

Peer review file

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Reviewer A

Comment 1: First, can you tell us more detail about the failure cases.

Reply 1: Thank you for your comments. We have presented the details of the failure cases in the table.

Table The detail of failure cases

	The 3rd case	The 9th Case	The 10th case	The 12nd case	The 13rd case	The 85th case
Learning curve Phase	I	I	I	II	II	III
Nodule size, mm	10	6	4	15	7	6
Distance from pleura, mm	15	10	4	4.9	14.18	3.8
Characteristics	GGO	GGO	Solid	GGO	GGO	Solid
Nodules location	LLL	LLL	LLL	LUL	LUL	RML
Location time,min	5	10	13	30	15	14
Pathology	MIA	AIS	Benign	MIA	MIA	MIA

RML, right middle lobe; LLL, left lower lobe; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma

Changes in the text: None.

Comment 2: Second, you only use one spot for localization via ICG. My experiences in the difficult cases, I will use two-three spots for localization and margin via ENB.

Reply 2: Thank you for your helpful suggestions. We agree that multipoint localization may be a more accurate strategy for difficult cases, such as pulmonary nodules without bronchus sign or in the upper lobes, compared with single-point localization. According to our experience for difficult cases used one spot, the nearest point to the nodule will

be marked, and then the PNs were resected according to the distance and direction from the marked point to the actual location presented in ENB system.

Changes in the text: None.

Reviewer B

Major

Comment 1. Access to pulmonary nodules through a bronchoscopy is generally easier in the lower lobe than in the upper lobe. I agree with the authors' opinion on this part. Furthermore, it could be possible to explain the increased operation time in phase II, which contains more pulmonary nodules located in the upper lobe. However, it is known that the amount of movement according to respiration is greater in the lower lobe than in the upper lobe. Therefore, in this study, the low diagnosis rate in phase I might be seen not as a lack of experience, but as a difference of pulmonary nodule characteristics. It is necessary to confirm how the learning curve appears when the location (upper vs lower lobe) of the lung nodule was adjusted.

Reply 1: Thank you for your comments. I agree with you that the amount of movement according to respiration is greater in the lower lobe than in the upper lobe. However, the success rate of localization is significantly higher in the lower lobe than in the upper lobe in phase I (77.8% v.s 50%), which indicated greater movement for the lower lobe may not influence the localization success rate. Moreover, in our study, we used the EXP (Expiratory) CT to reconstruct a virtual bronchial map from the 14th Case to reduce the influence of respiration movement.

Changes in the text: None

Comment 2: Men are generally known to have a larger diameter of bronchus than women. However, the study found that men took more time to perform the procedure than women. Please explain the opinions of the authors more clearly on this. (page 11 line 240-241).

Reply 2: Thank you for your comment. We agree with the reviewer that men are generally known to have larger diameter bronchus than women. It was also a surprising outcome to us that the men took more time to perform the ENB than women. And the

surprising outcome may be due to the small sample size of the study.

Changes in the text: None.

Comment 3. Please clarify why did you choose 14 mins to classify the easy and difficulty cases. Additional clarification is needed on the criteria for dividing easy and difficult cases.

Reply 3: Thank you for your helpful comments. We choose 14 mins to classify the easy and difficult cases according to the mean time of ENB in Phase II (14.4 mins). The learning curve Phase II represents the classical learning process with experience accumulation for the surgeon. We divided the operative time into two groups to identify other factors that affected the operative time except for the learning Phase. Therefore, the expressions of easy and difficult cases might be inaccurate. We have changed the expressions in revised manuscript.

Changes in the text: We have changed the expressions of easy and difficult cases in the revised manuscript (see lines 165-167, page 8).

Minor

Comment 1. I suggest that the authors add some figures in Fig 2 from the ENB system that they used.

Reply 1: Thank you for the suggestion. Figure 2A is the ENB system that we used. And the Legend of Figure 2A has been changed.

Changes in the text: We changed the legend of Figure 2A (see page 23, line 488).

Comment 2. The authors recommended the use of ICG rather than methylene blue based on their research experience. Was there no difference in the success rate according to the dye used for the localization? It would be nice if the authors added this information.

Reply 2: Thank you for your comments. There was no difference in the success rate between methylene blue and ICG. We recommend the ICG that does not hinder observing the lung lesion in VATS resection or jeopardize the further pathological evaluation.

Changes in the text: None.

Comment 3. In table 1 and table 2, please clarify the detailed location of the nodules such as RUL, RML, RLL, LUL, LLL.

Reply 3: Thank you for your suggestion. We have clarified the detailed location of the nodules.

Changes in the text: We illustrated the detailed location of the nodules in table 1 and table 2 (see page 21-22, table 1, and table 2).

Comment 4. In table 1, please clarify the detailed histologic results of benign and malignant nodules.

Reply 4: Thank you for your helpful suggestion. We have clarified the detailed histologic results of benign and malignant nodules in table 1.

Changes in the text: We have clarified the detailed histologic results of benign and malignant nodules in table 1 (see page 21, table 1).

Reviewer C

Comment 1. Line88: This localization technique was performed by a single thoracic surgeon. Years of the experience as a thoracic surgeon may affect the learning curve. How long have you been working for a thoracic surgeon? Moreover, how did you localize small nodules before ENB localization?

Reply 1: Thank you very much for your comments. The doctor (SB.L.) have been working in thoracic surgery for twenty years. The doctor (SB.L.) used CT-guided localization to mark pulmonary nodules before ENB localization. And he has the experience of routine bronchoscopy and not the experience of endobronchial ultrasonography (EBUS) and ENB-guided biopsy.

Changes in the text: None.

Comment 2. Line111: You used two dying materials: ICG and methylene blue. How did you select these two dye materials?

Reply 2: Thank you for your helpful comments. As we said in discussion, Although ICG and methylene blue were used in our study, we recommend the ICG dye, which

does not hinder observing the lung lesion in VATS resection or jeopardize the further pathological evaluation.

Changes in the text: None.

Comment 3. Line177: The success rate of ENB localization was increasing with the accumulation of learning experience in 3 phases (72.73%, 91.67%, and 97.62%, $p=0.049$). How many cases did you palpate the lung during VATS localization? Were all nodules removed by wedge resection except for the localization failure cases?

Reply 3: Thank you for your comments. In order to make sure surgical success, we would palpate the lung for the palpable pulmonary nodules during VATS surgery in the initial 20 cases whether ENB localization is a success or not. In the study, the nodules for localization success preferred to remove by wedge resection, and whether performed extended resection or not based on intra-operative frozen.

Changes in the text: None.

Comment 4. In our institution, we are using ENB of superDimension (Medtronic). Sometimes we encountered impossible registration cases, for example cases with past history of lung resection. Were there any cases where you couldn't finish registration process or perform ENB with other reasons?

Reply 4: Thank you very much for your helpful comments. We agree with the reviewer that some factors may be hinder the registration and operation of ENB, for example as the reviewer mentioned cases with past history of lung resection. We also encountered some cases that were difficult to perform ENB, such as very elderly patients and bronchiectasia with bleeding risk.

Changes in the text: None.

Reviewer D

Comment 1. Authors performed CUSUM analysis with operation time. However, as authors mentioned in discussion, operation time cannot explain entire learning curve of ENB because it is affected not only by the skill but also by the location of lesion and anatomy of patients.

Adding CUSUM analysis with marking success might give more information about learning curve of ENB. 2 dimensional (operation time and success rate) analysis would provide more accurate information. Thus, I would like to recommend adding CUSUM analysis with success rate.

Reply 1: Thank you for your comments. We have added the CUSUM analysis of locating success in the revised manuscript. The outcome indicated that the success rate had a significant improvement after the 31st case.

Changes in the text: We have added the CUSUM analysis of locating success in the revised manuscript (see Figure 3C).

Comment 2. Authors defined operation time as a period from the beginning of registration (construction of virtual trachea) to marking. In patients with multiple nodules, usually registration is performed only once and time for registration would not be included in second and third nodules. How authors adjusted this problem?

Reply 2: Thank you for your comments. It was also a difficult question for us when we analyze the learning curve. In the study, the registration time was added to each nodule for multiple nodules to adjust this problem.

Changes in the text: None.

Comment 3. Previous experience with bronchoscopy would affect the learning curve of ENB. This should mention this in the discussion section.

Reply 3: Thank you very much for your suggestion. We agree with the reviewer that previous experience with bronchoscopy might affect the learning curve of ENB. And we have added the statement in our limitations.

Changes in the text: We have added the statement, the surgeon with the experience of routine bronchoscopy might affect the learning curve of ENB, in our limitations (see lines 323-324, page 15)

Comment 4. Why 14 minute was chosen as a cut-off value for easy and difficult case? Authors should present the rationale in the method section.

Reply 4: Thank you for your comments. We choose 14mins to classify the easy and difficult cases according to the mean time of ENB in Phase II (14.4 mins). The learning curve Phase II represents the classical learning process with experience accumulation

for the surgeon. We have added the statements in revised manuscript.

Changes in the text: We have added the statements, and changed the expressions of easy and difficult cases in the revised manuscript (see lines 165-167, page 8).

Comment 5. Comparing effect of phase between easy and difficult case is not reasonable. A case cannot be an easy one or difficult one by the timing of procedure.

Reply 5: Thank you for your helpful comments sincerely. We agree with the reviewer that a case cannot be an easy one or difficult one by the timing of procedure. In the study, we divided the operative time into two groups to identify other factors that affected the operative time except for the learning Phase. Therefore, the expressions of easy and difficult cases might be inaccurate. We have changed the expressions in the revised manuscript.

Changes in the text: We have changed the expressions of easy and difficult cases in the revised manuscript (see lines 165-167, page 8).

Comment 6. Brand names (proprietary name) and the name and location (city, state, country) of the manufacturer in brackets should be presented when the equipment is first mentioned in the text.

Reply 6: Thank you very much for your comments. We have changed the Brand names of ENB.

Changes in the text: We have changed the expression of ENB (see line 138, page 7).