Peer Review File

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Reviewer A

The authors are to be congratulated for an interesting study looking at the real-world applicability of using intraoperative CT scans for ENB bronchoscopy to help reduce CT to body divergence. Overall it is a well written paper that follows the IDEAL framework and demonstrates their process. A few minor comments. The lesions were primarily in the upper lobe where atelectasis is not as big of an issue (only 24% in the lower lobes). It would be good to see the diagnostic accuracy defined based on the location of the lesion. Second, the authors did not use radial probe which is a standard adjunct when using ENB or RAB. It would be interesting to see the effect that its use may have had the outcomes. Third, can the authors comment on whether or not the use of an intraoperative CT scan reduced the need for a preoperative scan? If it did not then they were potentially subjected to more radiation than needed. Finally, it was not mentioned if all the procedures were done by one operator or by several. This also limits the ability to figure out if it has real world applicability if it was all done by one operator.

Comment 1: A few minor comments. The lesions were primarily in the upper lobe where atelectasis is not as big of an issue (only 24% in the lower lobes). It would be good to see the diagnostic accuracy defined based on the location of the lesion.

Reply 1: Thanks for your reminding. Because this is a small sample IDEAL Stage 2a (developmental phase) study. Ther were only 24% of the nodules located in the lower lobe in this project. Considering that many factors can affect the final diagnostic accuracy, it is difficult to complete a multivariate analysis with the current amount of data. Thus, this analysis was not conducted. And we have initiated a registered clinical trial to address this issue.

Changes in the text: None.

Comment 2: Second, the authors did not use radial probe which is a standard adjunct when using ENB or RAB. It would be interesting to see the effect that its use may have had the outcomes.

Reply 2: R-EBUS can help determine whether the probe has reached the target through ultrasound, but this is a virtual display method that may have some errors. Although radial probe is currently commonly used method in ENB/RAB research, its accuracy is only about 70% (Sryma, P B et al. “Efficacy of Radial Endobronchial Ultrasound (R-EBUS) guided transbronchial cryobiopsy for peripheral pulmonary lesions (PPL...s): A systematic review and meta-analysis.” Pulmonology vol. 29,1 (2023): 50-64. doi:10.1016/j.pulmoe.2020.12.006).

In this study, we can visually determine whether the probe has reached the target through CT imaging, which is a more intuitive and accurate method of judgment. Therefore, R-EBUS was not used in this study.

Changes in the text: None.

Comment 3: Third, can the authors comment on whether or not the use of an intraoperative CT scan reduced the need for a preoperative scan? If it did not then they were potentially subjected to more radiation than needed.
Reply 3: In this study, all patients underwent a chest CT scan to determine if the nodules have increased in size or solid components. And this is crucial for preliminarily determining whether the nodule is malignant. Thus, we believe that preoperative CT scan cannot be omitted. We also mentioned in the article that our method will increase the radiation exposure of patients to a certain extent. This is also one of the shortcomings of this study. And we are trying to develop an AI-based predictive algorithm using preoperative CT data to potentially eliminate intraoperative scanning. (see section Discussion, the last paragraph, Page 18, line 366-370)
Changes in the text: None.

Comment 4: Finally, it was not mentioned if all the procedures were done by one operator or by several. This also limits the ability to figure out if it has real world applicability if it was all done by one operator.
Reply 4: In this study, the same operator completed all the procedures. (see section Method-Preparation and prior experience, Page 6, line 103-109)
This is a small sample study, and we hope to reduce unnecessary interference factors to validate the effectiveness of this new method and avoid potential bias caused by operators. Therefore, in this study, all procedures were completed by the same doctor. Through this study, the accuracy and safety of this method have been verified. We will conduct a multicenter study in the next phase of research to further validate the generalizability of our technology.
Considering the issue you raised, the widespread applicability of this technology is currently insufficient. We have added an explanation about this point in the limitations section of the article. (see section Discussion, Page 18, line 371-373)
Changes in the text: Third, in this study, all the procedures were completed by the same operator. The widespread applicability of this technology is currently insufficient.

Reviewer B

1-Page 2, line 32-33, replace references (2-4) with this reference that combined major studies for ENB (Folch EE, Labarca G, Ospina-Delgado D, Kheir F, Majid A, Khandhar SJ, Mehta HJ, Jantz MA, Fernandez-Bussy S. Sensitivity and Safety of Electromagnetic Navigation Bronchoscopy for Lung Cancer Diagnosis: Systematic Review and Meta-analysis. Chest. 2020 Oct;158(4):1753-1769)
2-Authors should specify lung navigation ventilation protocol used and not only reference that
3-Main concern is that authors used the lung navigation ventilation protocol instead of the well-studied VESPA protocol (Salahuddin M, Sarkiss M, Sagar AS, Vlahos I, Chang CH, Shah A, Sabath BF, Lin J, Song J, Moon T, Norman PH, Eapen GA, Grosu HB, Ost DE, Jimenez CA, Chintalapani G, Casal RF. Ventilatory Strategy to Prevent Atelectasis During Bronchoscopy Under General Anesthesia: A Multicenter Randomized Controlled Trial (Ventilatory Strategy to Prevent Atelectasis -VESPA- Trial). Chest. 2022 Dec;162(6):1393-1401). They modified a protocol that is not commonly used in clinical practice rather than the most used protocol. Authors need to justify what they preferred such protocol over the other commonly used one.

4-Clarify what exactly you did for the adjustment of Recruitment Technique of gradual incremental-decremental approach based on lung-protective ventilation principles employing lower pressure thresholds instead of asking reader/reviewer to go back to your reference

Comment 1: Page 2, line 32-33, replace references (2-4) with this reference that combined major studies for ENB (Folch EE, Labarca G, Ospina-Delgado D, Kheir F, Majid A, Khandhar SJ, Mehta HJ, Jantz MA, Fernandez-Bussy S. Sensitivity and Safety of Electromagnetic Navigation Bronchoscopy for Lung Cancer Diagnosis: Systematic Review and Meta-analysis. Chest. 2020 Oct;158(4):1753-1769)

Reply 1: Thanks for your advice. We have replaced references (2-4) with the article you suggested.

Changes in the text: However, its diagnostic yield remains suboptimal, with the largest multicenter prospective studies reporting rates of only 77% for peripheral pulmonary lesions (2).

Comment 2: Authors should specify lung navigation ventilation protocol used and not only reference that.

Reply 2: We apologize for not providing a detailed description of LNVP. Now we have added a picture for supplementary explanation. Moreover, we have also added text in the main text to explain this part. (see Figure 2 below, section Result, Page 9-10, line 182-200)

Changes in the text: After case 7, milder modified recruitment maneuver mode was applied (increment-decrement recruitment maneuver, Figure 2). We selected the pressure controlled ventilation (PCV) mode. Meanwhile, we set inspiratory pressure at 10–15 cm H2O and positive end-expiratory pressure (PEEP) at 5 cm H2O. Then we increased the PEEP by 5 cmH2O each time until it reached 35 cm H2O, and then decreased the PEEP by 5 cm H2O each time until it reached 5 cm H2O. Every PEEP changing sustained for five complete respiratory processes.

In order to maintain pulmonary in inflation state while following the principle of lung ventilation protection. We set inspiratory pressure to maintain the end expiratory carbon dioxide pressure at 35-45 mmHg (usually 10–15 cm H_2O) and peak airway pressure to 30 cm H_2O.

And previous study on VESPA (another ventilatory strategy to prevent atelectasis) have shown that the dorsal and posterior basal segments often have a higher incidence of atelectasis. Considering the impact of excessively high PEEP on the circulatory system, excessive PEEP setting in LNVP were abandoned. Referring to LNVP and VESPA, we modified the ventilation strategy by reducing the PEEP level. For pulmonary nodules within 1 cm of the subpleura in the dorsal and posterior basal segments, the PEEP was set at 10–15 cm H_2O. For other pulmonary nodules, the PEEP was set at 5–8 cm H_2O. The lowest PEEP levels were selected as long as atelectasis did not affect the identification of pulmonary nodules in the intraoperative CT data.

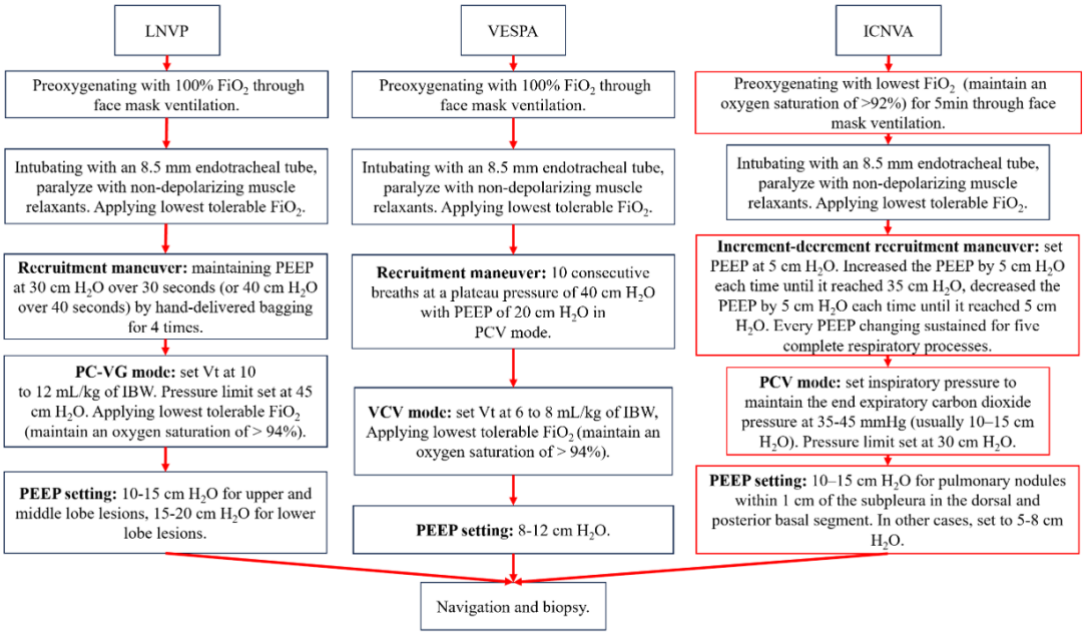


Figure 2 Flow charts demonstrating the LNVP (left), VESPA (middle) and ICNVA (right) ventilation strategies
LNVP, lung navigation ventilation protocol; VESPA, ventilatory strategy to prevent atelectasis; ICNVA, intraprocedural CT guided Navigation with Ventilatory Strategy for Atelectasis; FiO2, fraction of inspiration O2; PEEP, positive end expiratory pressure; IBW, ideal body weight; PC-VG, pressure control volume guaranteed; VCV, volume controlled ventilation; PCV, pressure controlled ventilation; Vt, tidal volume.

Comment 3: Main concern is that authors used the lung navigation ventilation protocol instead of the well-studied VESPA protocol (Salahuddin M, Sarkiss M, Sagar AS, Vlahos I, Chang CH, Shah A, Sabath BF, Lin J, Song J, Moon T, Norman PH, Eapen GA, Grosu HB, Ost DE, Jimenez CA, Chintalapani G, Casal RF. Ventilatory Strategy to Prevent Atelectasis During Bronchoscopy Under General Anesthesia: A Multicenter Randomized Controlled Trial (Ventilatory Strategy to Prevent Atelectasis -VESPA- Trial). Chest. 2022 Dec;162(6):1393-1401). They modified a protocol that is not commonly used in clinical practice rather than the most used protocol. Authors need to justify what they preferred such protocol over the other commonly used one.
Reply 3: We are sorry for not explaining this clearly, which may have caused confusion for the readers. Indeed, we referred to both LNVP and VESPA, and made certain improvements. Now we have added more explanations. (see Figure 2, section Result, Page 9-10, line 182-200)
Changes in the text: Same to reply 2.

Comment 4: Clarify what exactly you did for the adjustment of Recruitment Technique of gradual incremental-decremental approach based on lung-protective ventilation principles employing lower pressure thresholds instead of asking reader/reviewer to go back to your reference

Reply 4: We apologize for not providing a detailed description of incremental-decremental approach. Now we have added more explanation. (see Figure 2, section Result, Page 9-10, line 182-187)
Changes in the text: After case 7, milder modified recruitment maneuver mode was applied (increment-decrement recruitment maneuver, Figure 2). We selected the pressure controlled ventilation (PCV) mode. Meanwhile, we set inspiratory pressure at 10–15 cm H_2O and positive end-expiratory pressure (PEEP) at 5 cm H_2O. Then we increased the PEEP by 5 cmH2O each time until it reached 35 cm H_2O, and then decreased the PEEP by 5 cm H_2O each time until it reached 5 cm H_2O. Every PEEP changing sustained for five complete respiratory processes.

Reviewer C

There are a few errors when discussing technology which would need to be addressed prior to publication. First, Ion is not an ENB platform. Second, it would be beneficial to the reader to know the Superdimension software version (if post-illumisite). Third, when an EBUS needle is described, what needle is being described? Is this the periview flex, another needle?
While the manuscript outlines changes in PEEP/APL valve, it would be beneficial to the reader to have additional details on the ventilation strategies used such as goal TV, FiO2, use of breath holds, and breath hold duration.
The data on procedures/patients would be helpful to include additional data on patient comorbidities (COPD) and the follow-up on the benign lesions. If the lesion size/location changed as the technique involved, it would be beneficial to describe any changes in lesion/patient characteristics.
The correct diagnosis n does not match the post-op path. Would include the prelim path from the OR and postoperative path for comparison.
Additionally, the manuscript could be written to better narrate the evolution of the procedure over time. It is a novel technique being employed with older technology so would be beneficial to outline how the imaging technology is used to overcome CTBD with the platform.

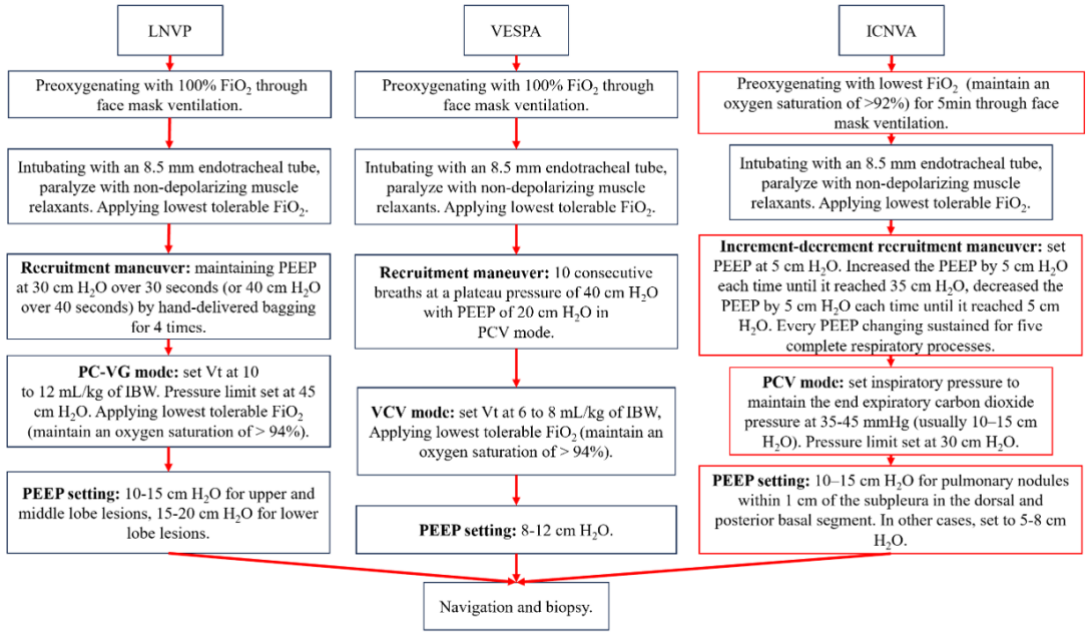
Comment 1: Ion is not an ENB platform.
Reply 1: As you said, Ion™ is not an ENB platform, but an endoluminal robotic bronchoscopy platform (see section Discussion, Page 17, line 339-342: **Since 2018, RAB has emerged, including the Food and Drug Administration-approved MonarchTM Platform by Auris Health (Redwood City, CA, USA) and the IonTM endoluminal robotic bronchoscopy platform by Intuitive Surgical (Sunnyvale, CA, USA)**). We did not describe Ion™ as an ENB platform.
Changes in the text: None.

Comment 2: it would be beneficial to the reader to know the Superdimension software version (if post-illumisite).
Reply 2: Thanks for your advice. In this study, the Superdimension software version is Version 7th. And we add the version number in article. (see section Method- Preparation and prior experience, Page 6, line 105-106)

Changes in the text: After training supplied by MedtronicTM, our institution authorized one doctor to use the SuperDimension navigation system (Version 7.0th, Medtronic, Minneapolis, Minnesota) for ENB biopsy of peripheral lung lesions beginning in September 2018.

Comment 3: when an EBUS needle is described, what needle is being described? Is this the periview flex, another needle?
Reply 3: We apologize for not providing a detailed description of the EBUS needle used in the study. Now we have added more description. (see section Result, Page 11, line 218).
This is a needle with limited flexibility. We believe that the poor flexibility limits the precise reach of the puncture site, thereby affecting the accuracy of ENB diagnosis. We have also described this in the article. (see section Result, Page 11-12, line222-227: **The EBUS needle's limited flexibility restricted puncture tunnel creation to second-level bronchial openings, often complicating vascular avoidance—particularly for challenging locations (e.g., posterior segment lesions). In two cases, this limitation prevented the probe from reaching within 1 cm of the target nodule.**)
Changes in the text: Beginning with Case 18, for nodules lacking direct bronchial connections, we employed an EBUS puncture needle (NA-201SX-4021, Olympus, Tokyo, Japan) to create a working tunnel at the opening of segmental bronchi.

Comment 4: While the manuscript outlines changes in PEEP/APL valve, it would be beneficial to the reader to have additional details on the ventilation strategies used such as goal TV, FiO2, use of breath holds, and breath hold duration.
Reply 4: Thanks for your advice. Now we have added two Figure2, 4 for description. (see section Method, Page 8, line 143-155); Moreover, we have also added text in the main text to explain this part. (section Result, Page 9-10, line 182-200)
Changes in the text: After case 7, milder modified recruitment maneuver mode was applied (increment-decrement recruitment maneuver, Figure 2). We selected the pressure controlled ventilation (PCV) mode. Meanwhile, we set inspiratory pressure at 10–15 cm H2O and positive end-expiratory pressure (PEEP) at 5 cm H2O. Then we increased the PEEP by 5 cmH2O each time until it reached 35 cm H2O, and then decreased the PEEP by 5 cm H2O each time until it reached 5 cm H2O. Every PEEP changing sustained for five complete respiratory processes.
In order to maintain pulmonary in inflation state while following the principle of lung ventilation protection. We set inspiratory pressure to maintain the end expiratory carbon dioxide pressure at 35-45 mmHg (usually 10–15 cm H_2O) and peak airway pressure to 30 cm H_2O.
And previous study on VESPA (another ventilatory strategy to prevent atelectasis) have shown that the dorsal and posterior basal segments often have a higher incidence of atelectasis. Considering the impact of excessively high PEEP on the circulatory system, excessive PEEP setting in LNVP were abandoned. Referring to LNVP and VESPA, we modified the ventilation strategy by reducing the PEEP level. For pulmonary nodules within 1 cm of the subpleura in the dorsal and posterior basal segments, the PEEP was set at 10–15 cm H_2O. For other pulmonary nodules, the PEEP was set at 5–8 cm H_2O. The lowest PEEP levels were selected as long as atelectasis did not affect the identification of pulmonary nodules in the intraoperative CT data.



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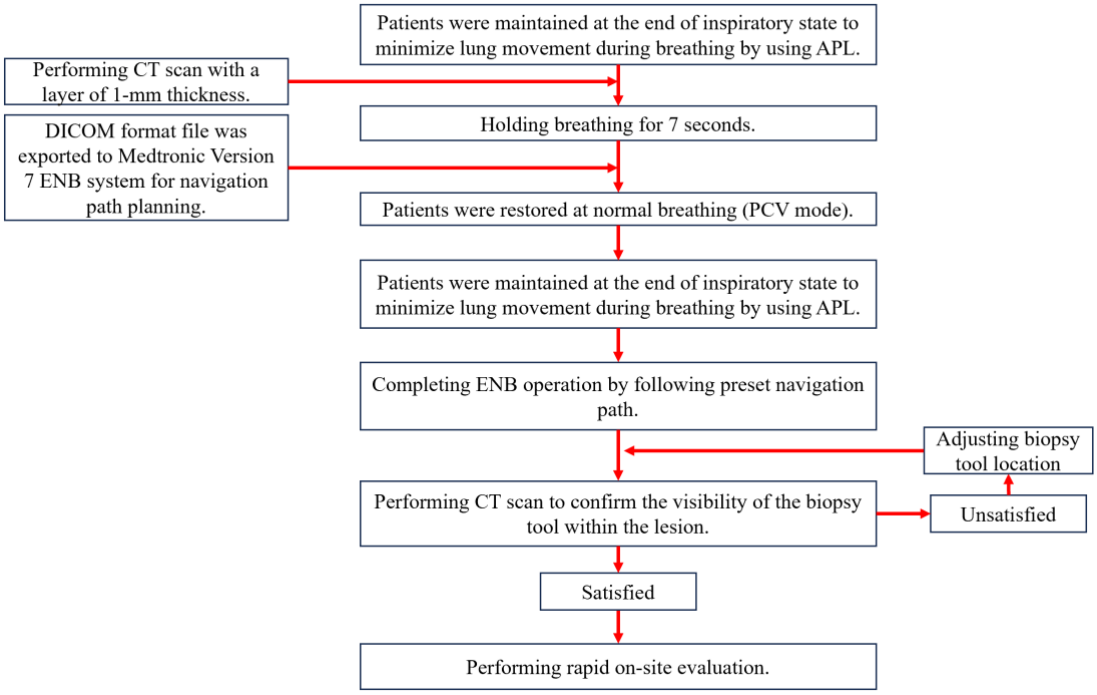

Figure 4 Flow charts demonstrating the ENB and biopsy procedures

APL, adjustable pressure limiting; CT, computed tomography; DICOM, Digital Imaging and Communications in Medicine, PCV, pressure controlled ventilation.

Comment 5: The data on procedures/patients would be helpful to include additional data on patient comorbidities (COPD) and the follow-up on the benign lesions. If the lesion size/location changed as the technique involved, it would be beneficial to describe any changes in lesion/patient characteristics.

Reply 5: We described the merger of underlying diseases. We described the patient's comorbidities in Tale 2, and there were no patients with COPD.

In this study, all nodules underwent resection surgery. Thus, we cannot give you any description on the changes of lesion/patient characteristics after technique involved. Based on your suggestion, we have provided additional explanations for this section. (see section Method, Page 8, line 156-159)

Changes in the text: After ENB operation and rapid on-site evaluation, we informed the patients' immediate family members of ROSE results, and all of them signed and agreed to the nodule resection surgery. Thus, in the end, we localized pulmonary lesions by injecting indocyanine green under the guidance of ENB and resected the lesions under the fluorescence thoracoscopy.

Comment 6: The correct diagnosis n does not match the post-op path. Would include the prelim path from the OR and postoperative path for comparison.

Reply 6: Thank you for your advice. We add the ROSE results and postoperative pathology and checked that the data is correct. (see Table 4)

Changes in the text:

Table 4 Comparison between rapid on-site evaluation and postoperative pathology

Patient	Case1-7		Case8-17		Case18-21		Case22-29		Case30-50	
	ROSE	Post-path	ROSE	Post-path	ROSE	Post-path	ROSE	Post-path	ROSE	Post-path
1	M	AIS	M	AIS	M	AIS	M	AIS	M	MIA
2	M	IA	M	MIA	M	MIA	M	AIS	M	MIA
3	M	IA	M	MIA	M	IA	M	IA	M	IA
4	B	B	M	AIS	M	AIS	M	MIA	M	MIA
5	M	MIA	B	MIA	/	/	M	AIS	M	MIA
6	B	AIS	B	MIA	/	/	M	MIA	M	AIS
7	M	AIS	M	MIA	/	/	M	MIA	M	MIA
8	/	/	M	MIA	/	/	M	AIS	M	MIA
9	/	/	M	MIA	/	/	/	/	B	AIS
10	/	/	M	AIS	/	/	/	/	M	MIA
11	/	/	/	/	/	/	/	/	M	MIA
12	/	/	/	/	/	/	/	/	M	MIA
13	/	/	/	/	/	/	/	/	M	MIA
14	/	/	/	/	/	/	/	/	M	MIA
15	/	/	/	/	/	/	/	/	M	AIS
16	/	/	/	/	/	/	/	/	M	AIS
17	/	/	/	/	/	/	/	/	B	B
18	/	/	/	/	/	/	/	/	M	AIS
19	/	/	/	/	/	/	/	/	M	MIA
20	/	/	/	/	/	/	/	/	M	MIA
21	/	/	/	/	/	/	/	/	M	AIS

ROSE, rapid on-site evaluation; pose-path, postoperative pathology; B, benign; M, malignant; AIS, adenocarcinoma in situ; MIA, microinvasive adenocarcinoma; IA, invasive adenocarcinoma.

Comment 7: Additionally, the manuscript could be written to better narrate the evolution of the procedure over time. It is a novel technique being employed with older technology so would be beneficial to outline how the imaging technology is used to overcome CTBD with the platform.

Reply 7: We described the evolution of the procedure over time in section Result. For the convenience of readers' understanding, we have made some language modifications and added two diagrams.

Changes in the text: Same to **reply 4**.