

Peer Review File

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Reviewer A: This report was interesting because the tumor localization has been a topic in small sized pulmonary nodules, however, it has a few limitations.

Comment 1: Although this method was very interesting because novel technologies were included, the number of the subjected patients was very small even if this study was set as a pilot study. I wondered why the authors evaluated this method with a small number of patients. Could the authors add more patients who underwent this method?

Reply 1: Thank you for your positive comment about our novel technologies to guide pulmonary nodule localization. We intended to firstly investigate the feasibility and safety of this novel method in this pilot study. Based on the satisfying results of this pilot study, the further multicenter prospective clinical trial is being conducted. The results will be reported in the future.

Comment 2: This method required the puncture of the visceral pleura. I thought that this method had no differences from previous methods, like some hook-wire methods using CT even if this method used the AR system in the marker setting process. Because the principal of the puncture method seems to be same as the hook-wire method, the complications such as pneumothorax, hematoma, and cerebral embolism are expected to be the same as previous methods. It is recommended for the authors to describe more differences or benefits compared with previous methods.

Reply 2: Indeed, with the application of this novel localization technology, it is still necessary to puncture the pleura like hookwire methods. One of the advantages of this novel localization method is that the localization can be performed in the operating room. Patients received the localization and surgery under a single general anesthesia, which reduced the risk of complications brought about during transportation of patient. If complications occur, for example pneumothorax and hematoma, the surgery could be performed immediately to minimize the impact of complications. In addition, the AR-guided localization is simple and does not require specialized equipment, which is conducive to promotion. Of course, as you mentioned, the sample size is small, and the feasibility needs to be verified through multicenter clinical trial with large sample size.

Changes in the text: We have improved the description about the benefits and differences between AR-guided localization and previous methods (see Page 16, line 256-270).

Comment 3: Unfortunately, I could not check the attached video file. Therefore, I didn't know whether I could sufficiently review this study.

Reply 3: Sorry for any issues that prevented you from watching the video. We have re-uploaded the video by following the author instructions of the journal.

Reviewer B: The authors report a pilot study of novel intraoperative localization technique using augmented reality navigation. Localization was performed intraoperatively within short period of time without any severe complications although three out of ten cases were unsuccessful. Further analyses of its efficacy and safety with more cases are necessary, but this technique is promising. My comments and questions are given below.

Major concerns:

Comment 1: The authors positioned the LungBrella marker according to AR navigation without confirming the exact place of the marker on CT, which would possibly punctuate the lung nodule. If the marker punctuates the nodule, the pathology of the tumor may be affected, and there is also a risk of dissemination. How do you prevent this risk?

Reply 1: Thank you for your comments. This is indeed a very important issue during pulmonary nodule localization. When we designed the puncture plan, the puncture path will be placed next to the nodule rather than passing through it. In this pilot study, none of the 10 patients experienced needles puncture through the nodules. With further application of this novel localization method, there is indeed a small probability of puncturing nodules, similar to CT-guided methods which could also result in puncturing nodules during the localization procedure.

Comment 2: When watching the attached video, the puncture point on the skin was relatively far away from the tumor. Although it does rarely matter for segmentectomy, part of the marker (tail string) may not be included in the resected specimen for wedge resection. How do you deal with such a case?

Reply 2: To avoid puncturing nodule, we placed location point next to targeted lesion. The puncture point on the skin was then decided to ensure that the puncture path was short, perpendicular to body surface and avoided ribs or blood vessels. During surgery, we would also pull the string to assess the general position of the marker, and ensure the complete resection of pulmonary lesion and the localization marker. Moreover, the distal end of our localization marker is umbrella-shaped, to reduce the possibility of displacement. Additionally, we would also check the integrity of the localization marker, ensure that part of the marker was not left inside the body.

Comment 3: There was little information of LungBrella marker. What is the marker made of? Can it be confirmed on CT or X-ray? Is it always fixed inside the lung once the marker is placed? Can you easily palpate the marker intraoperatively? Are there any articles using this marker?

Reply 3: Thank you for your comment. We have previously reported an animal experiment about using this AR-guided localization method on canine model, to preclinically test its safety and feasibility (*Transl Lung Cancer Res.* 2021). We have clearly introduced this LungBrella marker in this article. The marker is made of nitinol with a metal tail. It can be identified on CT or X-ray examination. With an umbrella-shaped design, this marker can be fixed inside the lung. We have not observed any marker displacement during the animal experiment and the pilot clinical trial. This marker can be easily palpated during surgery.

Changes in the text: We have modified the description about the LungBrella marker in the manuscript (see Page 9, line 139-146).

Minor concerns:

Comment 1: Three of ten cases were unsuccessful in the pilot study. Fortunately, the marker was included in the resected specimen. How should you manage if the marker is not included in the resected lung?

Reply 1: During the surgery, the metal tail of the marker can be seen. Based on the estimation of puncture depth, intraoperative palpation, and traction of the tail, we can identify the general position of the marker and ensure the complete resection of pulmonary lesion and the marker. If the marker was not included in the resected lung, it is necessary to further expand the resection range or use CT examination in the operating room to confirm the position of the marker. We have not encountered such situations yet.

Comment 2: You should mention advantages and disadvantages of this technique by comparing it with dye marking or bronchoscopic marking (ENB or VAL-MAP).

Reply 2: Thank you for your comment. Indeed, ENB-guided localization is already very mature, but there are limitations such as high cost and the need for specialized equipment. The novel AR-guided localization method does not require special medical equipment such as magnetic navigation and fluorescence endoscopy, and the localization process is also more concise.

Changes in the text: We have improved the description about the benefits and differences between AR-guided localization and dye injection or ENB in the Discussion section (see Page 16, line 256-270).

Comment 3: You should mention that this method contains a potential risk of air embolism, like CT-guided hookwire localization.

Reply 3: We agree that this AR-guided localization method contains a potential risk of air embolism, like hookwire localization. According to precious publications, the incidence of CT-guided air embolism is very low (*Ann Thorac Surg. 2013; J Thorac Dis. 2018*). We have not observed any similar cases in this pilot study. Indeed, as you mentioned, as the number of cases increases, this complication may still occur.

Changes in the text: We have mentioned the potential risk of air embolism in the Discussion section (see Page 17, line 279-282).

Comment 4: There are grammar mistakes in Table 3; RAST, VAST.

Reply 4: Thank you for pointing this out. We have corrected the grammar mistakes.

Changes in the text: We have corrected the mistakes in Table 3 (see Page 27).

Comment 5: I reckon that 9 out of 10 cases underwent segmentectomy, not wedge resection, in this pilot study considering the safety. There are some concerns mentioned above especially for wedge resection. These issues should be discussed in the limitation.

Reply 5: Thank you for this comment. Given that, this innovative localization method has not been used in human study before, segmentectomy was used for most cases to avoid residual localization marker in the lung, achieve complete resection margin and to fully confirm the accuracy of this method. In the subsequent multicenter clinical trial, the surgical method has been mainly wedge resection.

Changes in the text: We have discussed this limitation in the Discussion section (see Page 16-17, line 273-275).

Comment 6: In the discussion part, the authors wrote “One of the main disadvantages is the excessive reliance on CT, resulting in the need to transport patients between the radiology department and operating room”. However, the AR-guided localization also requires CT scans preoperatively, needing transport patients between the radiology department and operating room. Therefore, this part should be omitted.

Reply 6: Sorry for misunderstanding caused. The CT examination for AR-guided localization can be completed during patient's outpatient examination. The localization procedure can be performed in a regular operating room, right before surgery. Therefore, there is no need for a separate preoperative CT localization room to perform CT examination and localization again. Thus, the transportation between radiology department and operating room, after lung nodule localization, is unnecessary.

Reviewer C: This pilot study shows the new technique of lung localization using AT navigation guide in combination with intraoperative CT.

Although I think the manuscript is worth publishing, I have several concerns and suggestions to make the report easier to understand.

Comment 1: Although I think I understood the method by reviewing the video, it was hard for me to imagine how it works from the text and figures. I think one or two additional figures, a picture of the view through the Hololens would make it easier to be understood. You can take a capture from the video.

Reply 1: Thank you very much for this advice. We have added a figure about the view through the Hololens as figure 4.

Changes in the text: We have added a figure about the view through the Hololens as figure 4.

Comment 2: In the abstract, it was far more difficult to imagine what was done with the method. The background information (like screening for lung cancer) is absolutely unnecessary. The authors should use words more for explanation of the method.

Reply 2: Thank you for this comment. We have expended the method in the abstract as you advised.

Changes in the text: We have expended the method in the abstract (see Page 3, line 31-44).

Comment 3: How did the author consider about the safety of the method of puncturing the lung with needle? Many alternative methods have been developed to avoid puncturing the lung, which causes many complications particularly potentially fatal air embolism.

Reply 3: In our center, the majority of pulmonary nodule localizations are CT-guided hookwire method. A small portion of patients receive ENB localization. Both methods have some limitations including potential risk of complications, and requirement of specialized equipment or operators. The main advantages of our novel localization method could be localization process simplification, less requirement for specialized equipment and operators and potential less cost. As you mentioned, the risk of some complications including fatal air embolism still exist even with this AR-guided localization method. Therefore, when conducting this pilot clinical trial, the nodules we selected were all peripheral. And once the localization was done, surgery should be performed immediately to minimize the damage caused by complications.

Changes in the text: We have added the potential risk of complication in the Discussion section (see Page 17, line 279-282).

Comment 4: Localization failure happened in three out of 10 cases, which does not seem to be rare. Although the technique would be under the way of sophistication, from a critical viewpoint, I would wonder why not using conventional CT-guided method even with the operation-room setting. Although the instrument and technology are new, what was done was essentially the same as conventional hookwire method with increased complexity and failure. Please highlight the advantages of the method over the conventional method.

Reply 4: Thank you for this comment. The main advantages of our novel localization method could be localization process simplification, less requirement for specialized equipment and operators and potentially less cost. Intraoperative CT-guided localization requires hybrid operating room, which is not available in some hospitals, while the AR-guided method only need wearable AR device and localization marker (LungBrella). Most of our failed cases were due to software or equipment factors. We are conducting a subsequent multicenter clinical trial to further confirm the feasibility of this method.

Changes in the text: We have improved the description about the benefits and differences between AR-guided localization and previous methods (see Page 16, line 256-270).