

## Peer Review File

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### Reviewer A

Comment 1: The authors propose a description of their technique for intraoperative targeting of small pulmonary nodules using a triangulation method that involves calculating anatomical distances to fixed, recognizable anatomical landmarks using a 3D reconstruction with Synapse software.

The technique is original with a very high reported success rate (98.5%).

Nevertheless, some points should be clarified in order to evaluate the further publication of the study.

1- The introduction should be reconsidered: despite the improvement of patients' living standards, access to the chest scanner remains a medical issue and its use is rather linked to the increase of lung cancer screening programs and the improvement of oncological follow-up. These two elements should be mentioned in the text.

Reply 1: With the continuous improvement in people's living standards and the increase of lung cancer screening programs and the improvement of oncological follow-up, chest CT examinations have become increasingly popular, and the screening rate of lung nodules in the population has been rising.

Changes in the text:

we have modified our text as advised (see Page 4, line57-58).

Comment 2: At page 5 line 92, authors cite as inclusion criteria the fact that “the nodule is not visible to the naked eye during surgery”: this criterion should be objectified, for example by including the minimum distance from the pleura for which a nodule is considered not visible on the surface (more than 5 mm) or the absence of retraction of the visceral pleura on preoperative CT-scan, etc.

Reply 2: Nodules were not visible to the naked eye during the operation

--and the absence of retraction of the visceral pleura on preoperative CT-scan.

Changes in the text: We have modified our text as advised (see Page5, line94-95).

Comment 3: Surgical selection criteria should be clarified and included in the “inclusion criteria” section; for example: evolving nodules, positivity on 18-F-FDG Pet scan, highly suspicious nodules discussed during multidisciplinary tumor board. Otherwise, the paper will imply that all patients with detected pulmonary nodules underwent a diagnostic surgical resection.

Reply 3: Evolving nodules, highly suspicious nodules discussed during multidisciplinary tumor board; and the absence of retraction of the visceral pleura on preoperative CT-scan.

Changes in the text: We have modified our text as advised (see Page5, line94-95).

Comment 4: At page 6 line 122: patient positioning should be simplified with: lateral decubitus position. Otherwise, authors should better explain what “contralateral side” means.

Reply 4: All patients received general anesthesia in the operating room and underwent the double lumen endotracheal intubation technique as usual, and then they were placed in a 90-degree lateral decubitus position

Changes in the text: We have modified our text as advised (see Page6, line125-126).

Comment 5: Authors should better describe “localization time”, especially since the median time of the procedure is only 11 minutes: does this time include the targeting of line A + cotton ball fixation + ventilation of the lung + melanin injection + point A identification?

Reply 5: The target nodule localization time includes the whole operation process from the beginning of finding point B to determining point A on the pleura.

Changes in the text: We have modified our text as advised (see Page7, line152-153).

Comment 6: The authors report an extraordinary 98.2% result of nodule identification and resection and no conversion to thoracotomy. Authors should better describe what happened to the two unfused nodules. Indeed, they should better explain the phrase at page 12 line 273: “In this patient, the lung was ultimately completely removed by a second expansion wedge resection”.

Reply 6: We have modified our text as advised (see Page12-13, line284-293).

Changes in the text: We have modified our text as advised (see Page12-13, line284-293).

Comment 7: The authors should describe the management of patients who have been diagnosed with primary lung cancer: in this case, has an anatomical resection (lobectomy or segmentectomy) combined with radical lymphadenectomy been performed?

Reply 7: We have modified our text as advised (see Page8, line180-182).

Changes in the text: We have modified our text as advised (see Page8, line180-182).

Comment 8: The triangulation between points A, point B and line A is really interesting: in particular how the authors manage to precisely calculate linear distances on curved structures (ribs and chest wall) and then precisely recalculate the same distances intraoperatively using a soft ruler. The authors should describe whether the preoperative measurements are only possible using Synapse software or whether this calculation can also be performed using other radiological software. In addition, a short video showing the intraoperative use of soft ruler would be very

interesting and useful to understand the details of the targeting procedure.

Reply 8: As far as we know, there are many kinds of radiological software such as Synapse software or Minics software can precisely calculate linear distances on curved structures (ribs and chest wall) between two points. We provide a small video to help everyone to understand the process of preoperative measurement with Synapse software.

Changes in the text: there is no need to modify the text.

## **Reviewer B**

Summary and comments:

1. Interesting description of a thoracoscopic localization technique for small, peripheral pulmonary nodules
2. Moderate size, single-center, retrospective review demonstrating impressive accuracy and localization time
3. Slight variation from previously published techniques (eg, Sekimura A et al. Virtual thoracoscopic imaging-assisted pleural marking of pulmonary nodules. J Thorac Dis 2020; 12(8):4148-56.)

Questions / suggestions:

Comment 1: When attempted, how often was this method not successful? For example, due to extensive adhesions or inability to complete appropriate tattoo on visceral pleura? Could this be predicted pre-operatively based on the CT scan?

Reply 1: By retrospectively analyzing the data of this group of cases, we found that intraoperative application of the precise 3D positioning method based on anatomical landmarks has a positioning accuracy of 98.5%, which means that two cases of them deviations in positioning. In these two patients had inaccurate positioning and needed secondary extended wedge resection. We reviewed the preoperative CT films of these two patients, which did not indicate significant pleural adhesion beforehand.

Changes in the text: there is no need to modify the text.

Comment 2: Can you provide further specifications (eg, manufacturer) for the devices used in the procedure including the infusion catheter and Kangpai glue?

Reply 2: we have modified our text as advised (see Page7, line133-135).

Changes in the text: We have modified our text as advised (see Page7, line133-135).

Comment 3: Was the infusion catheter inserted through the surgical port? The description is slightly unclear.

Reply 3: Yes, the infusion catheter was inserted through the surgical port during the procedure.

Changes in the text: We have modified our text as advised (see Page 7, line 133-134)

Comment 4: p. 7, line 142: How was the distance from the marked point to the pulmonary nodule measured? From the images it appears that the inked area on the visceral pleural is an irregular area of dye, rather than one discrete point. For example, was this distance measured from any area of dye marking or was an estimate of the center made?

Reply 4: The distance from the center of the marked point to the visceral pleura closest to the pulmonary nodule on the specimen was measured and recorded.

Changes in the text: we have modified our text as advised (see Page 7, line 147-148)

Comment 5: p. 8, line 183: Bronchoscopic approaches (including robotic-assisted) are another major way to diagnose pulmonary nodules and may predominate depending on location/resources.

Reply 5: we have modified our text as advised (see Page 9, line 195)

Changes in the text: we have modified our text as advised (see Page 9, line 195)

Comment 6: p. 23, table 2, heading "Pathology": For the 12 cases (9.2%) which showed "no significant evidence of malignancy" was there a specific benign pathologic diagnosis found or was a nodule palpated intra-operatively? Otherwise, how can you ensure that the nodule on CT was appropriately sampled?

Reply 6: The nodules of each of the 12 patients were palpable during the operation and confirmed on the postoperative specimens

Changes in the text: we have modified our text as advised (see Page 7, line 143-145)

After the lung was collapsed for better exposure, we used oval forceps to clamp the pre-resected lung tissue with the melanin mark and then use fingers to feel if there is a nodule that can be palpated intra-operatively, then removed the lung tissue containing the palpable nodules with a thoracoscopic linear cutting stapler.

## **Reviewer C**

This is an interesting article about a novel non-invasive method of pre-surgical location of pulmonary nodules. The manuscript is well written but I consider that some modifications should be made in order to improve the manuscript

Introduction:

-location using radiotracers should be added since there are several publications that show that it is a good method.

Reply: We have modified our text as advised (see Page 4, line 66)

Changes in the text: We have modified our text as advised (see Page 4, line 66)

-The introduction only has a reference. I consider that a minimum of 10 articles must be referenced to make a correct introduction to an original article.

Reply: We have modified our text as advised (see references)

Changes in the text: we have modified our text as advised (see references)

Results:

-There is information that appears both in the manuscript and in the tables and that is redundant (for example, the location of the nodules. I recommend mentioning the table in the text and avoiding duplicating information.

Reply: We have modified our table1 as advised (see Table 1)

Changes in the text: We have modified our table1 as advised (see Table 1)

-It would be interesting to know the histology of benign nodules for more complete information.

Reply: All nodules were confirmed in the section of postoperative specimens.

Changes in the text: we have modified our table1 as advised (see Page 8-9, line 181-182)

Comments:

-I recommend including the different articles that cite the criteria that make a pre-surgical localization necessary (Daniel TM. A proposed diagnostic approach to the patient with the subcentimeter pulmonary nodule: techniques that facilitate video-assisted thoracic surgery excision. *Semin Thorac Cardiovasc Surg.* 2005;17:115-22; Zaman M, Bilal H, Woo CY, Tang A. In patients undergoing video-assisted thoracoscopic surgery excision, what is the best way to locate a subcentimetre solitary pulmonary nodule in order to achieve successful excision? *Interact Cardiovasc Thorac Surg.* 2012;15:266-72; Seo JM, Lee HY, Kim HK, Choi YS, Kim J, Shim YM, et al. Factors determining successful computed tomography-guided localization of lung nodules. *J Thorac Cardiovasc Surg.* 2012;143:809-14).

Reply: We have modified our table1 as advised (see Page 5, line 94-95)

Changes in the text: we have modified our table1 as advised (see Page 5, line 94-95)

-The authors should point out the inability to determine that the nodule is included in the specimen or the inability to assess the resection margins intraoperatively as a disadvantage compared to ultrasound or radiotracers (Vollmer I, Sánchez-Izquierdo N, Martínez D, Sánchez-Lorente D, Casanueva-Eliceiry S, Boada M, et al. Role of a portable gamma-camera with optical view for margins assessment of pulmonary nodules resected by radioguided surgery. *Eur J Nucl Med Mol Imaging.* 2021;49:361-70; Kondo R, Yoshida K, Hamanaka K, Hashizume M, Ushiyama T, Hyogotani A, Kurai

M, Kawakami S, Fukushima M, Amano J. Intraoperative ultrasonographic localization of pulmonary ground-glass opacities. J Thorac Cardiovasc Surg. 2009;138:837-42).

Reply: In addition, another disadvantage of this localization method compared with ultrasound or radiotracers is that sometimes it is unable to determine whether the nodule is included in the specimen or to evaluate the resection margins intraoperatively.

Changes in the text: we have modified our table1 as advised(see Page 13, line 295-298).

## **Reviewer D**

This study retrospectively evaluated the usefulness of the precise 3D method based on anatomical landmarks for localizing small peripheral pulmonary nodules during VATS. This localization method is minimally invasive, and can be performed during operation without fluoroscopy/CT guidance. The authors demonstrated the high accuracy and safeness in this study. This is a well-written paper and would provide useful information for readers. My comments are as follows.

### Minor Comments

1. Please describe the definition of the accuracy of localization.

Reply: The distance from the center of the marked point to the visceral pleura closest to the pulmonary nodule on the specimen was measured and recorded, which less than 20mm with negative surgical margin were identified as accurate positioning.

Changes in the text:

we have modified our text as advised (see Page7, line147-149).

2. Please describe the definition of the target nodule localization time.

Reply: The target nodule localization time includes the whole operation process from the beginning of finding point B to determining point A on the pleura.

Changes in the text: We have modified our text as advised (see Page7, line147-149).

3. Did you use intraoperative pathological diagnosis during operation?

Reply: Yes, we used intraoperative pathological diagnosis during operation for all cases.

Changes in the text: there is no need to modify the text.

4. What were the operative procedures? Did all patients successfully undergo VATS wedge resection?

Reply: All eligible patients with pulmonary nodules requiring surgery had thoracoscopic wedge resection firstly, once the pulmonary nodule was confirmed to be removed, the specimen was quickly frozen and sent to the pathology department for pathological examination to evaluate the nature of the pulmonary nodules so that the next step of the operation (segmental pneumonectomy or lobectomy) could be determined.

Changes in the text: there is no need to modify the text

5. What is the difference between Figure 3-1b and 2a?

Reply 5: Figure 3--2a is an enlarged view of 1b, so that everyone can see the detail of measured distance.

Changes in the text: There is no need to modify the text.

6. Please add “Point A, Point B, and Line A” in figures 3 and 4.

Reply 6: we have modified our figures (see figures 3 and 4)

Changes in the text: there is no need to modify the text.

7. Line 174. Change “pulomnary” to “pulmonary.”

Reply 7: We have modified our text as advised (see Page 9, line 185)

Changes in the text: we have modified our text as advised (see Page 9, line 185)