

Peer Review File

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Reviewer A

Comment 1: In order to demonstrate the novelty and effectiveness of the robotic-assisted navigation system, it is necessary to compare it with the results of conventional manual marking without it. Please show the results of a comparison group that does not use a robotic-assisted navigation system. Below are some questions.

Reply 1: We thank the reviewer for this valuable advice. We have selected 90 patients with 94 SPNs underwent the conventional CT-guided manual localization during the same time as the control group and compared the localization time, efficacy and complications between two groups. The results showed the proportion of pneumothorax in the robotic-assisted group (27.21%) was significantly decline compared with the conventional manual group (43.33%) ($P = 0.002$), while no significant differences in the time of localization procedure, distance between anchor and lesion, and parenchymal hemorrhage between two groups. We have added the description in the abstraction, methods and results part. (see Page 2, line 47-48, 58-60; Page7, line 252-255; Page 10, line 377-383; Page 13, line 533-543)

Comment 2: When marking, there are many situations where there is a slight deviation between the pre-planned plane and the insertion position due to the patient's breath-holding differences in the timing of stopping, and fine adjustments are required. Is the traditional manual method more flexible and can it allow immediate response? In particular, in the semi-lateral decubitus position as shown in Figure 2, the positioning will be more unstable and the marking operation time will be longer.

Reply 2: We thank you for your good and valuable question. As you mentioned, patients' breath-holding differences definitely result in deviations between the pre-planned plane and the insertion position. To avoid this issue, each of our operating doctors reminded patients to free breath calmly and avoid deep breathing before location. In addition, we applied the vacuum negative pressure pad for position fixation (see the following figure below). Most deviations were acceptable, but a small amount of marking required manual adjustment. In the early stages, these operations indeed required more time. As we mentioned in the article, we summarized our experience and improved the workflow. For patients who are prone to positioning deviation, we mainly adopt two countermeasures: 1. we trained patients to control breathing depth to ensure consistent breathing depth during puncture; 2. we performed a two-step puncture, firstly placed the needle tip near the nodules under robotic assistance and then

gave a small adjustment to avoid complete re-puncture. We have added the related description in the third paragraph of Discussion (see Page 7, line 242-243; Page 11, line 440-443)



Comment 3: Regarding what is stated in the second paragraph of the discussion, since the operation time is longer than the conventional method, it is questionable whether this method can be said to be superior in terms of the amount of time the patient suffers from mental pain while maintaining the posture.

Reply 3: We thank you for your valuable question. Like the above reply, before location, we applied the vacuum negative pressure pad to ensure that the patients were in a comfortable position to avoid any changes in position. Most patients reflected that they could accept the pad-assisted position fixation without obvious discomfort. As we mentioned in the article, all our operators are less experienced interventional radiologists, while most of the operators in the published studies were experienced interventional doctors. In addition, due to the less experienced beginners of our operators, we stipulated that most patients needed to undergo the delayed CT scan to detect the progressive complications after 5 minutes of finishing localization in the initial stage on the learning curve. These factors might cause our operative time was longer than the reported time using conventional manual method. After we mastered the robotic executive system, the operation time markedly decreased in the phase III stage in our study. We have discussed it in the end of second paragraph in Discussion. (see Page 13, line 533-543)

Comment 4: # In the case of the hook-wire method using a metal needle, the most fatal complications are cerebral infarction and myocardial infarction due to the occurrence of air embolism (for example, Tomiyama N, et al. Eur J Radiol 2006; 59: 60-4. Sakiyama S, et al. J Thorac Cardiovasc Surg 2003; 126: 1207-9) . Were there any patients who complained of loss of consciousness or chest pain after marking pulmonary nodules in this study?

Reply 4: We thank you for your good question. In this study, we did not meet the cases with severe fatal complications such as air embolism and cerebral or myocardial infarction. We used the modified hook-wire device (Senscure, Ningbo, China) to execute pulmonary

nodule localization. The device composed with an anchor claw connected with a soft suture, which is made of polyethylene terephthalate. We think it may avoid the reported major adverse events (air embolism and tension pneumopericardium) in the short hook wire (*J Thorac Cardiovasc Surg* 2003; 126: 1207-9) due to instead with the soft suture at the distal end of hook-wire. In addition, there was no need to require the patient to maintain a specific position during the waiting time for surgery. This device was well-tolerated by patients. Our results were similar with the previous studies about this device. (*J Thorac Cardiovasc Surg*. 2020;160(2):532-539.e2. *Eur Radiol*. 2022. 32(7): 4699-4706.) (see Page 12, line 471-472)

Comment 5: During surgery, cases diagnosed with invasive adenocarcinoma using frozen pathology are treated with additional lobectomy and lymph node dissection. But, is it difficult to evaluate the oncological invasiveness of tiny nodules (average 8 mm) using intraoperative frozen pathology?

Reply 5: We thank you for your valuable question. All of the pathologic diagnosis in this study were obtained from our electronic medical records. We have consulted to our director in pathologic department in our hospital again. Indeed, as the reviewer mentioned, sometimes it is difficult to evaluate the invasiveness of small lung nodules using intraoperative rapid frozen pathology and shows the low sensitivity. However, some histological patterns like micropapillary and solid of frozen section have the high specificity for predicting invasive adenocarcinoma. (*Yeh YC, Nitadori J, Kadota K, et al. Using frozen section to identify histological patterns in stage I lung adenocarcinoma of ≤ 3 cm: accuracy and interobserver agreement. Histopathology. 2015;66(7):922-938*). In our study, there were 9% nodules determined invasive disease stage by frozen pathology. We have added the relative description as “Sixty lesions (9.17%) were subsequently converted to lobectomy because of the invasive disease stage determined by the intraoperative frozen section with the specific micropapillary and solid histological patterns.” (**Surgery and pathological results of targeted nodules, Results**) (see Page 7, line 259; Page 9, line 337-340)

Comment 6: Number (Wedge 55, Seg 18) in Table 4 and number (Wedge 316, Seg 278) in Table 3 do not match. Wouldn't it be better to use all examples for the evaluation in Table 4?

Reply 6: We thank you for your valuable question. In our study, invasive video-assisted thoracoscopic surgery (VATS) were performed by multiple surgeons. To more accurately display the changes in operation time after localization, we selected a single surgeon, who had the most operations in our study and removed all nodules with single-port VATS after localization, and excluded multiple nodules in one VATS which could affect the surgical time. We have ruled out various factors that can affect the comparison of time such as surgeon's skills, operation techniques and methods, multiple nodules resection. If we enrolled all

examples to compare the surgical time, that might not reflect the true results due to many interference factors.

Reviewer B

Comment 1: Compared to what, was your method safe? I know there are safer marking methods in literatures 1-6. Hook-wire marking itself is recognized as a risky method with potentially fatal complications like air embolism.

Reply 1: We thank you for your valuable question and advice. The percutaneous situation of localizers is viewed as a generally safe and effective method (*Park CH, Han K, Hur J, et al. Comparative Effectiveness and Safety of Preoperative Lung Localization for Pulmonary Nodules: A Systematic Review and Meta-analysis. Chest. 2017;151(2):316-328*). At present, the most widely used method in clinical practice is CT-guided hookwire placement (*Li C, Liu B, Jia H, Dong Z, Meng H. Computed tomography-guided hook wire localization facilitates video-assisted thoracoscopic surgery of pulmonary ground-glass nodules. Thorac Cancer. 2018;9(9):1145-1150. doi:10.1111/1759-7714.12801*). In this study, we used the modified hook-wire device (Senscure, Ningbo, China) to execute pulmonary nodule localization. It composed with an anchor claw connected with a soft suture made of polyethylene terephthalate. we did not meet the cases with severe fatal complications such as air embolism and cerebral or myocardial infarction. In addition, there was no need to require the patient to maintain a specific position during the waiting time for surgery. This device was well-tolerated by patients. Our results were similar with the previous studies about this device. (*J Thorac Cardiovasc Surg. 2020;160(2):532-539.e2. Eur Radiol. 2022. 32(7): 4699-4706*.) The new claw-suture localization device is superior to traditional hookwire, with a higher success rate, fewer complications, and better patient tolerance for preoperative localization of small pulmonary nodules (*Fan L, Ma W, Ma J, et al. The improved success rate and reduced complications of a novel localization device vs. hookwire for thoracoscopic resection of small pulmonary nodules: a single-center, open-label, randomized clinical trial. Transl Lung Cancer Res. 2022;11(8):1702-1712. doi:10.21037/tlcr-22-555*).

Indeed, as the reviewer asked, we did not compare the safety of this technology with other marking methods. Our study focused on applying robotic assistance in localization. We have rewritten our conclusion as: “Robotic-assisted CT-guided percutaneous pulmonary nodules hook-wire localization could be effectively helpful for junior less experienced interventional physicians to master the procedure and potentially increase precision.” We thank you for your rigorous review. (see Page 12, line 471-472; Page 13-14, line 548-566)

Comment 2: Compared to what, was your method reliable? I think it can be proven if you compared between robotic-assisted group and No assist group in this study. However, you had no control arm.

Reply 2: We thank you for your valuable advice. We have selected 90 patients with 94 SPNs underwent the conventional CT-guided manual localization during the same time as the control group. And comparing the localization time, efficacy and complication between two groups. The results showed the proportion of pneumothorax in the robotic-assisted group (27.21%) was significantly decline compared with the conventional manual group (43.33%) ($P = 0.002$), while no significant difference in time of localization procedure, distance between anchor and lesion, and parenchymal hemorrhage between robotic-assisted group and conventional manual group. We have added the description in the abstraction, methods and results part. (see Page 2, line 47-48, 58-60; Page7, line 252-255; Page 10, line 377-383; Page 13, line 533-543)

Comment 3: What do you think about the relationship between marking-related complications and selection bias of study patients? As you mentioned in Methods, the criteria excluded patients with obvious emphysema, pulmonary fibrosis, and massive bullae or vessels in the puncture route. So, I think less complications were a predictable outcome, because you defined the exclusion criteria saying patients who were likely to have complications should be as outside this study.

Reply 3: We thank you for your good question. When we performed percutaneous lung puncture, we needed evaluate the condition of pulmonary and the puncture route and excluded the situations which were not suitable for CT-guided percutaneous puncture for ensuring the safety of patients. This was also the basic knowledge when we started learning this technology and consistent with most studies about CT-guided percutaneous pulmonary nodules localization (e.g. 1. Qin W, Ge J, Gong Z, et al. *The incidence and risk factors of acute pain after preoperative needle localization of pulmonary nodules: a cross-sectional study. Transl Lung Cancer Res.* 2022;11(8):1667-1677; 2. Huang YY, Wang T, Fu YF, Shi YB, Cao W, Hou JP. *Comparison of the effectiveness of anchoring needles and coils in localizing multiple nodules in the lung. BMC Pulm Med.* 2022;22(1):393. Published 2022 Nov 1. doi:10.1186/s12890-022-02192-8). If the patients combined with obvious emphysema, pulmonary fibrosis, and massive bullae or vessels in the puncture route, the nodules should not be marked via CT-guided percutaneous method, whether robotic-assisted navigation or conventional methods, because the risks are all equally high.

Comment 4: For the above reasons, I think your conclusions were overstated, and lacked sufficient evidence to prove them. In my idea, you had better conclude only that robot-

assisted hook-wire marking could be helpful for junior less experienced interventional radiologists. In other words, we can hope that robots would be able to provide any beginners more accurate and safe technology for localization of small pulmonary nodules.

Reply 4: We thank you for your excellent suggestion. We have re-written this part according to the Reviewer's suggestion as “Robotic-assisted CT-guided percutaneous pulmonary nodules hook-wire localization could be effectively helpful for junior less experienced interventional physicians to master the procedure and potentially increase precision. In other words, robots techniques would be able to provide any beginners more accurate and safe technology for interventional procedures.”. (see Page 13-14, line 548-566)