Peer Review File

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Reviewer A

This retrospective single-center study explores the safety and anxiety/depression related to two different methods of pulmonary nodule localization followed by surgical VATS resection. The two methods/groups are compared on numerous variables – some more sounds and relevant that others.

I respectfully do not think this manuscript in its current form is suitable for publication in JTD or any other indexed journal. I hope the authors will find the following comments useful to revise/re-write the manuscript.

1) English language and grammar

- Overall, the paper is not particularly well written, which to some extend makes it cumbersome to read and sometimes hard to understand (it is like some of the paragraphs or sentences have lost their meaning after they have been through google translate or Chat GPT?). This also includes the sudden use of foreign words not normally used in medical academic writing - example line 183: decoupling?? Not sure I'm familiar with this wording/categorization of complications – please explain and use standard nomenclature.

- Proof reading by a native English-speaking person before next submission may be useful and advisable.

- There is clearly a biased tone in favor of the ENB-guided localization method, which is unnecessary and distracting – let the results speak for themselves.

Reply:

Thank you very much for your feedback on the language and grammar aspects of our manuscript. We have carefully reviewed the language issues in the paper and made modifications to enhance readability and understanding. We apologize for any shortcomings in the expression of certain content, as none of the authors are native English speakers.

Prior to this submission, we have made revisions to the language in the manuscript, using red text and blue strikethrough to indicate the changes. However, if you and the journal feel that professional language editing is necessary, please let us know. We would be grateful for your guidance in this regard, and we will make every effort to complete the process accordingly.

Regarding the term 'decoupling' we referred to its usage in the referenced paper (Reference 23) before using it in our manuscript. In this context, the term refers to the displacement of the localization hook-wire. After unanimous discussion among all authors, we have opted to substitute it with "Hook-wire migration" a usage derived from relevant literature (Vollmer, Ivan et al. "Preoperative localization of lung nodules: a comparative analysis of hook-wire and radio-guided procedures." Journal of thoracic disease vol. 14,11 (2022): 4329-4340. doi:10.21037/jtd-22-552) published in JTD, aiming to enhance reader comprehension and maintain consistency with medical academic writing.

Once again, we sincerely appreciate your valuable input and consideration. If you have any further suggestions or concerns, please do not hesitate to let us know.

Changes in the text:

We have opted to substitute the term ‘decoupling’ with " Hook-wire migration " (page 10 section1, table2).

We have made modifications to the language in the manuscript as per the request, using **red text** and **blue strikethrough** to indicate changes.

2) Design, methods, and objectives

The study has significant methodical issues, and the objectives are muddy and unclear – as a reader you are missing a common tread from the introduction to discussion/conclusion.

- Selection – explain the specific criteria that were applied when deciding whether the patient should undergo ENB or CT guided hook localization. Specific nodule or patient characteristic – like position in the lung; +/- bronchus sign etc.?

- Line 108: “…after professional assessment” – very vague and what do the authors specifically mean by that? After/based on a MDTA decision? I certainly don’t hope that any patient at any hospital in the world is scheduled for a VATS resection based on an “unprofessional assessment.”

- Is it fair to compare the complication rate and HADS score of these to localization methods based on the current design? One is done in GA and the other one in LA. The increased complication rate and anxiety/depression related to CT-guided localization done in LA must come as a huge surprise to the authors.

- Where the HADS score recorded/obtained prospectively? Via telephone interview or a questionnaire in writing (anonymously)?

- How is pulmonary function relevant in this context? I suspect the surgical procedures were identical in both groups.

Reply:

Dear reviewer, thank you very much for your valuable comments and suggestions on our research. We have revised the introduction and the relevant sections in response to your queries, making the research rationale and objectives of this article clearer.

1. As this article is a retrospective study, we reviewed and summarized the localization of these nodules. However, due to the varying judgment criteria among different doctors in our hospital regarding the patient's condition, nodule position, economic status, and personal choices, it is difficult to provide a specific analysis in the retrospective study. Therefore, we are unable to specify a complete and uniform standard in this article. Nevertheless, we can ensure that the localization procedures for all patients were discussed and agreed upon by the preoperative department expert committee and deemed necessary and feasible. Additionally, all patients signed informed consent forms before the interventional and surgical procedures.

2. In line 108 of the original text, we have amended that in all cases, the multidisciplinary committee of lung neoplasms unanimously decided whether preoperative localization and surgery were necessary. Thank you for your question.

3. ‘ENB is performed under general anesthesia, while CT-guided localization is carried out under local anesthesia. Therefore, comparing the incidence of complications and the HADS scores between the two procedures may be relatively unfair. The increase in the incidence of complications and anxiety/depression scores associated with CT-guided localization under general anesthesia would undoubtedly be a significant surprise for the authors.’We appreciate your raising this question, as it will contribute to the scientific rigor of our research.

At the outset of our study, similar questions were raised by members of our team. However, based on clinical practice and analysis, we have found that in the majority of hospitals worldwide, percutaneous puncture

positioning under CT guidance is performed under local anesthesia. This is due to the specific requirements of the equipment, the need for the procedure to be conducted in the CT scanning room, and the necessity for multiple CT scans to complete the puncture. Consequently, performing CT scanning and puncture positioning under general anesthesia is considered impractical in most hospitals. Similarly, it is challenging for the majority of hospitals worldwide to construct composite operating rooms equipped with CT machines and apply them for CT localization under general anesthesia.

We consider your opinion to be very important, rigorous, and valuable; however, it is difficult to implement in actual practical applications. We believe that the CT-guided localization method described in this study, as well as the ENB localization method, are both operational in the majority of hospitals worldwide or are being implemented. Therefore, comparative studies under these conditions can assist clinical decision-making and align more closely with clinical practice. We have added relevant descriptions of this content in the discussion section of the article to facilitate a better understanding for the readers.

I hope the revised response meets your needs. If you require further assistance, feel free to ask.

4. In accordance with our departmental regulations, we administer patient satisfaction surveys, including the HADS scoring scale, to the majority of patients upon admission, discharge, and during postoperative follow-ups. This protocol enables our department to implement improvements and effectively serve a greater number of patients. All surveys are conducted anonymously through online questionnaires or with the assistance of medical staff, and patient consent is obtained verbally or through self-completion of the forms.

5. Thank you for raising this question. In our study, we compared the postoperative lung function following VATS surgery using two different localization methods. The surgical records and postoperative pathological reports for all patients confirmed the effective resection of nodules. However, we were unable to determine the impact of the extent of lung resection on postoperative outcomes for the patients. Therefore, we collected pre- and postoperative lung function data for comparison. While different localization methods do not alter the surgical approach for the same nodules, we cannot assess whether the different localization methods may influence the intraoperative resection range or have an impact on postoperative lung function for the patients. Therefore, we have conducted research and analysis on this in this manuscript.

Changes in the text:

In response to the reviewer's request, we have made detailed revisions to the "Methods" section in the manuscript, indicating changes using red text and blue strikethrough. (page 6-8).

3) Results

- Tables are not used properly – no need to write the same data in text, which are already displayed in the tables.

- Table 1: For better comparison of the groups, please also display frequencies with a percentage instead of just absolute numbers (CT guided has twice as many patients)

- Table 2: Please add total time for both techniques?

- Figures 1 and 2 are reversed according to the references in the text.

- What happened in those cases where the localization failed?

- The lung infiltrate/nodule was localized satisfactory in most cases 156/177 – by which criteria? When localized - why not just take a biopsy in the first place – after all 150/177 nodules proved either benign or with very low degree of malignancy. This would also enable better preoperative surgical planning.

Reply:

Thank you for the valuable feedback on the results section of our research. We will make appropriate modifications to the tables and figures based on your suggestions and ensure that the presentation of data is clearer and more complete in the revised article. However, due to the inability to retrospectively review and

record the preparation time for CT localization (including patient waiting time, preparation of materials before puncture, and physician preparation time), we did not include the total localization time in the tables. Instead, we focused on documenting the procedural time for localization. Among the patients undergoing ENB-guided localization, there were 5 cases of failure due to inability to reach the designated location. In the CT-guided localization group, there were 6 cases of failure due to needle-hook position deviation. After failed localization, the operating surgeon relied on preoperative CT scans, personal experience, and surface palpation of the lungs to complete the surgery. Intraoperative rapid pathology confirmed successful removal of the nodules in all cases of failed localization. In this study, if the surgeon can quickly locate and remove the nodule from the localization point during the operation, it is considered successful localization. Out of the 156 localized cases in this study, all nodules were confirmed to be effectively removed through tactile examination or rapid frozen section pathology in the resected specimens. Due to the lower accuracy of pathological biopsy compared to surgical resection for nodules smaller than 2cm, we have opted for direct surgical intervention rather than needle biopsy.

Changes in the text:

In accordance with the reviewer's feedback, we have made revisions to Table 1, Figure 1, and Figure 2. Additionally, we have diligently modified the "Results" section (page 9-12) of the manuscript as per the reviewer's request, using red text and blue strikethrough to indicate changes, in order to meet your requirements.

4) Discussion

- Line 222-247: bland review of the literature and speculations with no discussion related to the study results.

- The authors mention several limitations – e.g.: "...the results may have been affected by selection bias". I think it's fair to say that this study most certainly has significant selection bias. Furthermore, the limitations mentioned are not reflected in the interpretation of the results and final conclusion.

Reply:

Thank you for the valuable feedback from the reviewers on the discussion section. We have reviewed the literature review and discussion section to ensure its relevance to the research results and provide a more in-depth analysis and discussion. We have addressed the issues of selection bias and other limiting factors in the discussion section. Once again, we appreciate the guidance from the reviewers, and we are committed to improving the quality of the study. We look forward to further guidance from you.

Changes in the text:

In response to the reviewer's comments, we have diligently and thoroughly revised the "Discussion" section (page 13-17) of the manuscript as per the reviewer's request, incorporating red text and blue strikethrough to indicate changes, in order to meet your requirements.

Reviewer B

This is a retrospective study comparing ENB-guided method with CT-guided hook-wire method for preoperative localization of peripheral pulmonary lesions. In this study, the authors demonstrated that the ENB-guided method had greater advantages in terms of safety and short-term psychological outcomes of the patients. I have some comments:

Major comments:

1. This is a retrospective study, but includes some data such as HADS scores on preoperation, a day after surgery, 2 weeks after surgery, and 3 months after surgery, which seems not to examine in the routine daily clinical practice. In addition, the retrospective collection of very detailed procedure duration also seems to be difficult, and the regular follow-up by telephone seems to be the study purpose. Did the authors plan this retrospective study before the study duration? If so, it leads to a significant selection bias, as this is a comparative study.

Reply:

Thank you for your valuable input and suggestions regarding this article. You raised concerns about whether our retrospective study was planned in advance. I would like to clarify that this article presents a retrospective study, where all data were collected and analyzed from patient records. In adherence to departmental regulations, our department routinely conducts patient satisfaction surveys, including the HADS scoring scale, for the majority of patients upon admission, discharge, and during postoperative follow-ups. This practice not only helps us identify areas for improvement but also enables us to provide better care for our patients.

For this study, we conducted a retrospective analysis of the relevant patient data that had been collected by our department. It is important to note that there was no human intervention involved in this study. All surveys were collected anonymously through online questionnaires or with the assistance of medical staff. Prior to data collection, patient consent was obtained either verbally or through their self-completion of the forms.

Changes in the text:

In response to the reviewer's comments, we have made the following addition to the "Methods" section of the manuscript (page 6) in red text: "We administer patient satisfaction surveys, including the HADS scoring scale, to the majority of patients upon admission, discharge, and during postoperative follow-ups. All surveys are conducted anonymously through online questionnaires or with the assistance of medical staff, and patient consent is obtained verbally or through self-completion of the forms."

2. How did the authors choose the procedures, the ENB-guided method or CT-guided method?

Reply:

As this article is a retrospective study, we reviewed and summarized the localization of these nodules. However, due to the varying judgment criteria among different doctors in our hospital regarding the patient's condition, nodule position, economic status, and personal choices, it is difficult to provide a specific analysis in the retrospective study. Therefore, we are unable to specify a complete and uniform standard in this article. Nevertheless, we can ensure that the localization procedures for all patients were discussed and agreed upon by the preoperative department expert committee and deemed necessary and feasible. Additionally, all patients signed informed consent forms before the interventional and surgical procedures.

3. The authors showed 5 inclusion criteria, so some patients might be excluded. In the study period, how many patients underwent preoperative localization? What were the reasons? Please add a figure on patient flow.

Reply:

Thank you for your valuable input. The subjects of this study were patients who underwent preoperative localization using ENB guided ICG or CT-guided hook-wire placement for VATS resection of solitary pulmonary nodules between January 2022 and December 2022. During the study period, approximately 600 patients underwent preoperative localization. Based on our inclusion and exclusion criteria, we selected 57

cases of ENB localization and 120 cases of CT-guided localization for patients with solitary pulmonary nodules.

4. Please describe the definitions of “satisfied” and “failed” localization results in the Method Section.

Reply:

Thank you for the valuable feedback. Among the patients undergoing ENB-guided localization, there were 5 cases of failure due to inability to reach the designated location. In the CT-guided localization group, there were 6 cases of failure due to needle-hook position deviation. After failed localization, the operating surgeon relied on preoperative CT scans, personal experience, and surface palpation of the lungs to complete the surgery. Intraoperative rapid pathology confirmed successful removal of the nodules in all cases of failed localization. In this study, if the surgeon can quickly locate and remove the localization point during the operation, it is considered successful localization. Out of the 156 localized cases in this study, all nodules were confirmed to be effectively removed through tactile examination or rapid frozen section pathology in the resected specimens. We will describe the definitions of ‘satisfied’ and ‘failed’ localization results in the Method Section.

Changes in the text:

We have described the definitions of ‘satisfied’ and ‘failed’ localization results in the Method Section.(page7-8)

5. Please explain HADS briefly, as many readers may not know about the scale.

Reply:

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment tool designed to measure the severity of anxiety and depression in patients receiving treatment in a hospital. It includes two subscales: one for anxiety and one for depression, each consisting of 7 items. The questionnaire aims to identify and quantify symptoms of anxiety and depression, providing healthcare professionals with valuable insights into the psychological well-being of patients. HADS is frequently employed in both clinical research and practical healthcare settings to assist in the assessment and management of patients' mental health. We have included a brief explanation of the HADS in the Introduction section to aid readers in better understanding.

Changes in the text:

We have included a brief explanation of the HADS in the Introduction section to aid readers in better understanding.

6. Please add the information of “air bronchus sign” to Table 1, as it is a well-known factor for successful bronchoscopy.

Reply:

Thank you for your suggestion. Following your instructions, we have reviewed the imaging data of the patients and added the relevant information regarding bronchial signs to Table 1.

Changes in the text:

We have reviewed the imaging data of the patients and added the relevant information regarding bronchial signs to Table 1

Minor

1. Who performed CT-guided hook-wire localization and ENB-guided localization? Interventional radiologists? Bronchoscopists? Thoracic surgeons?

Reply:

CT-guided localization was performed by qualified thoracic surgeons, while ENB localization was conducted by qualified endoscopists. We have provided an explanation of this in the Method section of the article.

Changes in the text:

In accordance with the reviewer's feedback, we have made revisions to the "Methods" section of the manuscript (pages 7-8) as per the reviewer's request.

2. Please describe the details of instruments (e.g. size of needles, the bland name of hook-wire) during the CT-guided hook-wire localization.

Reply:

The detailed information of the puncture needle is as follows: 18Gx10cm, BLR18/10, GALLINI S.R.L.

Changes in the text:

In the "CT-guided localization with hook-wire" section of the "Methods" chapter, we have included "18Gx10cm, BLR18/10, GALLINI S.R.L."(page8 line1)

3. Page 6 line 133; Fig 1 seems to be Fig 2. Similarly, Fig 2 in line 140 seems to be Fig 1.

Reply:

Thank you for your guidance and suggestions on this article. We apologize for the oversight in the labeling of the image sequence, and have made the necessary corrections based on your prompts.

Reviewer C

I read this paper, and I would like to agree with acceptance for publication in this journal.

This paper was described about Electromagnetic navigation bronchoscopy (ENB)-guided localization compared with CT-guided Hook-Wire localization for small pulmonary nodules. This study design was a retrospective, single-center cohort study. A total 177 patients were enrolled into this study, and they divided them into two groups; one was ENB group (n=50) and another was hook-wire group (n=120). There was a significant statistical difference of localization complication between ENB-and hook-wire groups (0/57 versus 61/120, P<0.001). And then, they focused on patients' anxiety and depression before localization by ENB or hook-wire, and pulmonary function after localization. To investigate the anxiety and depression, Hospital Anxiety and Depression Scale (HADS)* was adopted into quantify the anxiety and depression in patients after surgery. HADS-A and HADS-D were used to evaluate anxiety and depression, respectively.

The results demonstrated that the baseline mean anxiety scores indicated 2.54±0.76 (normal) in ENB group and 2.48±0.89 (normal) in hook-wire group, respectively (P=0.658). Anxiety scores increased in both groups on the first day after surgery. The mean anxiety score was significantly higher in hook-wire group (8.71±0.98; mild) than that in ENB group (4.89±1.28; normal) (P<0.001). At the 2-week

postoperative, there was still statistical significant difference between hook-wire and ENB groups about anxiety scores (4.48±1.00 versus 4.02±0.81, P=0.003). Finally, the anxiety score decreased and the difference was no longer recognized between two groups at the 3-month postoperative. On the other hands, the mean depression scores was also increased temporarily on the first day after surgery and at the 2 week postoperative, afterward it was decreased at the 3-month postoperative in both groups similar to the mean anxiety scores. The mean depression scores were recorded on the first day after surgery as 7.27±1.12 (mild) in hook-wire group which was higher than 4.82±0.95 (normal) in ENB group (P<0.001), and that demonstrated 4.58±0.82 (normal) and 3.53±0.60 (normal) (P<0.001).

In conclusion, the authors described that the HADS-A/HADS-D scores of hook-wire groups were higher than those of the ENB group on the initial postoperative day, and also at 2-week postoperative. These findings may indicate that the temporary elevation of HADS score subsequent to CT-guided hook-wire localization implies a potential correlation between the distress caused by percutaneous lung puncture and the subsequent development of anxiety or depression in patients. As they mentioned that the correlation between pain and postoperative anxiety or depression remains inadequately explored, I agree with what the authors claimed.

In this study, there were several limitations including 1) selection bias by a retrospective single-center cohort, 2) small sample size, 3) no assessment of longitudinal changes in anxiety and depression postoperatively and 4) assessment bias by a self-evaluation questionnaire (HADS). However, I think this study could be worthy for publication in Journal of Thoracic Disease, and many readers would be interested in it.

*The HADS scale is a questionnaire commonly used by medical doctors to assess patient levels of Anxiety and Depression.

1. HADS – One questionnaire, comprising of 14 questions

2. The questionnaire features 7 questions for anxiety and 7 for depression of which can be answered within 2-5 min.

3. Responses are scored on a scale of 3 to 0 (The maximum score is 21 for Anxiety and 21 for Depression)

The two sub-scales, anxiety and depression, have been found to be independent measures. In its current form the HADS is now divided into 4 stages.

Scores of:

☐ 0-7 (normal)

☐ 8-10 (mild)

☐ 11-15 (moderate)

☐ 16-21 (severe)

Reply:

I would like to express my sincere gratitude for your support and valuable feedback on our manuscript. Your insights and suggestions have been instrumental in improving the quality of the article, and I truly appreciate the time and effort you have dedicated to reviewing our work. Thank you once again for your support, and I look forward to addressing any further comments or concerns you may have.

Reviewer D

It's a good idea.

The two groups have very different clinical results, so that has an important impact on anxiety that could make them unable to compare the anxiety produced by the procedure per se.

The measure is for anxiety and depression and not for safety, so you can't say this is a safe and feasible method because of the result.

Reply:

We are sincerely grateful for your support and valuable feedback on our manuscript. Your insights and suggestions have significantly contributed to the improvement of the article's quality. In this study, we conducted a retrospective collection of preoperative and postoperative HADS scores to further analyze the impact of different localization methods on patients' anxiety and depression. Additionally, the article compares multiple indicators such as time, success rate, and incidence of complications between the two localization methods, and evaluates the changes in postoperative lung function. The findings suggest that both localization methods have similar impacts on postoperative physiological function and recovery, indicating a comparable safety profile between the two methods.

Reviewer E

there is a numerical difference between the two groups: 57 ENB, 120 CT-guidance: explain the reasons

Reply:

We are sincerely grateful for your support and valuable feedback on our manuscript. The study included patients who underwent preoperative ENB-guided ICG localization or CT-guided hook-wire localization for VATS lung solitary nodule resection between January 2022 and December 2022. During the study period, approximately 600 patients underwent preoperative localization. Based on our inclusion and exclusion criteria, we selected 57 cases of ENB localization and 120 cases of CT-guided localization for patients with solitary pulmonary nodules. As the ENB technique was implemented later than CT-guided localization, we were unable to achieve a sample size for ENB localization equivalent to that of CT-guided localization. Therefore, according to our research standards, we endeavored to present an objective and realistic data set to the readers.

anxiety and depression are subjective sensations wth great heterogeneity of distribution among the subjects: risk of bias

ENB was done under general anaesthesia and CT-guidance under local anaesthesia: this different approach can be justifie the results? please comment this point

Reply:

At the outset of our study, similar questions were raised by members of our team. However, based on clinical practice and analysis, we have found that in the majority of hospitals worldwide, percutaneous puncture positioning under CT guidance is performed under local anesthesia. This is due to the specific requirements of the equipment, the need for the procedure to be conducted in the CT scanning room, and the necessity for multiple CT scans to complete the puncture. Consequently, performing CT scanning and puncture positioning under general anesthesia is considered impractical in most hospitals. Similarly, it is challenging for the majority of hospitals worldwide to construct composite operating rooms equipped with CT machines

and apply them for CT localization under general anesthesia. We believe that the CT-guided localization method described in this study, as well as the ENB localization method, are both operational in the majority of hospitals worldwide or are being implemented. Therefore, comparative studies under these conditions can assist clinical decision-making and align more closely with clinical practice. We have added relevant descriptions of this content in the discussion section of the article to facilitate a better understanding for the readers.

I hope the revised response meets your needs. If you require further assistance, feel free to ask.

ENB is a expensive method compare to CT-guidance. on the basis of your results do you encourage this technique taking in account that finally, several weeks after surgery the results in the of anxiety are similar?

Reply:

Thank you for your feedback and suggestions regarding our manuscript. In this article, we acknowledge that both methods have their advantages and disadvantages. Although ENB is a more expensive technique compared to CT-guidance, it offers a better surgical experience and has a lower impact on short-term postoperative anxiety and depression compared to the CT localization group. With the continuous popularization and development of ENB technology, the cost of utilization is expected to decrease. Additionally, in certain countries or regions, ENB may be included in the medical insurance reimbursement list. The objective of this article is to provide an unbiased presentation of the safety profiles and impacts on anxiety and depression of both localization methods, aiming to assist clinicians in selecting the appropriate localization method based on individual patient conditions.