Peer Review File

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Response to Reviewer A:

The authors describe a novel robotic system used for localization of pulmonary nodules. It seems to be a good and novel work in terms of analyzing outcomes of a novel technique for localizing pulmonary nodules. As far as I know, this is the first paper analyzing this kind of robotic system on humans in lung interventions. I believe that robotic systems are going to revolutionize many of our routines.
The paper is well structured and narrated. However, there are some issues that should be resolved/addressed in order to improve the manuscript for its publication.

Highlight box:

1. Page 5, line 86-87: What can be crucial for lung cancer diagnosis and treatment is preoperative localization of nodules. CT guided percutaneous localization technique is only one of the possible techniques. There are many others. I suggest rethinking this first sentence.

   Reply 1: We greatly appreciate the reviewer's valuable suggestion, and we have revised the original statement. The updated sentence now reads as follows: "Preoperative localization of pulmonary nodules is of paramount importance in the context of lung cancer diagnosis and treatment." We have modified our text as advised (see Page 5, line 85-86).

2. Page 5, line 88: Suggested edit: This novel robotic system…
3. Page 5: line 92: Suggested edit: The robotic-assisted navigation system has shown promising results for precise and safe lung nodule localization.

   Reply 2 & 3: We have modified our text as advised (see Page 5, line 88 & line 92).

4. Page 5, line 94-96: I suggest rethinking this sentence structure.

   Reply 4: We appreciate your suggestion, and we have made the necessary adjustments to the sentence structure as per your recommendation. We have modified our text as advised (see Page 5, line 91-94).

ABSTRACT

1. Page 6, line 99: The correct order is: “Preoperative percutaneous computed tomography (CT)-guided localization of pulmonary nodules. Please proceed to correct it in the entire manuscript.
   Reply 1: We have modified our text as advised (see Page 5, line 85-86).

2. Methods: I think that it is important to mention here that it is a percutaneous puncture and the marker that was used.

   Reply 2: We have made the necessary additions to our description of the puncture procedure. The updated passage now encompasses the following details: "The robotic-assisted navigation system generated a three-dimensional (3D) model based on the patient's CT images, determining the optimal puncture path. Subsequently, the robotic arm accurately identified the nodule and, following a percutaneous puncture, introduced indocyanine green (ICG) into the target site." We have modified our text as advised (see Page 6, line 105-108).

3. Results: I think that it is important to mention the lung resection approach (VATS). I suggest to specify that the 33 nodules were successfully localized and resected using the…
   Reply 3: We have modified our text as advised (see Page 6, line 113-114).

4. Page 6, line 116: I suggest changing nodule instead of target point.
   Reply 4: We have modified our text as advised (see Page 6, line 115).

5. Page 6 line 122: I suggest deleting the process.
   Reply 5: We have modified our text as advised (see Page 6, line 121).

Introduction

1. Page 7, line 134: Suggested edit: small and non-solid nodules, …
   Reply 1: We have modified our text as advised (see Page 7, line 133).

2. Page 7, line 137-140: An inaccurate localization or mislocalization of the nodules can also lead to a positive margin or even to a failed resection of the nodule, which can make the patient undergo a second surgery.

   Reply 2: We have made supplementary adjustments to the relevant content as follows: "An imprecise localization or mislocalization of pulmonary nodules may result in positive margins or unsuccessful nodule resection. This, in turn, contributes to extended surgical durations, increased radiation exposure, elevated occurrence of adverse events, and the potential necessity for secondary surgical interventions." We have modified our text as advised (see Page 7, line 136-140).

3. Page 7, line 153: I suggest deleting: particularly for less experienced surgeons (these techniques can be also developed by radiologists, pneumologists…)
   Reply 3: We have modified our text as advised (see Page 7, line 152).

4. Page 8, line 158: Suggested edit: …that enables percutaneous robotic-assisted nodule localization through…
   Reply 4: We have modified our text as advised (see Page 8, line 157-158).

Methods

1. Page 8, line 173: I recommend defining what you consider peripheral.

   Reply 1: We appreciate your suggestion, and we have provided a precise definition for "peripheral" as follows: "The term 'peripheral' refers to nodules with a minimum distance from the outer edge of the nodule to the nearest pleural surface exceeding 10 mm." We have modified our text as advised (see Page 8, line 157-158).

2. Page 10: I recommend to specify if the ICG marker was used in all cases or if you have used other markers.

   Reply 2: We have made it explicit that indocyanine green (ICG) was uniformly administered during a deep inspiration phase **for all patients**. We have modified our text as advised (see Page 10, line 224-227).

3. Page 10: I suggest specifying if the marking procedure is done in the OR or if the patient is transferred to the OR after the procedure. The latter you should specify if it transferred immediately or how much time has been between the marking procedure and the resection.

   Reply 3: We localized the lung nodules in the CT room. Following the successful localization of pulmonary nodules within the CT room, all patients were transferred to the operating room. The median time interval between nodule localization and surgery was 70 minutes (IQR, 45-120 minutes). We have modified our text as advised (see Page 12, line 293-295).

4. Page 10: It is not clear in the manuscript that it is the operator who inserts the needle. In addition, it is not clear and explained in the manuscript and video how the operators know how deep to insert the needle.

   Reply 4: We are grateful for the suggestion. In the study, the needle was inserted manually. To be clearer, we have added the information according to the comment as follows: “A puncture needle is then inserted manually, facilitating the placement of the marker for intraoperative localization.” (Page 9, line 202-203). Additionally, insertion depth is automatically calculated by the robotic system according to the planned needle path. We have added a brief description of the puncture depth as follows: “The operator, assisted by the robotic arm, inserted the needle to a depth automatically measured and displayed on the screen.” (Page 10, line 226-227)

Results

1. Page 11, line 267: The majority of the nodules were classified as pure ground glass opacities (29/33). I suggest specifying if the others were mixed or solid.

   Reply 1: The majority of nodules were classified as pure ground glass opacity (pGGO) (29/33) with a median density of -633.0 Hounsfield units (HU) while the remaining 4 were

mixed nodules. We have modified our text as advised (see Page 11, line 268-270).

2. Page 12, line 288: what do you mean with pleural reactions? Authors should comment if there were any complications regarding ICG visualization.

   Reply 2: We apologize for any confusion caused by our previous wording. To clarify, what we intended to convey is that "asymptomatic pneumothorax" was observed in four patients during the CT scan, and this condition did not necessitate further medical intervention (see Page 12, lines 290-291). Furthermore, we can confirm that there were no instances of ICG diffusion or leakage into the thoracic cavity (see Page 12, line 297-298).

3. Page 12: I recommend analyzing the operating time, specifically the wedge resection time, in order to be able to compare this technique with others.

   Reply 3: We have revisited the surgical records of our patients. The median operating time for the wedge resection procedure was 50 minutes (IQR, 40-65 minutes). We have modified our text as advised (see Page 12, line 298-299).

4. Page 12, line 299-300: Could you measure distance of the nodule to margin? In the discussion, you stated that you achieve oncologically safe margins, but don't report what margins you had. It will be interesting also to report the pathology sizes of the nodules.

   Reply 4: We have reviewed the pathology reports of our patients. Frozen section analysis provided information on nodule size and margin distance, with a median diameter of 8.0 mm (IQR, 7.0-10.0 mm) and a median margin distance of 20.0 mm (IQR, 16.0-21.0 mm) (see Page 12, line 307-309).

Discussion

1. Page 12, line 309: You can't conclude this without analyzing margin distance in mm.

   Reply 1: We have reviewed the pathology reports of our patients. Frozen section analysis showed that a median margin distance of 20.0 mm (IQR, 16.0-21.0 mm). It is noteworthy that the margin distance consistently exceeded the nodule diameter in all resected specimens, thereby establishing the presence of oncologically safe margins for all patients.

2. The authors should explain in discussion why they use/prefer ICG as a marker.

   Reply 2: The utilization of ICG for preoperative lung nodule localization can be attributed to several factors. Firstly, it is the standard procedure in our hospital to perform CT-guided ICG localization before VATS-based lung nodule resection. Furthermore, drawing from our clinical experience, ICG localization has demonstrated a higher degree of safety compared to hook-wire localization. Importantly, ICG introduces no disruption to the surgical field, as it remains invisible without the application of a near-infrared (NIR) imaging system. This feature not only enhances the precision of the procedure but also ensures compatibility

with histopathological analysis (see Page 14-15, line 360-374).

Response to Reviewer B:

This is a prospective study evaluation feasibility, efficacy and safety of preoperative lung nodule localization using a robotic-assisted navigation system. The authors demonstrated high feasibility, high accuracy, short procedure time and excellent safety profile. This manuscript is well written, and the procedure seems to be quite attractive. I have a few comments:

1. I agree with the data; a median deviation of 6.1 mm from the target point, a first pass success rate of 100%, a median procedure duration of 4.0 min, and no significant complications, is excellent, however, some readers may not know the data of traditional localization techniques. Please discuss the current results by comparing with the published data of traditional methods in the Discussion Section.

   Reply 1: We appreciate your agreement with our data. To provide a clearer context for our results, we have conducted a review of relevant literature. In a randomized clinical trial comparing a 3D-printed navigation template with traditional CT-guided needle insertion, it was found that the average deviation in the CT-guided group was 9.6 mm, surpassing the notably lower 6.1 mm median deviation observed in our robotic-guided group. Moreover, the conventional CT-guided approach exhibited a significantly higher rate of insertion attempts, with 94% of cases requiring repeated needle adjustments. In stark contrast, our robotic-guided system achieved a remarkable 100% first-pass success rate. This discrepancy can likely be attributed to the reliance of the traditional CT-guided method on the operator's experience, necessitating iterative adjustments in needle depth and angle based on CT images. These frequent adjustments not only lead to patient discomfort but also elevate the potential for associated complications (see Page 13, line 323-334).

2. Please describe the potential limitations of this procedure (not the limitation of this study) by comparing the traditional techniques. (e.g. cost, availability of equipment, learning curve).

   Reply 2: The potential limitation of this procedure may be the increased treatment costs. However, these initial costs could potentially translate into savings in terms of complication-related expenses. To comprehensively assess the economic implications and weigh the benefits against the costs, future health economics evidence is warranted to estimate the total medical expenditures associated with the application of this technology. This balanced evaluation of costs and benefits will be important in making informed decisions about the integration of robotic-assisted navigation systems into clinical practice (see Page 15, line 388-395).

   As for the learning curve, compared with the traditional method, the robotic-assisted percutaneous puncture is easier to master since it is less dependent on clinical experience.

Response to Reviewer C:

1. Information regarding the robot used by the authors in this study, particularly regarding approval from Chinese authorities and post-market surveillance, is missing.
2. The authors declared nothing to disclose in terms of COI**,** however, did they purchase the robot? Did the True Health Medical provide the device for the study? If so, authors should make it clear on the manuscript.

Reply 1 & 2: The robotic system employed in our study is a class III medical device that has received approval from the National Medical Products Administration (NMPA). Specifically, we used a commercially available robotic-assisted navigation system (TH-S1) sourced from TrueHealth Medical Technology Co. Ltd. in Hengqin, China, for the purpose of percutaneous lung puncture. To address the comment, we have incorporated this information into our manuscript (see Page 8, line 182-185).

Response to Reviewer D:

This is a single center explorative study on robotic assisted transthoracic ICG marking, immediately preceding surgical resection of non- or subsolid nodules.
I have a number of issues that need further clarification and re-phrasing.

1. Of 48 eligible patients only 33 were analyzed which induces a large selection bias.

   Reply 1: We sincerely appreciate your valuable input and concerns regarding our study. The exclusion of patients was based on specific criteria, including patient declinations, surgical schedule changes, nodule locations near the mediastinum, and reports of brain metastasis. The primary objective of this preliminary study was to evaluate the accuracy and safety of the robotic-assisted navigation system. To ensure the safety and well-being of our patients, we exercised stringent control over the inclusion criteria.

   While we recognize the limitation of our sample size and its potential for bias, we would like to inform you that a larger, more rigorously designed randomized clinical trial is currently underway to comprehensively assess the superiority of the robot-assisted navigation system compared to traditional methods. Your feedback is greatly valued in improving the robustness and credibility of our research.

2. Methodology: The system uses photo-electric navigation: this technique requires calibration of an onsite CT scan to externally positioned markers. All in all, it seems to me that all this prep-time is not included in the repeatedly underlined procedure time of 4 minutes. So this procedure time may give a false impression on the real procedure length.

   Reply 2: We appreciate your insightful observation and acknowledge the need for clarity regarding the procedural time in our methodology. To address this concern, we have redefined the operational time as follows: " The length of procedural time was measured from the time a patient was lying on the examining bed of the CT scanner to the time he/she received the second CT scan to confirm the localizer placement. " (see Page 10, line 237-239). The median duration of the localization procedure was 25.0 minutes (IQR, 18.0-29.0 minutes) (see Page 12, line 285-286).

3. More importantly: they report a 6 mm mismatch between real and the intended target position, which on a mean lesion size of 10 mm is a big difference. This indicates that the technology is not accurate enough for support of diagnostic procedures, and must also be used with caution for marking purposes in pre surgical scenarios.

   Reply 3: Thank you for your valuable feedback. We appreciate your concern regarding the 6 mm deviation between the nodule and target point.

   Firstly, we apologize for any misunderstanding that may have arisen due to our previous phrasing. To clarify, we intended to refer to nodules with a radius smaller than 10mm, which

translates to nodules with a diameter of less than 20mm. This correction has been implemented in this version of the manuscript.

Furthermore, it's essential to recognize that even with this level of variance, our robotic-assisted system still outperforms the 9.6mm deviation associated with traditional CT-guided methods. Moreover, we would like to highlight that the resection margin consistently exceeded 1.5 cm from each target point. With this approach, all nodules could be resected within an oncologically safe margin. While we remain committed to further improving accuracy in the future, our findings suggest that this technology remains a viable and valuable choice for preoperative lung nodule localization.

Your feedback is highly appreciated, and we will continue to work towards enhancing the precision and reliability of our system.

4. Further, the authors use DLP to express radiation dose were dose AREA products are used more commonly. Please convert.

Reply 4: We appreciate the reviewer's suggestion regarding the use of DLP (dose–length product) to express radiation dose, as DAP (dose–area product) is more commonly employed. However, it is worth noting that in the context of studies on robotic-assisted percutaneous puncture, DLP appears to be the more prevalent metric, as evidenced by several related studies, such as:

1. Heerink WJ, Ruiter SJS, Pennings JP, et al. Robotic versus Freehand Needle Positioning in CT-guided Ablation of Liver Tumors: A Randomized Controlled Trial[J]. Radiology, 2019, 290(3):181698. DOI:10.1148/radiol.2018181698.
2. Hiraki T, Kamegawa T, Matsuno T, et al. Robotically Driven CT-guided Needle Insertion: Preliminary Results in Phantom and Animal Experiments[J]. Radiology, 2017:162856. DOI:10.1148/radiol.2017162856.
3. Smakic A, Rathmann N, Kostrzewa M, et al. Performance of a Robotic Assistance Device in Computed Tomography-Guided Percutaneous Diagnostic and Therapeutic Procedures[J]. CardioVascular and Interventional Radiology, 2018. DOI:10.1007/s00270-017-1841-8.

Given this context, we have opted to use DLP as the metric to express radiation dose in our study, as we believe it facilitates more straightforward comparisons of results across different studies.