

Peer review file

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# Reviewer A

**-Major COMMENT 1**

-page/line

7/112-113 “EBUS-TBNA is performed as much as possible to check all lymph nodes.”  
11/189 “EBUS-TBNA was performed in 147 lymph nodes (rate: 1.41 per patient).“ [as much as possible € but just 1.4/pt].....These sentences are the only described method and result by authors about ETBNA procedure that authors did. Guidelines recommend “TBNA at least 3LN stations; needling number of 3 or more or, 2 or more (if core tissue+)” [Endoscopy 2015;47:545-59; Eur J Cardiothorac Surg 2014;45:787-98.]. EBUS-TBNA methodology of the present study should be described more precisely and more in detail such as including number of LN stations for TBNA. And as a results, Table 1 should include number of LN stations for TBNA (median, IQR or range). If authors feel like having limitations. Honestly describe limitations. Furthermore, in 8/130, authors told that LN "more than 1 cm in the short-axis on chest CT" is a subject of EBUS-TBNA...but The average size of lymph nodes was 8.55 mm (range: 3 – 22 mm).

-REPLY to comment 1: Thank you for your advice. In our facility, preoperative EBUS-TBNA was performed for the lymph nodes that could affect the surgical procedure or policy. As a result, the number of lymph nodes examined was slightly smaller than previous reports. And we described the number of LN stations for TBNA on Table 2. The reason why the average size of the lymph nodes is small is that patients with too large maximum minor axis are not treated by surgery, and EBUS is performed for cases with small minor axis and FDG accumulation. As there was a little explanation in Methods and limitation, we corrected it as follows;

In our institution, preoperative EBUS-TBNA was performed for patients who has at least one target lymph node larger than 10 mm or with FDG uptake. EBUS is performed as much as possible to check all lymph nodes. We check the presence of at least 3 stations of lymph nodes, and TBNA is only performed for the lymph nodes that could affect the surgical procedure or policy. (page 9, line 118-123)

Fourth, this study was targeted at the lung cancer patients who underwent preoperative EBUS-TBNA and surgery, and not all patients who underwent EBUS-TBNA in our hospital. As a result, the number of lymph nodes evaluated is less than in previous reports.

(page 21, line 314-318)

**-Major COMMENT 2**

24/ Table 3..... I can't understand "LN-SUVmax" in the regression analysis table...Do you meant "LN-SUVmax per 1". Please describe precisely in Table as well as in the text. Also "size" too. >10mm vs <10 or per 1???

-REPLY to comment 2: Thank you for this advice. In regression analysis, hazard ratio was calculated in LN-SUVmax per 1 and the size of lymph node per 1 mm. So we edited table 3 and added descriptions in continuous variables as follows;

**TABLE 3. Univariate and multivariate analysis for factors associated with LN metastasis among sonographic features and SUVmax**

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
<b>Sonographic features</b>				
Size*	1.50 (1.26 – 1.78)	< 0.01	1.26 (1.02 – 1.56)	0.03
Shape: round	28.33 (6.36 – 126.25)	< 0.01	23.21 (4.30 – 125.15)	< 0.01
Margin: distinct				
Central hilar structure: absence	8.17 (1.85 – 36.14)	< 0.01	8.86 (1.61 – 48.86)	0.01
Echogenicity: homogeneous				
Necrosis signs	4.05 (1.52 – 10.80)	< 0.01		
Vascular pattern: avascular				
Calcification: present				
<b>LN-SUVmax*</b>	1.27 (1.12 – 1.43)	< 0.01	1.24 (1.04 – 1.47)	0.02

\*hazard ratio for 1 mm increment of the size, 1 increment of LN-SUVmax.

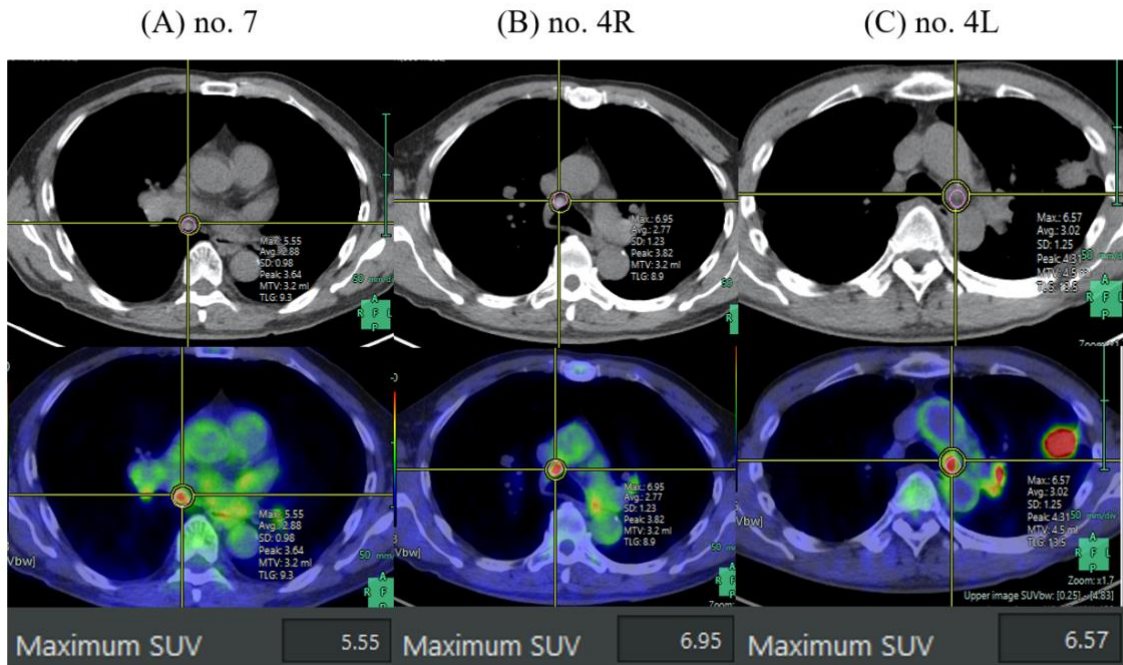
CI = confidence interval; LN = lymph node; LN-SUVmax = maximum standardized uptake value of lymph node.

**-Minor COMMENT 1**

27/ Figure. The CT images, not PET-CT images, should be a mediastinal setting (not lung setting) for viewing of LN.

-REPLY to comment 1: Thank you for your advice. We collected all Figures as follows;

**FIGURE 2.**

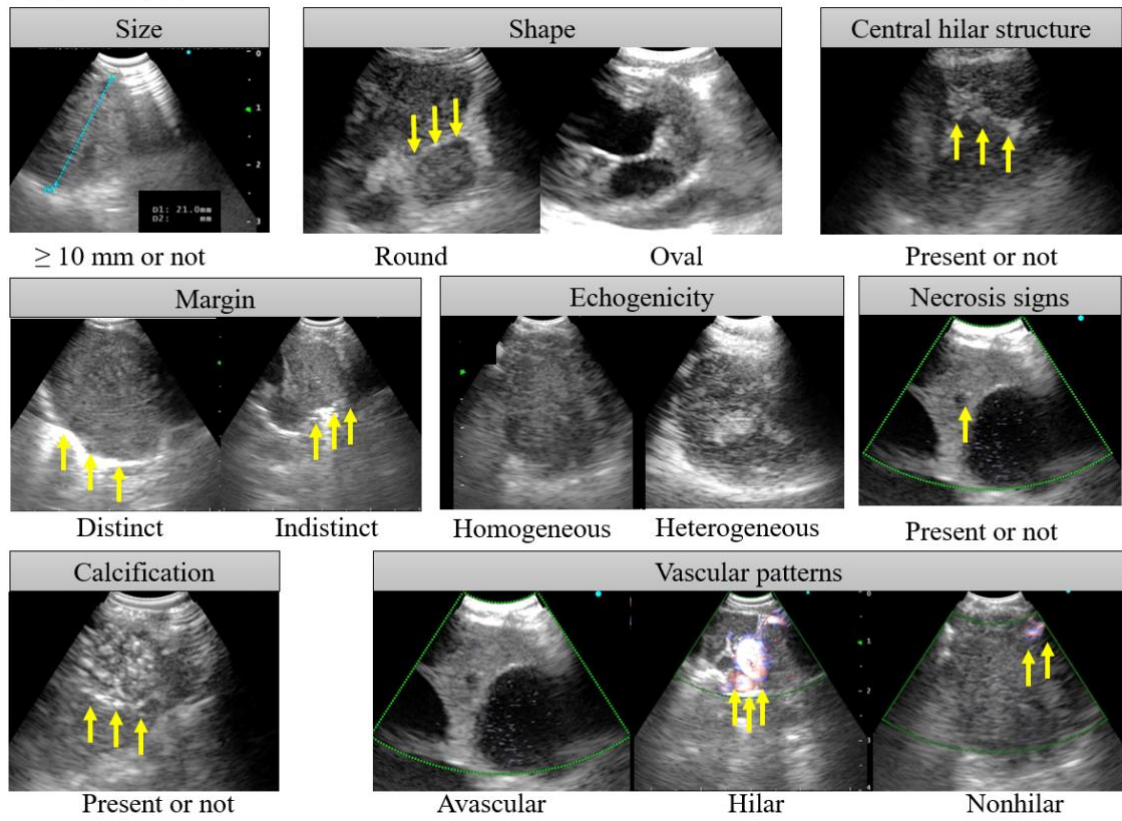


**-COMMENT 2**

28/ Figure. The quality of EBUS figures is poor. Please make it more high resolution and High quality.

-REPLY to comment 2: Thank you for your advice. We collected all Figures as follows;

**FIGURE 3.**



**-COMMENT 3**

22/ Table 1 What is the “Brinkman index”? Maybe it is a smoking related parameter. Readers want more familiar term like “pack years”.

-REPLY to comment 3: Thank you for your advice. We collected Tables as follows;

**TABLE 1. Patient characteristics**

Variable	LN metastasis (-) n = 79 (%)	LN metastasis (+) n = 25 (%)	p-value
Age, years	25 – 86 (72.2 ± 9.0)	49 – 82 (67.6 ± 9.0)	0.03
Sex, male	49 (62.0)	19 (76.0)	< 0.01
Any smoking history	58 (73.4)	20 (80.0)	0.51
Smoking index (pack-years)	0 – 172 (40.5 ± 35.5)	0 – 2500 (47.0 ± 37.3)	0.44
Lung cancer histology			0.61
Adenocarcinoma	52 (65.8)	16 (64.0)	
Squamous cell carcinoma	12 (15.2)	6 (24.0)	
Others	15 (19.0)	3 (12.0)	
Pathology stage*			< 0.01
0	3 (3.8)	0 (0)	
I	46 (58.2)	0 (0)	
II	17 (21.5)	2 (8.0)	
III	13 (16.5)	23 (92.0)	

Values are range (average ± standard deviation) or n (%).

\*based on the eighth edition of the TNM Classification of Malignant Tumors.

LN = Lymph node

#### **-COMMENT 4**

3/49 "were assessed." should read "were retrospectively assesses"

-REPLY to comment 4: Thank you for your advice. We collected the sentence as follows; From January 2014 to December 2019, a total of 147 lymph nodes from 104 patients with lung cancer, who underwent preoperative EBUS and FDG-positron emission tomography / computed tomography followed by surgery were retrospectively assesses. (page 4, line 50-51)

#### **-COMMENT 5**

5/82-85 The guideline authors quoted advocate "No mediastinal LN Bx like EBUSTBNA when peripheral cT1N0M0". However authors wrote and described conversely.

-REPLY to comment 3: Thank you for your advice. What we wanted to describe is that we performed a preoperative lymph node biopsy for some small lymph nodes to diagnose accurately. We collected the sentence as follows; In accordance with the American College of Chest Physicians guidelines on nodal staging, additional lymph node biopsy has become increasingly accepted in patients with a radiologically normal mediastinum to evaluate accurate stagings. (page 6, line 84-87)

#### **-COMMENT 6**

6/94 "matting" what is it stand for? "inhomogeneous nature"? Please describe. Readers cannot read all referenced papers.

-REPLY to comment 6: Thank you for your advice. We edited the texts as follows;

A simplified approach of using at least 2 of the 4 predictive factors, which includes round shape, absence of a central hilar structure, presence of matting and nonhilar vascular pattern perfusion may assist in the prediction of lymph node metastasis. The reason is that metastatic nodes always tend to be larger, round, having no visible hilum<sup>7</sup>. In addition, it was reported that matting of the LN is a sign of malignancy<sup>7</sup>, which suggests the extracapsular spread of malignancy. (page 7, line 96-102)

#### **-COMMENT 7**

6/98 Same comment as like the above: Please describe shortly (short axis 10cm, roundness, distinct margin, heterogeneous, CHS-, CNS+) Readers cannot read all referenced papers.

-REPLY to comment 7: Thank you for your advice. We edited the texts as follows;

A simplified approach of using at least 2 of the 4 predictive factors, which includes round shape, absence of a central hilar structure, presence of matting and nonhilar vascular pattern perfusion may assist in the prediction of lymph node metastasis. The reason is that metastatic nodes always tend to be larger, round, having no visible hilum<sup>7</sup>. In addition, it was reported that matting of the LN is a sign of malignancy<sup>7</sup>, which suggests the extracapsular spread of malignancy. (page 7, line 96-102)

#### **-COMMENT 8**

7/125 IRB number is needed.

-REPLY to comment 8: Thank you for your advice. We added IRB number to the sentence.

#### **-COMMENT 9**

8/145 figure 2 □ figure 3. You'd better to change the order of figures.

-REPLY to comment 9: Thank you for your advice. We collected the sentence as follows; The lymph nodes were characterized based on EBUS sonographic images, including gray scale and power Doppler; the characteristics analyzed were as follows: (1) size, short axis;

(2) shape, round or oval; (3) margin, indistinct or distinct; (4) central hilar structure, presence or absence; (5) echogenicity, homogeneous or heterogeneous; (6) necrosis signs, present or absent; (7) calcification, presence or absence; and (8) vascular patterns, avascular, hilar perfusion, and nonhilar perfusion. Representative B-mode imaging features are shown in Figure 3. (page 11, line 150-157)

**-COMMENT 10**

12/200 univariate  multivariate

-REPLY to comment 10: Thank you for your advice. We collected the sentence as follows;

In addition, size ( $p = 0.03$ ), round shape ( $p < 0.001$ ), absence of a central hilar structure ( $p = 0.01$ ), and LN-SUVmax ( $p = 0.02$ ) were independent factors on multivariate analysis for lymph node metastasis (Table 3). (page 14, line 215-218)

**-COMMENT 11**

14/245-253 In terms of EBUS's malignancy prediction, I agree with your opinion that roundness and more than 10mm are important, but inhomogeneous echogenicity and margin distinctness are not good predictor. I think that inhomogeneous/homogeneous and distinct/indistinct are pretty subjective to examiner, so objective prediction of malignancy with these parameters is not precise. If possible, you are encouraged to find out if there are similar research results to you and quote them in the manuscript.

-REPLY to comment 11: Thank you for your advice. We also think these factors are subjective to examiner. But previous report included these factors for predicting lymph node metastasis. In our study, as the previous report, these factors are not associated with lymph node metastasis. We repeat these explanations in the limitation section. We collected the limitations as follows;

Third, subjective interpretation of the EBUS images was inevitable. For example, homogeneous and margin distinct are particularly likely to be objective evaluations. To reduce these bias, the final characteristics of the EBUS findings were determined based on the agreement of 2 sonologists to whom the pathology results were not disclosed. (page 21, line 310-314)

**-COMMENT 12**

15/269 surgery  biopsy like EBUS-TBNA or surgery

-REPLY to comment 12: Thank you for your advice. We collected the sentence as follows;

In this case, it was difficult to obtain an adequate diagnosis by sonographic features and LN-SUVmax, and biopsy like EBUS-TBNA or surgery was required to determine the diagnosis. (page 20, line 289-291)

### **# Reviewer B**

Congratulations for the authors. The article has shown important information regard the utility of EBUDS and LN-SUVmax for the diagnosis of LNM.

I have suggested some minor revisions.

#### **-COMMENT 1**

line 59: the number "10" should be separated form "mm".

-REPLY to comment 1: Thank you for your advice. We collected the sentence as follows;

The optimal cutoff value for lymph node size and LN-SUVmax were 10 mm and 6.00, respectively. (page 5, line 60-61)

#### **-COMMENT 2**

line 59-62: I don't use the word "respectively" so much....try to rewrite the phrase with a different structure to better express the results.

-REPLY to comment 2: Thank you for your advice. We collected the sentence as follows;

The optimal cutoff value for lymph node size and LN-SUVmax were 10 mm and 6.00, respectively. By combining of the 2 modalities, we obtained the results with sensitivity of 76.9%, specificity of 95.1% and accuracy of 93.2%. (page 5, line 60-63)

#### **-COMMENT 3**

Line 82-85: The sentence regarding LN biopsy for tumor < 3 cm is not correct. The guideline cited says "4.4.8.1. For patients with a peripheral clinical stage IA tumor (negative nodal involvement by CT and PET), it is suggested that invasive pre- operative



evaluation of the mediastinal nodes is not required (Grade 2B)."

-REPLY to comment 3: Thank you for your advice. We collected the sentence as follows;

In accordance with the American College of Chest Physicians guidelines on nodal staging, additional lymph node biopsy has become increasingly accepted in patients with a radiologically normal mediastinum to evaluate accurate stagings. (page 6, line 84-87)

#### **-COMMENT 4**

line 151: There is a "-" after the number 4. It should be corrected.

-REPLY to comment 4: Thank you for your advice. We made a mistake and collected the sentence as follows;

Unenhanced CT images of sections 2 to 4 mm thick that matched the PET images were acquired for each patient using a standard protocol. (page 11, line 163-165)

#### **-COMMENT 5**

line 358: It lacks other information about the article cited.

-REPLY to comment 4: Thank you for your advice. We collected the reference section.

#### **# Reviewer C**

##### **-COMMENT 1**

**This is an interesting study. The authors present, in a small cohort, a study looking at sonographic and PET factors predicting possible lymph node metastasis using a reference standard of surgical dissection. The findings need to be validated in a larger cohort, but if validated may allow EBUS to be performed with fewer lymph nodes sampled per procedure.**

-REPLY to comment 1: Thank you for your comment. We want to validate these findings in a larger cohort. So we plan to perform multicentral study.