Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1234

Reviewer A

Thank you for the great study. I applaud the results and can be very helpful for practicing pulmonologist and interventional pulmonologist to guide their decisions.
I have following suggestions:

Comment 1: Were you able to classify CT bronchus sign as an adjacent or within. If yes, did It correlate with r EBUS - for example, if CT showed within air bronchus sign and those are the same patients where "A to W" transition occurred, then it is easy to conclude that CT should be evaluated first and then they should be used to guide to achieve transition from " A to W". and if CT showed only adjacent airway, then bronchoscopist should not make multiple try to achieve A to W.

Reply 1: Thank you for your valuable comment. Following your suggestion, we evaluated the CT bronchus sign, classifying it as either adjacent to or within the lesion. For this classification, we adhered to the definitions provided in the reference "Tomoyuki Minezawa et al. BMC Med Imaging. 2015 Jun 21;15:21. doi: 10.1186/s12880-015-0060-5. PMID: 26092497". According to this reference, type A is defined as the responsible bronchus clearly extending into the interior of the target lesion, which denotes the “within” category in CT imaging. Type C is characterized by the absence of any detectable bronchus sign in relation to the lesion. When the CT findings did not fit the criteria for type A or C, we classified them as type B, which corresponds to the “adjacent to” category in CT imaging. We reanalyzed the data by categorizing the bronchus sign into three groups: Positive Type A (classified as the 'within' category in CT imaging), Positive Type B (classified as the 'adjacent to' category in CT imaging), and Negative (equivalent to Type C). The results are presented in Table 3 (only for review). The findings indicated no significant difference in the proportions of Positive type A, type B, and Negative between the "A to W" group and the "not A to W" group. In the "A to W" group, the proportions were 63.9% for Positive type A, 24.1% for Positive type B, and 12.0% for Negative, while in the "not A to W" group, they were 57.6%, 28.5%, and 14.0%, respectively, suggesting relatively similar distributions. Additionally, using this classification, we recalculated the odds ratios for diameter, dBC, and the CT bronchus sign, which are displayed in Table 4 (only for review). However, the main results remained unchanged, with significant differences observed only in the diameter (Odds Ratio 1.022, 95% CI 1.002-1046). For the CT bronchus sign, the results were not significant, with an odds ratio of 1.171 (95% CI 0.520-2.787) for Positive type A and 1.126 (95% CI 0.455-2.901) for Positive type B. Therefore, we concluded that classifying the CT bronchus sign as either adjacent to or within did not significantly alter the main results. We considered adding these results to the supplementary file, but given that the classification of adjacent to and within in CT imaging is not widely recognized and could potentially complicate the reader's understanding, we decided against it and opted to retain only the original description. Nonetheless, the concept of adjacent to and within in CT imaging, as highlighted in " Tomoyuki Minezawa et al. BMC Med Imaging. 2015 Jun 21;15:21. doi: 10.1186/s12880-015-0060-5. PMID: 26092497" is intriguing and warrants further research using this

classification.

<Tables in the additional analysis (only for review)>

Table 3. Characteristics of the study participants (only for review)

Characteristics	Missing	"Adjacent to" to "within" (n = 84)	"Adjacent to" to not "within" (n = 176)	p value
Age (mean (SD)), years	0	69.35 (10.77)	70.35 (9.74)	0.454
Sex	0			0.436
Male (%)		56 (66.7)	107 (60.8)	
Female (%)		28 (33.3)	69 (39.2)	
Smoking history (%)	1	55 (66.3)	123 (69.9)	0.658
Cancer history (%)	1	35 (42.2)	57 (32.4)	0.163
Period from CT examination to bronchoscopy (mean (SD)), day	0	12.63 (11.93)	11.94 (29.78)	0.839
CT slice thickness, mm	0			0.842
<1 (%)		2 (2.4)	4 (2.3)	
1 (%)		44 (52.4)	93 (52.8)	
1< <2 (%)		0 (0.0)	1 (0.6)	
2 (%)		22 (26.2)	46 (26.1)	
2< <5 (%)		9 (10.7)	12 (6.8)	
5 (%)		7 (8.3)	20 (11.4)	
Side of target lesion	0			0.248
Right (%)		43 (51.2)	105 (59.7)	
Left (%)		41 (48.8)	71 (40.3)	
Lobe of target lesion	0			0.786
Upper lobe (%)		43 (51.2)	98 (55.7)	
Middle lobe and lingular segment (%)		11 (13.1)	20 (11.4)	
Lower lobe (%)		30 (35.7)	58 (33.0)	
Part of target lesion	0			0.295
Central part (%)		4 (4.8)	7 (4.0)	
Middle part (%)		28 (33.7)	43 (24.9)	
Peripheral part (%)		51 (61.4)	123 (71.1)	
Diameter (mean (SD), mm	7	26.91 (14.88)	22.91 (11.73)	0.021
CT bronchus sign positive (%)	5			0.630
Positive type A		53 (63.9)	99 (57.6)	
Positive type B		20 (24.1)	49 (28.5)	
Negative		10 (12.0)	24 (14.0)	
Appearance of target	3			0.082

lesions				
Solid (%)		70 (84.3)	135 (77.6)	
Solid with cavity (%)		3 (3.6)	12 (6.9)	
Part-solid GGO (%)		9 (10.8)	17 (9.8)	
Pure GGO (%)		1 (1.2)	0 (0.0)	
Others (%)		0 (0.0)	10 (5.7)	
Visibility on chest radiograph (%)	7	74 (90.2)	142 (83.0)	0.184
Type of bronchoscope	1			0.612
BF-P260F (%)		57 (67.9)	124 (70.5)	
BF-1T260 (%)		17 (20.2)	31 (17.6)	
BF-P290F (%)		8 (9.5)	12 (6.8)	
BF-Q290 (%)		2 (2.4)	9 (5.1)	
Type of guide sheath	1			0.499
K201 (%)		68 (81.0)	150 (85.1)	
K203 (%)		16 (19.0)	26 (14.9)	
NBB (mean (SD))	1	3.38 (1.03)	3.29 (0.98)	0.500
NBC (mean (SD))	0	4.88 (1.17)	5.11 (1.24)	0.162
dBC (mean (SD))	0	1.50 (1.11)	1.82 (1.19)	0.042
Visibility on fluoroscopy	0			0.279
Fine (%)		55 (65.5)	94 (53.4)	
Equivocal (%)		14 (16.7)	38 (21.6)	
Not in use (%)		8 (9.5)	28 (15.9)	
Invisible (%)		7 (8.3)	16 (9.1)	
2% xylocaine usage (mean (SD)), mL	43	19.29 (4.13)	19.80 (3.68)	0.361
Pethidine usage (mean (SD)), mg	0	32.71 (7.07)	32.41 (7.02)	0.753
Midazolam usage (mean (SD)), mg	0	2.01 (1.15)	1.85 (0.93)	0.233
Procedure time (mean (SD)), min	0	30.92 (10.38)	32.19 (9.71)	0.335
Biopsy count (mean (SD))	0	6.71 (1.51)	6.28 (1.73)	0.052

NBB, number of branches reached by the bronchoscope; NBC, number of branches before reaching the lesion on computed tomography imaging; dBC: difference between the number of branches before reaching the lesion on computed tomography imaging and the number of branches reached by the bronchoscope; SD: standard deviation; CT: computed tomography; GGO: ground glass opacity

Table 4. Odds ratios for diameter, dBC, and CT bronchus sign (only for review)

Characteristic	Odds ratio (95% CI)
Diameter	1.022 (1.002-1.046)
dBC	0.831 (0.647-1.058)

CT bronchus sign*	
Positive Type A	1.171 (0.520-2.787)
Positive Type B	1.126 (0.455-2.901)

*The odds ratio is calculated with the negative CT bronchus sign serving as the reference category, assigned a value of 1.000.

Abbreviations: dBC: difference between the number of branches before reaching the lesion on the computed tomography imaging and the number of branches reached by the bronchoscope; CT: computed tomography; CI: confidence interval

Reviewer B

This is the first paper to evaluate the EBUS image changes during the procedure, and showing new insights into an effective strategy for bronchoscopists in the diagnosis of peripheral lung lesions, especially when the diameter is over 29.25 mm. It is good enough for publication, with some revision as bellows.

Comment 1. English writing should be revised by native English speaker.

Reply 1: Thank you for your comment. We have been using Editage for English language editing, and based on your recommendation, we have sought additional editing from another native English speaker and have obtained a certificate to verify this.

Changes in the text: Throughout the document, revisions are indicated in blue.

Comment 2. The method of changing EBUS images should be described in detail, adding photo images.

Reply 2: Thank you for your comment. We have added a new figure 1, showing a typical case of "A to W" findings. This case was of a 70-year-old female, who exhibited a 28-mm nodule in the right upper lobe and underwent EBUS-GS. The initial EBUS findings, before sampling, were categorized as "adjacent to" (Figure 1A). However, the findings transitioned to "within" after performing multiple biopsies (Figure 1B). She was diagnosed with lung adenocarcinoma.

Changes in the text:

Page 8, Lines 132-136

Outcome variable

The appearance of "A to W" (change from "adjacent to" to "within" lesion status) was considered as the primary outcome. Typical findings of the "A to W" change are shown in Figure 1. Initial EBUS imaging findings showed "adjacent to" lesion status before sampling (Figure 1A), but finally showed "within" lesion status as biopsies were performed repeatedly (Figure 1B).

Page 17, Lines 324-330

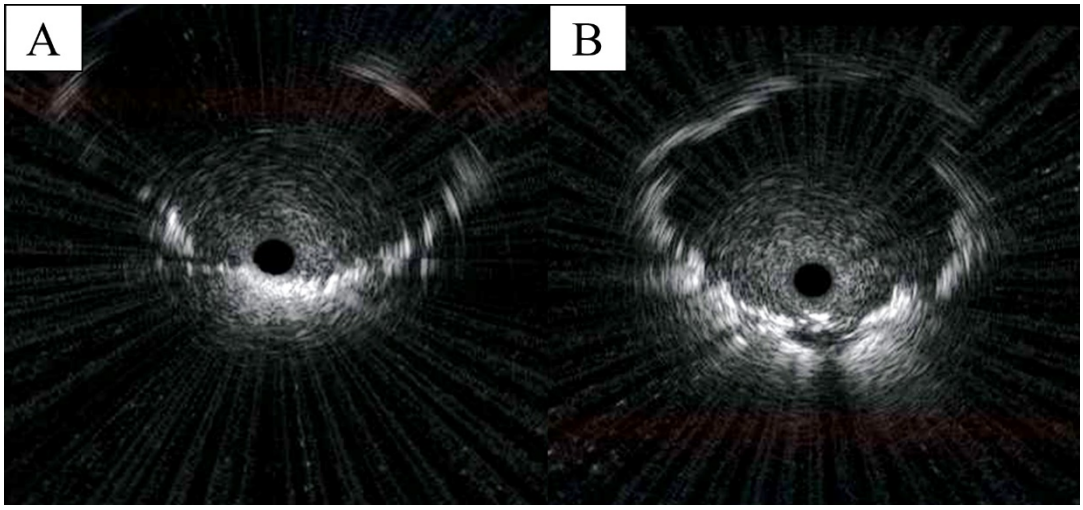
Figure Legend

Figure 1. Typical findings of the "A to W"

A 70-year-old female was referred to our department due to abnormal chest shadows. A 28-mm nodular shadow was observed in the right upper lobe on chest CT, and EBUS-GS was

performed on the nodule. The initial EBUS findings, before sampling, were categorized as "adjacent to" (Figure 1A). However, the findings transitioned to "within" after multiple biopsies were performed (Figure 1B). The patient was diagnosed with lung adenocarcinoma.

[Added new Figure 1]
Figure 1



Reviewer C

The authors provide an analysis of factors that predict the change from an adjacent to within radial EBUS sign for patients undergoing lung nodule biopsies. They provide a sound description of their approach and suggest a means to improve procedures in the future based on a cut off of 29.25mm as a size criteria to use to proceed with biopsy rather than spend anesthesia time trying to improve radial EBUS signal. The paper is well written and quite informative with the potential to impact the way procedures are performed in the future. Well done.

Reply: Thank you for your kind words and positive review. We are pleased to hear that you found our study informative and impactful. Your feedback is greatly appreciated.

Reviewer D

I appreciated this study that focused on a hotly debated issue.
In fact, it remains unclear whether lesion diameter, nodule consistency and lesion location influence the diagnostic sensitivity of EBUS-GS. Some studies have shown that the diagnostic sensitivity of EBUS-GS is similar for lesions with different diameters and different consistency (larger vs smaller and solid vs GGO). However, other studies underlined that a diameter less than 20mm or pure GGO and part-solid lesions were associated with a lower sensitivity.
This study can give some additional and practical information.

However I have some questions.

Comment 1: How long did the procedures take? This should be reported.

Reply 1: Thank you for your comment. My apologies for the unclear documentation. The time for the procedure is listed at the bottom of Table 1 under "Inspection time." The mean procedure time was 30.92 minutes for the group with "A to W" changes and 32.19 minutes for the group without "A to W" changes, showing no significant difference (p=0.335). To clarify, we have updated this to "procedure time" and have also added a description about the time in the results section of the text.

Changes in the text:
Page 10, Lines 172-174
The mean procedure time was 30.92 min for the group with "A to W" and 32.19 min for the group without "A to W", showing no significant difference (p=0.335).

Changed in Table 1

Midazolam usage (mean (SD)), mg	0	2.01 (1.15)	1.85 (0.93)	0.233
Procedure time (mean (SD)), min	0	30.92 (10.38)	32.19 (9.71)	0.335
Biopsy count (mean (SD))	0	6.71 (1.51)	6.28 (1.73)	0.052

Comment 2: Did the authors perform the procedures with the help of an anesthesiologist for intravenous opioid drug administration and for managing of possible drug related complications?
Reply 2: No, we did not have the assistance of an anesthesiologist. Sedation was administered by the pulmonologists assisting the operator. All pulmonologists involved in this role have undergone training for sedation within our hospital and are attentive to possible complications while administering opioids. In Japan, most hospitals operate under similar conditions, where assisting pulmonologists are also responsible for administering sedation. We have updated the Methods section accordingly. The section also now includes adjustments to opioid administration and details on ventilation support, addressing Comment 3. The revisions are as follows.

Changes in the text:
Page 7, Lines 103-112
Next, bronchoscopy was performed after administering 1–2 mg of midazolam and 35 mg of pethidine intravenously, with the anesthetic dose adjusted based on the patient's general condition. These drugs were administered by pulmonologists assisting the operator, all of whom were trained in sedation. Typically, a combination of 35 mg of pethidine and 1 mg of midazolam is used, but for older patients, only 17.5 mg of pethidine is administered, and midazolam is omitted. If the sedative effect is insufficient, additional doses of midazolam are administered in increments of 0.5–1 mg as required. Ventilatory support, such as a laryngeal mask, was not employed during bronchoscopy. Throughout the procedure, an additional 2% lidocaine solution was sprayed into the airway as necessary, taking into account the patient's cough reflex and general condition.

Comment 3: Pethidine is an opioids medication, that can cause respiratory depression. Did the authors use some ventilation support, such as laryngeal mask, in order to avoid possible complications related to respiratory depression?

Reply 3: No, we did not utilize ventilation support such as a laryngeal mask. Our pulmonologists have been trained in sedation techniques and administer anesthetic drugs cautiously, taking into account the patient's age and weight. Typically, we use 35 mg of pethidine and 1 mg of midazolam, but for older patients, we administer only 17.5 mg of pethidine and omit midazolam. If the sedative effect is insufficient, additional doses of midazolam are administered in increments of 0.5–1 mg as needed. We have included these details in the Methods section as shown in Reply 2 above.

Comment 4: Did the authors use fluoroscopy in order to verify the correct position of the EBUS-GS?

Reply 4: Thank you for your comment. Yes, we did use fluoroscopy to verify the correct position of the EBUS-GS. This information is provided in the Methods section on Page 7, Lines 113-115 as shown below.

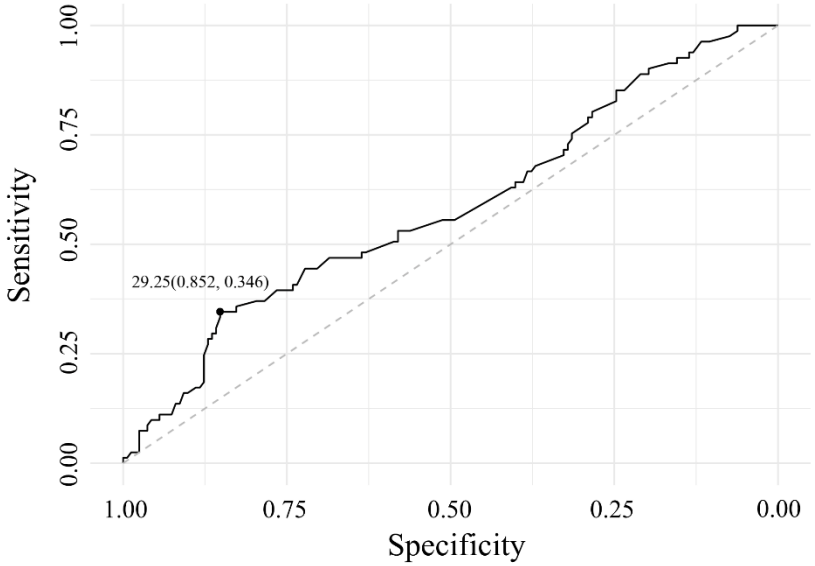
The corresponding section in the text.
Page 7, Lines 113-115.
The endoscopic ultrasound probe was then inserted through a conduit in the bronchoscope along with a guide sheath into the bronchus leading to the target lesion under fluoroscopy (Versi FLEX, Hitachi Ltd., Tokyo, Japan).

Other minor corrections

1 In Table 1, we mistakenly used the product name “Opistan” and have now changed it to “Pethidine”.

2 In revised Figure 3 (ROC curve of the lesion diameter), I removed the percentages next to Sensitivity and Specificity, as they were unnecessary.

Revised Figure 3 (ROC curve of the lesion diameter),


Sensitivity
1.00
0.75
0.50
0.25
0.00
29.25(0.852, 0.346)
1.00
0.75
0.50
0.25
0.00
Specificity