemithorax (central) or in the outer two-thirds of the hemithorax.1,2 I suggest the authors use this classification to categorize central and peripheral lesions.
1. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013; 143: e211S-e250S.
2. Casal RF, Vial MR, Miller R, et al. What Exactly Is a Centrally Located Lung Tumor? Results of an Online Survey. Ann Am Thorac Soc. 2017; 14: 118-23.

Reply 5:
We would like to thank the reviewer for this suggestion.
We have changed the classification of central or peripheral diagnosis in accordance with your suggestion.
We have also changed our references to those listed above. As with classification by subsegmental bronchi, there were no significant differences in diagnostic yield in univariable analysis.

Changes in the text:
In the Methods, we have changed the sentence to "Lesions located in the outer 2/3 and those located in the inner 1/3 of the thorax were defined as peripheral and central lesions, respectively (16, 17)." (see Page 7, line 111)

Page 5, Line 111
- To determine and measure the adjacent angle for adjacent lesions, I suppose that the authors used the ultrasonography image that would present the maximum visualization and adjacent angle of the lesions. Please clarify which point and image were used for evaluation since EBUS findings are real-time images that are highly dependent on the operator.

Reply 6:

We would like to thank the reviewer for this suggestion.

We have evaluated the image of the EBUS findings prior to biopsy and used it to determine the shortest diameter and the adjacent angle.

Changes in the text:

In the Methods section, we have revised the corresponding part as follows: " We used images taken prior to biopsy EBUS to determine the shortest diameter and adjacent angle." (see Page 8, line 125)

Statistical analyses

-The statistical methods used for univariable and multivariable needs to be clarified. Were logistic regression models used? In addition, please change "univariate" to "univariable" and "multivariate" to "multivariable" throughout the manuscript. The term univariate and multivariate is often misused in the medical literature

Reply 7:

We would like to thank the reviewer for this valuable comment.

We used a logistic regression model in our multivariate analysis. We have added this information in the Methods section.

We have also made changes to those terms.

Changes in the text:

In the Method section, we have revised the corresponding part as follows: " If more than one factor was statistically significant in univariable analysis, multivariable analysis with logistic regression models was performed on those factors." (see Page 8, line 130)

Results:

Page 6, Line 125

This sentence should clarify that 239 lesions underwent biopsy via EBUS-GS-TBB, and 179 lesions that were finally diagnosed with primary lung cancer were included in the analyses.

Reply 8:

We would like to thank the reviewer for this valuable comment.

Changes in the text:

In the Methods, we have revised the corresponding part as follows:

"In total, 239 lesions were assessed using EBUS-GS-TBB. Thirty-one cases with a diagnosis other than lung cancer and 29 unknown cases were excluded. The median observation period from bronchoscopy to the end of follow-up in unknown cases was 856 days (range 659–1,058 days). In total, 179 lesions whose final diagnosis was primary lung cancer were included in the analysis." (see Page 8, line 138)

Page 7, Line 143
- Please state that findings of within lesions were the 'only' significant factor associated with higher sensitivity for lung cancer diagnosis.

Reply 9:
We would like to thank the reviewer for the valuable comment.

Changes in the text:
In the Results section, we have revised the corresponding part as follows:
" In the multivariable analysis, within lesions had a significantly higher diagnostic yield than did adjacent lesions and was the only factor associated with diagnostic yield (OR [95% CI]: 8.56 [3.70–19.83], P<0.001)." (see Page 9, line 160)

Tables 2-4
- Results of the univariable analyses must be presented in odd ratios and 95% confidence intervals, and p-values provide limited information. I suggest adding these values to the tables. Usually, single p-values are presented as results from chi-square or Fisher's exact test.

Reply 10:
We would like to thank the reviewer for this valuable comment.
We have added the OR using the chi-square test in the univariate analysis results in Tables 2–4.

Table 3.
- It is hard to understand that the median short diameter measured is 4.5 to 5 mm in lesions with a median size of 39 to 52.5 mm by CT size. Even regarding it may represent the minor axis of the lesion, it is still too short compared to the full size of the lesion. Can the authors give explanations for these findings?

Reply 11:
We would like to thank the reviewer for this valuable comment.
The difference between lesion size and within short diameter can be explained by the fact that the within case does not necessarily contain the branch to be biopsied in the center of the lesion.