

Peer Review File

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Reviewer A

Comment 1: Virtual reality, augmented reality and mixed reality are widespread in all technology areas, including health care. For example, in thoracic surgery, they are used in multiple forms to know the exact 3D anatomy of the lung to plan minimally invasive sublobar anatomic resections (segmentectomy) and now to localize intraoperatively small lesions in peripheral areas of the lung as proposed in this study. In fact, localization of small lesions is currently an important achievement concerning the common finding of these small nodules in lung cancer screening programs. Thus, this localization is vital for the procedure's success, and several techniques are used to accomplish this localization. For example, electromagnetic navigation, robotic bronchoscopy, hybrid operating room with tomography or radioscopy, CT-guided dye injection or wire or other metallic marks, intra-operative ultrasound, etc., are currently being used for this purpose. However, all these methods are expensive and need specialized material or personal to achieve success. Therefore, the possibility of using augmented reality navigation-guided localization as presented here is important and requires the Holo-Lens glasses and some other particular material (the marker named "Lungbrella" and the QR label) and apparently two special software (Jedivision and for and six-axis manipulator) that are not available in all hospitals. It is an excellent idea that really simplifies and accelerates the process for the procedure, but it needs more explanation about those specific subjects. Furthermore, we also need a cost-analysis for these materials and software. I want to congratulate the authors on this idea and its results.

Reply 1: Thank you very much for your positive comments and suggestions. As you mentioned, the Lungbrella Marker Device and corresponding software (Jedivision) are currently not available in other hospitals. The six-axis manipulator was used to evaluate and calibrate the AR navigation system before the conduction of this animal study, and is not needed before each localization procedure. No specialized large-scale equipment is involved in this method and all these devices and software could be easily introduced in other hospitals without high expense and difficult training.

Currently, the Lungbrella Marker Device and the Jedivision software are not on the market, therefore, the exact cost of this AR-guided localization method cannot be calculated. Given that, the consumable materials used in the AR-guided localization procedure is similar to that of the traditional CT-guided hookwire localization, the cost could be reduced because of fewer medical professionals and specialized equipment associated with this procedure.

Changes in the text: We have improved the description about the expense, the generalization and adaptation capability of this AR navigation-guided methods in the Discussion section (Page 15, line 249-255).

Reviewer B: Researchers in this manuscript are attempting to demonstrate that AR is a viable and technically non-taxing technique in localizing pulmonary nodules in large animal models. In their study they created 12 pulmonary lesions in 4 canines since June 2019. They were able to rapidly identify and marker the lesions using the model with high fidelity.

Comment 1: Abstract: 44: Were there any complications in the canine model? Researchers discuss marker displacement, but biggest concern with peripheral localization techniques is pneumothorax development.

Reply 1: Thanks for pointing this out. Only 3 moderate pneumothorax and 3 moderate bleeding were observed after a total of 12 marker implantation procedures. No severe pneumothorax, which needed further intervention, occurred. We have added the description of pneumothorax in the Abstract.

Changes in the text: We have added the description of pneumothorax in the Abstract (Page 3, line 43).

Comment 2: Introduction: Introduction should be expanded upon, the authors outline the problem, describe how AR complements the problem but do not describe the limitations of other technologies and how AR would be advantageous. This I believe deserves a paragraph on its own.

Reply 2: Thank you very much for this suggestion. We have added a paragraph in the Introduction section which describe the limitations of other technologies and how AR would be advantageous.

Changes in the text: We have added a paragraph in the Introduction section as suggested (Page 5, line 64-71).

Comment 3: 56: Intraoperative localization techniques used twice in the same line and obscures the meaning of the sentence.

Reply 3: Thanks for pointing this out. We have modified this sentence as suggested.

Changes in the text: We have modified this sentence as suggested (Page 5, line 51-54).

Comment 4: 58: What do authors mean by intraoperative procedures? The authors seem to contradict themselves in the same sentence.

Reply 4: Thank you for pointing this out. The “intraoperative procedures” in this sentence referred to those previously published intraoperative pulmonary nodule localization technologies, such as electromagnetic navigational bronchoscopy and intraoperative CT-guided localization in an hybrid operating room. Even though, these techniques have been proven to be safe and effective, their infrastructure requirement has limited patients’ access. The former expression may be confusing. We have modified the expression in the text.

Changes in the text: We have modified the expression in the text (Page 5, line 54-58).

Comment 5: 63: Should be natural vision.

Reply 5: Thanks for this suggestion. We have corrected this phrase as suggestion.

Changes in the text: We have corrected this phrase (Page 5, line 60).

Comment 6: Methods: This section is written very well and authors clearly describe the development of the protocols and animal models. The video complements the section very well. Authors do not describe statistical analysis in the section which is a weakness.

Reply 6: Thank you very much for this suggestion. We have added the description of statistical analysis in the Methods section.

Changes in the text: We have added the description of statistical analysis in the Methods section (Page 10, line 167-171).

Comment 7: Results: This section as mentioned above is a weakness of the manuscript. It consists of 14 lines in total which for an article of this magnitude is exceedingly short. Suggestions for authors would be to construct their results section like their methods subsections. This would allow the authors to populate data and present detailed findings.

Reply 7: Thank you very much for this suggestion. We have constructed the Result section into subsections for better presenting our data and findings.

Changes in the text: We have modified the Result section as advised (see Page 11-12, line 172-196).

Comment 8: 168: Why did the two dogs require two procedures?

Reply 8: After each marker implantation procedures, an immediate follow-up CT scan was performed to exclude potential complications, including pneumothorax and bleeding. Each dog received 3 implantation procedures. If pneumothorax was identified after the first or the second procedure, the next marker implantation would be rescheduled at least 4 weeks later, to allow for lung tissue recovery. There was a total of 3 moderate pneumothorax observed, 2 of which occurred after the first or second procedure. Therefore, two dogs required one additional procedure to complete marker implantations.

Changes in the text: We have added the explanation in the Results section (Page 11, line 178-179).

Comment 9: Discussion: 206-217: This information could be represented pictorially which would make it easier for the reader.

Reply 9: Thanks very much for this suggestion. We have added the Figure 6, which presents the estimated nodule localization procedure workflow, in the manuscript.

Changes in the text: We have added the Figure 6, which presents the estimated nodule localization procedure workflow, as suggested.

Comment 10: 220: How do the authors come to this conclusion? The results section does not expand on the complications type apart from marker migration.

Reply 10: Thanks for pointing this out. This AR navigation-guided localization procedure can be performed under general anesthesia in a standard operating room. Right after the completion of marker implantation, pulmonary nodule resection can be performed. Due to the significantly shortened wait time between marker implantation and surgery, the complication rates and the need for patient mobilization could be reduced. Therefore, we concluded that, the risk of pneumothorax or bleeding should be well controlled compared with the traditional 2-stage preoperative CT-guided nodule localization. We have modified the expression in the text (Page 14, line 234-240). We have also added the description of complications in the Results section (Page 11-12, line 191-196).

Changes in the text: We have modified the expression in the text (Page 14, line 234-240). We have also added the description of complications in the Results section (Page 11-12, line 191-196).

Comment 11: 225: How long did it take for the researchers to learn the device? This would be a limitation of the claim, if it takes 20-30 procedures for the surgeon to become proficient, this should

be made clear. From analyzing the images and video, average surgeon would need substantial training in order to operate the device as it is novel.

Reply 11: Thank you very much for this suggestion. We agree that, surgeons would need certain training in order to successfully perform the AR-guided nodule localization procedure. Dr. Chengqiang Li, who performed all the marker implantation procedures in this study, had practiced more than ten times before the conduction of this animal experiment. However, under the guidance of AR navigation, the localization procedure has been greatly simplified. We felt it is much easier for beginner to learn than the traditional CT-guided methods. Surgeons could also get trained on dummies or virtual system before performing on the real patient. We have improved the explanation in the Discussion section (Page 15, line 242-245).

Changes in the text: We have improved the explanation in the Discussion section (Page 15, line 242-245).

Comment 12: 227: Have the authors explored the ergonomic limitations of mounting large devices? Also, laparoscopic and thoracoscopic procedures require low ambient light in the room, would the surgeons be able to safely proceed with surgery in that case. Video shows very well lighted room which would not be possible during thoracoscopic procedures.

Reply 12: No large-scale equipment is involved in the AR navigation-guided localization procedure. The AR-guided localization could be performed under general anesthesia and before surgery. After the completion of marker implantation, light could be dimmed for thoracoscopic lung surgery.

Comment 13: 229: What is the average time required for CT guided localization? Authors should present the data in the results section with appropriate statistical analysis.

Reply 13: According to Yinkai Chao et al. (J Thorac Dis. 2018), the mean localization time for intraoperative CT-guided localization was 21.19 min. We did not conduct the CT-guided localization in the canine model as control arm.

Changes in the text: We have added the data of intraoperative CT-guided localization in the Discussion section (Page 15, line 246-248).

Reviewer C

Comment 1: In this study, Augmented Reality Navigation-Guided Pulmonary Nodule Localization in a Canine Model was introduced. The authors report that pulmonary nodule localization technique using Augmented Reality (AR) Navigation System is safe and effective. However, in terms of effectiveness and feasibility, the use of AR Navigation System is considered negative.

In the actual VATS procedure, the patients were placed in the lateral decubitus position.

As mentioned in the limitation part of this study, the patient's position in the CT scanning procedure and in the operating room must be the same, which is a very difficult problem. It looks like the system will have to be changed again to overcome this.

Reply 1: Thanks for this comment. The patient's position must be identical during CT scan and marker implantation procedure for accurately simulating the actual structures in the thorax. After the completion of marker implantation, patient's position could be changed into the lateral decubitus

for VATS procedure. The former expression may certainly cause misunderstanding. And we have corrected the expression in the text (Page 15, line 257-258).

Changes in the text: We have corrected the expression in the text (Page 15, line 257-258).

Comment 2: Because there is movement of the lungs by respiration. So, the Marker implantation process requires holding patient's breath for a certain amount of time. Marker implantation under anesthesia is considered quite negative.

Reply 2: Thanks for this comment. According to our results, the marker implantation procedure was greatly simplified under AR navigation, the median registration and implantation time was only 6 minutes. Therefore, we think it is feasible to have the marker implantation completed by holding patient's breath intermittently under general anesthesia. However, patient's respiration level should be well matched during the CT scanning procedure with that during the AR navigation procedure, which constitutes a limitation of this methods. Further software update will be needed to overcome this problem.

Comment 3: If the marker tail extends to the lung surface like a hookwire, the probability of creating a pneumothorax is quite high. In fact, in this study, pneumothorax (moderate degree) occurred in 30% of cases (3/12).

Reply 3: According to our results, the incidence of pneumothorax was 25% (3/12), all of which were at moderate degree, and no further intervention was needed. Due to the limited sample size of this animal experiment, the actual incidence and degree of pneumothorax after AR navigation-guided marker implantation need further verification. On the other hand, patients could undergo lung surgery right after the completion of marker implantation. The wait time is greatly shortened, and therefore, pneumothorax could be immediately managed by surgery.

Comment 4: According to this study, it takes two days from pulmonary nodule localization to VATS procedure. This is considered inefficient. In actual clinical practice, it takes an average of 60 -70 minutes.

Reply 4: Thanks for this comment. According to our estimated localization procedure workflow, patients will undergo a low-dose CT scan with attached skin markers on the day before surgery (day 0). The images of CT scan will be used to virtually simulate the 3D structure in the thorax, according to which, the transthoracic puncture plan is generated. On the surgery day (day 1), patients will firstly receive general anesthesia in the operating room. Marker implantation will then be performed under general anesthesia, followed by pulmonary nodule resection. Therefore, the interval between AR-guided nodule localization and VATS surgery would be shorter than the conventional 2-stage CT-guided localization. We have added the Figure 6, which presented the estimated localization procedure workflow pictorially, to make it easier for readers to comprehend.

Changes in the text: We have added the Figure 6 to better explain the localization procedure workflow.