

Peer review file

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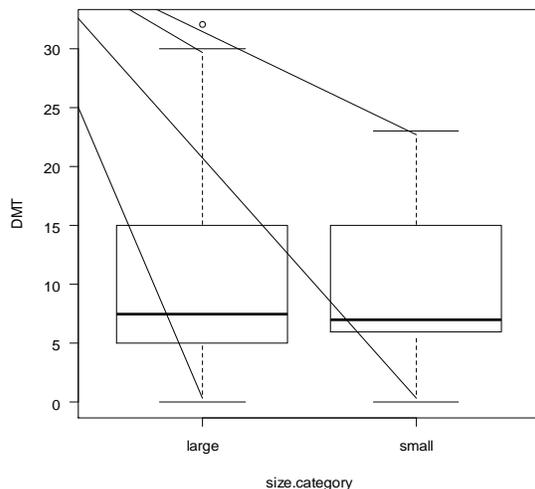
Reviewer A

Comment:

1. It is an easily and applicable method to help lesion localization.
2. I am looking forward to your research team to improve your marking accuracy.
3. Please challenge on smaller nodule, I mean your inclusion criteria could change to a peripheral pulmonary nodule ≤ 10 mm.

Reply: The association between DMT and tumor size has not been present.

Following your advice, we also analyzed DMT in groups with tumors <10 mm, but there was no change when compared to groups larger than that.



The large group tumor size was ≥ 10 mm, and the small group was < 10 mm.

large group DMT =

(10.437500 ± 8.976448)

small group DMT = (9.727273 ± 6.512924)

$p=0.811$ (Student t-test)

Since a marker dragging is likely to have lowered the accuracy, we are currently testing more suitable materials as markers. This point has been described in P11, Line2-4.

Changes in the text: none

Reviewer B

Comment 1: I would appreciate more detail in the actual technique. If you could describe what is required to obtain the virtual thoracoscopic image. From the paper, it appears to simply be a 3D reconstruction of a CT scan of the chest. If it is more than that I think it would be useful for the reader to know what is required to obtain a virtual thoracoscopic image.

Reply 1: As you pointed out, the virtual thoracoscopic image is a 3D reconstructed image created from normal CT.

However, it is needed to subtract the caudal object from the diaphragm to obtain a similar view of the chest wall from the inside with a thoracoscope. And if the pulmonary blood vessel is covered, the chest wall is difficult to see correctly. Therefore, the work was required to remove the pulmonary blood vessel from this object. We have added the actual technique.

We have added the text in the method section.

Changes in the text: we have added the text as follows: “The method of creating the virtual thoracoscopic image was as follows. 3D reconstruction was performed from the preoperative CT image. The caudal object from the diaphragm was subtracted. At this point, a similar view to that of a thoracoscope was obtained by looking at this object from the caudal side.

The location of the tumor was confirmed on the axial image, and the chest wall region closest to this was marked on the 3D image. However, since the pulmonary vascular were also synthesized in this image, by selecting the pulmonary blood vessels and subtracting them from the 3D reconstructed images, an image closer to the chest wall image observed by the thoracoscope can be obtained.” (page 4, line 22 to page 5 line 8).

Comment 2: It would be helpful to describe the actual surgical technique in more detail. Describe the number of ports that are used to perform the VATS procedure, The location of the ports. Describe the size of the ports that are used to perform the VATS procedure. Were surgical ports actually used or small incisions. How is the dye applied to the pleura.

If this is injected percutaneously at the time of thoracoscopy or if it is applied directly to the pleura through a thoracoscopic port. If it is applied directly to the pleura via a thoracoscopic port, does this require that the operating surgeon add an additional port for localization.

Reply 2: Thank you for your point. The detail of the technique has been added in the technique section. The surgical approach was 3 port VATS. The location of the ports was that: operator's port was 4 cm incision on the 4th intercostal space on the anterior axillary line. Camera port was 2 cm incision on the 7th intercostal space on the middle axillary line, and assistant's port was the same size incision on the 7th intercostal space on the caudal side of the scapula. The pleural marker with dye was imported from the operator's port using forceps.

We have described a detail technique in the technique section.

Changes in the text: “The surgical approach was as follows. The operator's approach port was a skin incision of 4 cm in size on 4th intercostal space on the anterior axillary line. The camera port was a 2 cm skin incision in 7th intercostal space on the middle axillary line. And the assistant's port was a 2 cm skin incision in the 7th intercostal space of caudal side of a scapula. Under the thoracoscopic view, “ (page 5, lines 9 to 13).

Comment 3: You mentioned using the number of the rib as well as an additional landmark to establish the approximate location of the nodule. Was the number of the rib and landmark based on surface anatomy prior to thoracoscopy or is the rib counted after thoracoscopy and is established at the time of VATS.

Reply 3: The number of the rib was recognized during VATS, referring to virtual thoracoscopic images. We have described the detail in the technique section, but we have added more detail to the sentence

Changes in the text: “Under the thoracoscopic view” (page 5, lines 12 to 13).

Comment 4: The CT scan of the chest is performed while the patient is typically in a supine position however VATS is normally performed with the patient in a lateral position. Please comment on the position of the patient at the time of surgery in your discussion and how that may impact your landmark, your rib count and thus the position of the nodule in relationship to the rib number.

Reply 4: In the previous study, we made a cutaneous marking under preoperative CT performed in the lateral position. The result was similar to the present study. Therefore, we considered that the position in preoperative CT does not affect the location of the tumor so much.

Changes in the text: We have added the sentence, “However, all patients are positioned in a lateral position during surgery. Initially, there was concern about the location of the tumor in the supine and lateral positions. In the previous study, we marked the body surface under the CT guide in the lateral position before the surgery (7). However, in this study, since the previous study and DMT were almost unchanged, it was considered that even the CT imaged in the supine position had the same accuracy as under the marking in the lateral position.” in the discussion section (see page 10 line 10 to 15).

Comment 5: You mentioned using an ultrasound or ultrasound gel. It was unclear in the manuscript how this was utilized at the time of surgery. Overall, I think this has the potential to add useful information as well as groundwork for a technique to help surgeons better localize and biopsy subcentimeter pulmonary nodules.

Reply 5: Ultrasound gel was used for the solution of dye because mixed gel and dye can stay on the pleural surface. And, we did not use ultrasound during surgery. Please forgive us if it seemed like we used ultrasound.

Changes in the text: We have described how to make the mixed dye gel in the technique section “The mixed dye was prepared by mixing 0.5 ml of dye and 1.5 ml gel.” (page 5, line 19). And we have added the reason for using echogenic gel for mixing the dye in the discussion section “The echogenic jelly was suitable for solutes of liquid pigments, and the mixture of pigments and gel was useful for keeping the pleural surface of the lungs. Since the liquid dye easily spreads widely from the lung surface, the target area is easily blurred. Therefore, the mixed gel was suitable for pleural marking. “(see page 10, line 18 to 21).

Reviewer C

Comment 1: There are some data different in the abstract and in the main text, which confuses me. You summarized 28 cases (82%) were palpable nodules in the abstract, but 39 (84.7%) in the results. I do think this is a major problem. You should have checked the whole data before you confirmed proofreading.

Reply 1: After reviewing the data, the number in the abstract was incorrect, so we would like to correct it (see page 2, line 16).

Changes in the text: page 2, line 15; 28 cases (82%) to 42 cases (92%).

Comment 2: The statistical presentation could be better. For example, you should have not mentioned the t-test in the method section, because you even did not perform any comparison in this single-arm study. Besides, please unify your descriptive statistics. For example, use mean (SD: xxx-xxx) or median (IQR: xxx-xxx, or range: xxx-xxx). And, you also have to mention these in your tables.

Reply 2: Following your comment, we have modified tables.

Changes in the text: Tables 1, 2 added the legend. (page 16 line 2, page 17 line 5)

Comment 3: I do enjoy your innovation, but there are some problems regarding this technique. Here are five of them:

First, how you prevent the surgical tape sliding during two-lung ventilation. It seemed that you did not suture it to the pleura, so it could be pushed by the lung parenchyma, resulting in wrong markings.

Reply: We have prevented dragging by squeezing, expanding lung just before contact. At the time of contact, the lung can be expanded fully. This procedure is established in the previous study using the pleural marker, so we have added the procedure.

Changes in the text: We have added the sentence, “To avoid marker dragging by expanding the lungs, we squeezed until the lungs were completely expanded.” (page 5, line 23 to 24)

Second, you did not mention how you managed on the 2 cases in whom the marker could not be placed. I think this is important to convince readers by showing trouble-shooting.

Reply: In these cases, we performed finger palpation and could detect the location of the nodules, fortunately. In these anatomically difficult cases, to overcome, we have changed the access port to insert the pleural marker by forceps, and for the case of nodule behind the diaphragm, we have squeezed the diaphragm until two-lung ventilation.

We have added the explanation in the discussion section.

Changes in the text: (“Fortunately, the finger palpation without marking was able to detect the nodule, in these cases.” page 9, line 24 to 25)

(“Therefore, after case 10, we have caudally excluded the diaphragm during marking and transferred dye to the lung surface by bilateral ventilation. This enabled marking on the lung surface even on the dorsal side of the diaphragm.” Page 10, line 6 to 8)

Third, you repeated in the introduction and the discussion that some methods by other authors cannot be applied near the heart and great vessels. However, you also excluded these patients in your study. So, why you mention this? Or, have you solved this problem?

Reply: As you pointed out, we have excluded the cases that needed putting the marker on the heart or the diaphragm, because the mechanical stimulation of the heart can be a risk of arrhythmias and heart damage. However, we did not exclude the tumor contacts to the major vessels. Even if the nodule was near the heart or major vessels, putting the pleural marker onto the chest wall was possible. However, we have avoided putting the marker on the heart or diaphragm. We excluded from the present study if we could not make a marking without putting a marker on the heart or the diaphragm. Based on these, we recognize that the exclusion criteria for this study are correct.

Therefore, at this point, we have added an explanation to the discussion section.

Changes in the text: (“Furthermore, in the present study, we have excluded the cases that needed putting the marker on the heart or the diaphragm because doing so has a risk of arrhythmia and injury, and it is difficult to put the marker on the correct point with the rib coordinate system. However, even with the nodule near the heart or major vessels, putting the pleural marker onto the chest wall was possible, but we have avoided putting the marker on the heart or diaphragm. For the cases in which putting the marker on the heart or diaphragm cannot be avoided, the present method is difficult to perform.” Page 11, line 6 to 12)

Fourth, it is the biggest question for me that you mentioned a large portion of your cases were "palpable". Then, why you need this technique, which would prolong the procedure time and increase risks for patients?? It means that you have to provide more solid evidence. For example, please validate your data with a proper model if your goal is to do a validation study. Or reconfirm your inclusion criteria to be non-palpable nodules... etc.

Reply: The primary endpoint of the present study was DMT.

As you pointed out, at the result, many nodules were palpable in this study. To compare with the cases without marking, the comparison study will be needed.

However, this method was helpful for surgeons to confirm whether a palpated tumor was really the targeted one (page 9, lines 9 to 12).

As you pointed out, we think that it is somewhat problematic to discuss whether palpation is possible in this report, so we delete the explanation about the palpation in the abstract.

Changes in the text: We have deleted “In 28 cases (82%) the surgeon could palpate the nodules” (page 2, line 16).

Fifth, if feasible, please share the video with we readers to understand the procedure step by step.

Reply: We have tried to upload the video, but it was impossible. We would like to ask the Editor if we can upload it again.

Comment 4: Please try not to use the emotional word because I believe every technique has its value, or you have to provide solid evidence to say that word. For example, lines 40-41 in the introduction section.

Reply 4: The words just like “terrifying maneuver” and “cumbersome” were inappropriate. So we have changed the words.

Changes in the text: “maneuver with the risk of a vascular injury.” Page 3, line 10. “complicated.” Line 16.

Comment 5: Please try to clarify the references in the discussion section. I know you have done the reference review, but sometimes I was confused with it. It means that I have no idea why you mention this reference. Please try to lead your readers swimming cross the ocean of literature, not drawn them. Besides, you don't have to make a table to compare the methods because your study is not a systemic review.

Reply 5: As you pointed out, table 3 was superfluous. We have deleted it. As for Discussion, the content duplicated with the introduction section was seen, so this is deleted.

The flow of discussion contents for each paragraph was

- 1) Classification of Marking methods
- 2) Problems with conventional pleural marking
- 3) The connection between Previous study and Present study
- 4) Explanation of Costal Coordinate system
- 5) Regarding the above, the role of virtual thoracoscopic image
- 6) Explanation of marking accuracy
- 7) Explanation of problems in our present methods and their countermeasures
- 8) Necessity and safety of echo jelly
- 9) Limitation
- 10) Conclusion.

We do not think there is any discrepancy in the discussion flow.

Changes in the text: We have deleted table 3 and the sentence, “Small pulmonary nodules, which are suspected to be malignant, but lack a preoperative pathological diagnosis, require surgical resection and frozen section diagnosis. However, small nodules are difficult to localize on palpation via a small access port during VATS. For small nodules that are more than 5 mm deep to the visceral pleura, preoperative marking is recommended before surgery (4).” was deleted from the discussion section. (page 7, line 12-)

Comment 6: Major problems with the table. I am not sure it is the system problems or something other. I noted that the typesetting of the tables was really....you know. I could not even read it. Please! Please do proofreading before you sent your PDF. I think this is your responsibility.

Reply 6: We apologize for the broken table that was still in proof. We have rechecked it and deleted it.

Comment 7: If feasible, please consider English editing. There were too many grammar problems, such as tense and phrases.

Reply 7: This report has been checked by native English speakers. We again requested English editing and submitted the modified version.

Reviewer D

Comment 1: How many patients were excluded according to the exclusion criteria? I recommend the authors take a figure to show the screening process.

Reply 1: As you pointed out, we have added Figure 5 as a selection flow diagram.

Changes in the text: We have added “Figure 5” (page 6, line 18) and Figure 5.

Comment 2: How many pyoktanin blue was used, and what was the proportion of the mixture in this plot study? Did this localization approach have problem with the diffuse staining of the parietal pleura in your experience? If the authors could describe with more detail, other clinicians could repeat this localization approach.

Reply 2: The mixed dye was prepared by mixing pyoktanin blue 0.5 ml and gel 1.5 ml. As you pointed out, the mixed dye is useful for keeping on pleural surface, avoiding diffuse staining.

Changes in the text: We have added the sentence, “The mixed dye was prepared by mixing 0.5 ml of dye and 1.5 ml gel. The prepared marker with mixed dye was then attached to the identified pleural point from the operator’s port using forceps.” (page 5, line 19 to 21).

And we have added the sentence, “The echogenic jelly was suitable for solutes of liquid pigments, and the mixture of pigments and gel was useful for keeping the pleural surface of the lungs. Since the liquid dye easily spreads widely from the lung surface, the target area is easily blurred. Therefore, the mixed gel was suitable for pleural marking.” (page 10, line 18 to 21).

Comment 3: The abbreviations of PDS (page 4, line 85) and EZR (page5, line 97) should be defined the first time it was used within the text.

Reply 3: As you pointed out, we have corrected them.

Changes in the text: “Polydixone” added in page 6, line 2. Easy R added in page 6, line 14.

Comment 4: All abbreviations of the histological types in the Table 2 should be written out.

Reply 4: As you pointed out, we have added abbreviations in table 2.

Changes in the text: Added “adeno: adenocarcinoma, squamous: squamous cell carcinoma, pleomorphic: pleomorphic carcinoma, meta: metastatic lung tumor” in table 2 legend (page 18, line 3,4).

Comment 5: As a study on the surgical treatment of lung cancer, the pathological TNM staging must be presented.

Reply 5: In the present study, we have included nodules within 2 cm in size. And all of the patients with lung cancer had no metastatic lesion involving a lymph node. Although TNM classification is needful for the report about lung cancer, we have described the pulmonary nodule localization involved in metastatic lung tumor, benign tumor and so on. Therefore, we would like to omit the TNM classification.