Peer Review File

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Reviewer A

Comment #1: The search for new methods that make the identification of non-palpable nodules easier is always a coveted project. There are many techniques, but none without defects and less than optimal results. The work proposed is interesting even if personally complex. Position Clips based on previous CTs respecting the previous position, repeat scans, resect and recheck, probability of enlargement. Improve the description of the technique and linguistic exposure.

Reply #1: Based on your suggestion, we added the following description to the "Step-by-step Description" section.

Changes in the text:

(Lines93-95). … prior to the day of surgery (Figure 2A,B) and considering the location of the intercostal, vertebral and interlobar fissures, the tumor location is estimated, or based on the results of prior presumptive palpation, the first marking is placed on the lung surface…

(Lines102-105). Although most tumors can be located based on either preoperative CT-scan or palpation, several Marking-scans may be required if identification is challenging. Alternatively, some cases are more easily identified by palpation than expected by preoperative CT, owing to the natural growth of the tumor.

Reviewer B

This is an interesting report including clear and full description of the procedures and high-quality images and videos. I just have two comments and I thank the authors for reading and considering them.

1. To my understanding this procedure is very useful and adds value to the current techniques used for peripherally located lung nodules. I don't this your procedure could help in the detections and adequacy of the resection margins for central tumours or nodules I the proximity of lobar vessels. I'm kindly suggesting discussing this in the manuscript.

Reply #1: Although no clear criteria have been established for the indication of this method, it is mainly indicated for peripheral lung nodules within approximately 1/3 external of the lung field, and for pure/part-solid GGOs or small solid lesions less than 1 cm in diameter. As you pointed out, it is not indicated for

proximal tumors or nodules. We added the description of the indication for this method to the “Preoperative Preparations and Requirements” section.
Changes in the text:
(Lines77-79). We adopted this method for peripheral lung nodules within approximately 1/3 external of the lung field, and for pure/part-solid GGOs or small solid lesions than 1 cm in diameter.

2. My second suggestion is related to your statement on the feasibility of standard ORs. Hybrid ORs equipped with all your requirements are currently an exception in many places or its availability must be shared with other different surgical specialities. The last could decrease the availability of your technique in real world practice, especially as the numbers of the detection of small pulmonary nodules is rapidly increasing. Some comments on this would be welcome.
Reply #2: As you pointed out and mentioned in the “Highlight box”, the opportunities for resection of nonpalpable lung tumors will continue to increase. Therefore, in order to stably perform this method, the prevalence of hybrid operating rooms and the the shortening of the operating time through standardizing the procedure are considered necessary.
The following description is added to the “Discussion” section.
Changes in the text:
(Lines241-243). The opportunities for resecting nonpalpable lung tumors will continue to increase. Therefore, the prevalence of hybrid operating rooms and standardization of techniques aimed at shortening operative time are necessary to ensure the stability of this method.

Reviewer C

Comment #1: I suggest to include data regarding smoking exposure, pack-years and comorbidities
Please, include the functional data of patients who underwent surgery
Please, better explain the type of CT scan used
A reference about the relationship between smoke and lung nodule should be added for discussion
Cancer Invest. 2014 Oct;32(8):388-93.
Reply #1: Smoking history, respiratory function data, and comorbidities of the patients who underwent our method are added to Table 1. The model of the Hybrid operating room has already been described in “Preoperative Preparations and

Requirements," and we have added a description of a "stationary digital cardiovascular fluoroscopy system." A discussion of the relationship between smoking and pulmonary nodules is added in the "Discussion" section.

Changes in the text:

(Lines73-74). …a stationary digital cardiovascular fluoroscopy system.

(Lines202-204). Fibrosis due to interstitial pneumonia or emphysematous changes due to smoking make it more challenging to identify the location of the lung nodule, and preoperative smoking cessation might reduce tumor size (17).

Changes in the Table 1:

We added sections on smoking history, respiratory function, and comorbidities in Table 1. In addition, the symbol indicating ranges of number was changed from a hyphen to en dash.

Changes in the References:

Reference 18 was added and the former reference number 18 and after was moved back in sequence.

Reviewer D

Comment #1: Abstract. Line 39;

What does OS-MRCH stand for? What is its full spelling?

Reply #1: OS-MRCH is an abbreviation of a capitalized portion of "One-stop Solution for a nonpalpable lung tumor, Marking, Resection, and Confirmation of the surgical margin in a Hybrid operating room." We considered capitalizing it as described here, but decided to follow the guidelines for authors. When presenting at congresses, the capitalized parts are underlined for emphasis.

Comment #2: Preoperative Preparations and Requirements. Line 72:

I think that it was probably aimed at obliterated lung field lesions, but I would like to see a description of which part of the lung was involved in tumors. For example, "in the outer third of the lung".

Reply #2: Although no clear criteria have been established for the indication of this method, it is mainly indicated for peripheral lung nodules within approximately 1/3 external of the lung field, and for pure/part-solid GGOs or small solid lesions less than 1 cm in diameter. As you pointed out, it is not indicated for proximal tumors or nodules. We added the description of the indication for this method to the "Preoperative Preparations and Requirements" section.

Changes in the text:

(Lines77-79). We adopted this method for peripheral lung nodules within

approximately 1/3 external of the lung field, and for pure/part-solid GGOs or small solid lesions than 1 cm in diameter.

Comment #3: Step-by-step Description. Line 105;" If the margin is found to have been insufficient," Clearly indicate what criteria are used to determine that the surgical margin is insufficient in the "Resected-lung-scan". If the SM is determined by the distance between the excision line and the tumor edge, wouldn't there be a difference depending on the degree of air injected?

Reply #3: A surgical margin is considered insufficient when the "Resected-lung-scan" after air injection does not ensure a margin of approximately 2-5 mm. As you pointed out, the judgment depends on the degree of air injection, therefore, we do not set strict criteria and apply the forementioned criteria in general.

The description in the "Step-by-step Description" section was changed as follows.

Changes in the text:

(Lines114-116).

~~If the margin is found to have been insufficient, additional resection of the lung, including partial resection, segmentectomy or lobectomy is performed.~~

If the Resected-lung scan does not ensure a surgical margin of approximately 2–5 mm, it is considered insufficient and additional resection, including partial resection, segmentectomy or lobectomy is performed in the same operating room.

Comment #4: Postoperative Considerations and Tasks lines 121-123;

In two cases where surgical margin was considered insufficient during surgery, additional partial resection was performed. If you want to add a segmentectomy or lobectomy, will it be done at a later date? Is it because it is difficult to get into a lateral decubitus position?

Reply #4: If it is determined during surgery that the surgical margins are insufficient and a segmentectomy or lobectomy is required, the procedure can be performed immediately. The operating table in our hybrid operating room is narrower than usual, making the surgeon's workload greater than in a regular operating room, but the surgery itself is still possible. In one of these 60 cases, a segmentectomy was performed on a concurrent lesion in segment 6, which was not a target lesion for OS-MRCH. However, none of the cases in this study required additional segmentectomy or lobectomy. This point was not clearly described, therefore, the description in "Step-by-step Description" was changed as follows.

Changes in the text:

(Line115). …segmentectomy or lobectomy is performed immediately in the same operating room.

Comment #5: 2nd and 3rd paragraphs of the Discussion;
I think the authors could have emphasized more that the method of marking the surface of the lung with surgical clips and identifying the tumor location by CBCT is superior to other methods. Specifically, there are no serious complications, a high lesion identification rate (145 lesions, including pure GGN, 100% have been reported in the previous literature), and all surgical procedures can be completed in the operating room, so there is less stress on the patient. It is recommended that you add a paper that reports these things in detail to the citation; Cone-beam computed tomography-guided marking of small pulmonary nodules with surgical clips. Kurume Medical Journal, 68; 183-189. 2021.

Reply #5: As you pointed out, we should emphasize that no complications have occurred due to this method. We include additional information about complications in the "Postoperative Considerations and Tasks" section to indicate that there were no serious complications and that no complications were attributed to this method. Table 2 is also modified as follows. The statement about the high identification rate of lesions is consistent with a recommended article; therefore, we added the description and renewed the Reference list in the "Discussion" section.

Changes in the text:

(Lines 138-140). Regarding postoperative complications, prolonged air leak was observed in two cases, and chest wall bleeding in one case. No unique complications were attributed to this method including air embolization owing to clipping (Table 2)

(Lines 229-231). The results are consistent with the report by Mitsuoka et al. (21) that 145 lesions, including pure GGO, were identified 100% by CBCT, indicating that CBCT is sufficient to detect GGO and small lung nodules.

Changes in the Table 2:

We added the results on complications.

Changes in the References:

Reference 22 was added.

Reviewer E

Comment #1: Page 5 - line 71-82: Please report the selection criteria to consider non-palpable pulmonary nodules for hybrid room surgery (e.g. dimension and depth thresholds).

Reply #1: Although no clear criteria have been established for the indication of this method, it is mainly indicated for peripheral lung nodules within approximately

1/3 external of the lung field, and for pure/part-solid GGOs or small solid lesions less than 1 cm in diameter. As you pointed out, it is not indicated for proximal tumors or nodules. We added the description of the indication for this method to the "Preoperative Preparations and Requirements" section.

Changes in the text:

(Lines77-79). We adopted this method for peripheral lung nodules within approximately 1/3 external of the lung field, and for pure/part-solid GGOs or small solid lesions than 1 cm in diameter.

Comment #2: Page 7 - lines 110-125: Authors reported the resection of primary lung cancer in 45 cases but only one patient had a completion lobectomy, and he had a two-stage procedure. Can authors comment on this? Did you consider a wedge resection ontologically correct in 44 patients? Why don't you consider lobectomy as a one-stage procedure in patients with frozen section positive for primary lung cancer?

Reply #2: As you pointed out, lobectomy is the standard procedure for lung cancer. Alternatively, the JCOG0802/WJOG4607 trial showing better results of segmentectomy in non-small lung cancer less than 3 cm with appropriate patient selection than lobectomy or CALGB140504 trial showing favorable results of sublobar lung resection in small non-small lung cancer in the peripheral lung field, indicate that reduced surgery for small lung cancer is likely to increase in the future. In addition, cases with multiple lung cancer are increasing, and we believe that sublobar lung resection benefits appropriate patients. We perform such reduced surgery both on patients with small peripheral lung cancer and on patients intolerant to lobectomy for reasons including poor respiratory function, and this study includes both types of patients. In other words, for the 44 cases of primary lung cancer you mentioned, we considered the wedge resection appropriate based on oncological or surgical tolerability factors.

We added the following description about reduced surgery to "Postoperative Considerations and Tasks," and about recent findings and prospects for sublobar lung resection to "Discussion," indicating a tendency for reduced surgical resection for lung cancer. We also would like to note that we did not quote the JCOG0802 trial since there were no cases of segmentectomy in our study.

Changes in the text:

(Lines 135-138). The final procedure in 44 of the 45 primary lung cancer cases was wedge resection not lobectomy, which included both "radical reduced surgery," for small peripheral lung cancer, and "palliative reduced surgery" for the patients intolerant of lobectomy due to such factors as poor respiratory function.

(Lines159). ….sublobar resections, especially for peripheral small lung tumors.

Comment #3: Page 9 – lines 167-180: The proposed localization technique does not consider an intraoperative surgical margin evaluation. Localization was performed by the placement of a fiducial (metal clips) on lung surface only. By placing a radiopaque marker near the deep edge of the target nodule, intraoperative CBCT can be effectively used to ensure good surgical margins by a real-time cross-check of the relative position between nodule and stapler line before firing, avoiding the need of further parenchymal resection [Mazza F, Venturino M, Peano E, Balderi A, Turello D, Locatelli A, Melloni G. Single-Stage Localization and Thoracoscopic Removal of Nonpalpable Pulmonary Nodules in a Hybrid Operating Room. Innovations (Phila). 2020 Nov/Dec;15(6):555-562.]. Both superficial and deep marking techniques have pros and cons, please comment on this in the discussion section.

Reply #3: As you pointed out, CBCT in the hybrid operating room is useful to confirm deep surgical margins as Mazza et al. reported. Since our method can be considered a modified version of their method, we added the following description to the "Discussion," and added the article to the References.

Changes in the text:

(Lines 188-191). Mazza et al. reported a method of superficial and deep edge marking in a hybrid operating room during surgery for nonpalpable lung tumors (17), and our method is a more simplified version of their method eliminating the need for the bronchoscopic marking by CBCT-scanning of resected lung to confirm the deep margin.

Changes in the References:

Reference 17 was added.