

Peer Review File

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Reviewer A

Comment 1: Why was VAL-MAP DS limited to patients who were likely to have anthracosis, emphysema, or pleural adhesions in the first 1-5 patients but expanded to all patients from the 6th patient onwards?

Reply 1: We appreciate the reviewer's comment. The purpose of usage of VAL-MAP DS was for clinical use, not for experimental use. In terms of clinical benefit, VAL-MAP DS would be beneficial for patients in which conventional VAL-MAP would be likely to result in failure due to anthracosis, emphysema or pleural adhesions. After experiencing 5 cases, we expanded the indication to all patients because the novel method would seem harmless. We have modified our text as advised (see Page 6, line 76-77).

Changes in the text:

Before changes:

From the sixth patient on, we used VAL-MAP DS for all the patients with indications for conventional VAL-MAP and no history of allergy to ICG.

After changes:

From the sixth patient on, we used VAL-MAP DS for all the patients with indications for conventional VAL-MAP and no history of allergy to ICG **because VAL-MAP DS seemed harmless based on the experience of previous 5 cases.**

Comment 2: Would it have been possible to have performed the mapping procedure the same day as the surgery?

Reply 2: Yes. It would be feasible to perform the VAL-MAP DS the same day as the surgery. In the current series, all cases underwent VAL-MAP DS 1 day before surgery because of availability of bronchoscopy and surgeons. We have modified our text as follows (see Page 6, line 83-84).

Changes in the text:

Before changes:

The mapping procedure was conducted 1 day before surgery.

After changes:

The mapping procedure was conducted 1 day before surgery **because of availability of bronchoscopy and surgeons.**

Comment 3: Apical location of the lesion is also a possible risk for failure of standard VAL-MAP. How many apical lesions were in the study which may have been revealed by VAL-MAP DS?

Reply 3: Seven apical lesions were in the present study. Following the reviewer's question, we have added the sentence as follows (see Page 11, line 165).

Changes in the text:

Before changes:

Sixteen patients (80%) had one target lesion; the remainder had multiple lesions.

After changes:

Sixteen patients (80%) had one target lesion; the remainder had multiple lesions. **Seven lesions (26%) were localized apically.**

Comment 4: What was the size of the lesion in the first failure case?

Reply 4: It was 14 mm in the first failure case. We have modified our text as follows (see Page 13, line 200-201).

Changes in the text:

Before changes:

One lesion was not resected in the initial procedure and required additional resection.

After changes:

One lesion **with the size of 14 mm localized from 15 mm from pleura** was not resected in the initial procedure and required additional resection.

Comment 5: For further study: investigate how much to reduce the amount of ICG to preload with indigo carmine for patients with a history of heavy smoking.

Reply 5: We highly appreciate the reviewer's suggestion. We have added the sentence as follows (see Page 18, line 268-270).

Changes in the text:

Before changes:

To decrease problematic ICG grade C markings, the amount of ICG preloaded with indigo carmine should be reduced or modified for patients with a history of heavy smoking.

After changes:

To decrease problematic ICG grade C markings, the amount of ICG preloaded with indigo carmine should be reduced or modified for patients with a history of heavy smoking. **We need to investigate how much to reduce the amount of ICG to preload with indigo carmine for patients with a history of heavy smoking.**

Comment 6: For 11 primary lung cancers, there were only 2 segmentectomies in this study. Why was anatomic sublobar resection not favored?

Reply 6: We have two reasons for it. The first one was that most of lesions appeared non-invasive or minimally invasive adenocarcinoma. Indeed, 5 of 11 lesions had no solid part. In addition, 9 out of 11 lesions had ground-glass nodule with less or equal to 0.5 of consolidation-to-tumor ratio. The second reason was that most of patients had considerable morbidity. Due to morbidity, wedge resection was preferably selected in fear of complications. For those reasons, anatomic segmentectomies were not favored in this study. We have added the sentence as follows (see Page 11-12, line 168-171).

Changes in the text:

Before changes:

Twenty-five lesions (93%) were surgically resected by wedge resection, and the remainder by segmentectomy.

After changes:

Twenty-five lesions (93%) were surgically resected by wedge resection, and the remainder by segmentectomy. **Because most of the ground-glass lesions appeared non-invasive/minimally invasive and most patients had comorbidities, wedge resection was preferably selected even for cases with primary lung cancer.**

Comment 7: In table 3, the diameter of lesions was 10 +/- 5. A 1.5 cm lesion should be palpable. Was it too deep to locate without VAL-MAP DS?

Reply 7: Yes. Some of the 1.5 cm lesions were deeply localized and others had ground-glass opacity in whole. For those reasons, they needed VAL-MAP DS. The reasons should correspond to II-A (i) or (iii) in Table 1. We have added the sentence as follows (see Page 11, line 162-164).

Changes in the text:

Before changes:

The characteristics of the lesions and surgeries are summarized in Table 3.

After changes:

The characteristics of the lesions and surgeries are summarized in Table 3. **Although the diameter of lesions was 10.0 ± 5.3 mm as shown in Table 3, all the lesions satisfied the criteria represented in Table 1.**

Comment 8: Comment on your technique versus additional alternate modifications of VAL-MAP in the literature.

Reply 8: We profoundly thank the reviewer for the suggestion. Although we had tried to mention our technique versus another form of modified technique, it would be challenging to understand our discussion. We have corrected the sentences to comment on our method and another as follows (see Page 16, line 242-243).

Changes in the text:

Before changes:

A previous report also demonstrated the use of ICG in VAL-MAP (10). However, the report only utilized ICG to identify marking intraoperatively.

After changes:

A previous report also demonstrated **modified VAL-MAP technique using ICG** (10). **Unlike our method, they** only utilized ICG to identify marking intraoperatively.

Reviewer B

Comment 1: This study (1 center, 20 patients) is only a proof of concept. There is no randomization of the patients between 2 techniques. The conclusions (page 18) are in consequence overstated and should be attenuated with the need of randomized multi center trials.

Reply 1: We appreciate the reviewer's comment. As the reviewer pointed out, this study is a preliminary one. To our regret we have overstated the conclusions. We have corrected the sentences as follows (see Page 4, line 46, Page 20, line 301-304).

Changes in the text:

Before changes:

VAL-MAP DS is efficacious and safe in enhancing the detectability of markings.

After changes:

VAL-MAP DS **is likely to be** efficacious and safe in enhancing the detectability of markings.

Before changes:

In summary, VAL-MAP DS would improve the detectable marking rate because of dual staining with both ICG and indigo carmine. The VAL-MAP DS technique should be one of the preferred preoperative marking procedures used in general thoracic surgery.

After changes:

In summary, VAL-MAP DS **could** improve the detectable marking rate because of dual staining with both ICG and indigo carmine, **making it** one of the preferred preoperative marking procedures used in general thoracic surgery. **A multi-center prospective study would be needed to prove efficacy and safety of VAL-MAP DS.**

Comment 2: Same statement in the discussion (page 15). Too few patients and the study design is only able to demonstrate the proof of concept of this technique.

Reply 2: We thank the reviewer for the comment. The current series only showed the proof of concept. We have corrected the sentence as follows (see Page 19, line 293).

Changes in the text:

Before changes:

First, this was a non-randomized, retrospective, single-center study. Further analyses with more numerous experiences in multiple institutes would be necessary to validate our outcomes.

After changes:

First, this was a non-randomized, retrospective, single-center study, **only showing the proof of concept.** Further analyses with more numerous experiences in multiple institutes would be necessary to validate our outcomes.

Comment 3: On page 16, concerning the safety. With only 20 patients, this study is not able to detect rare and severe adverse events that occur in 1 or 2 %. The conclusions on safety should be attenuated.

Reply 3: We greatly thank the reviewer for the comment. We attenuated the statements on safety as follows (see Page 17, line 251).

Changes in the text:

Before changes:

The present study also confirmed the safety of VAL-MAP DS.

After changes:

The present study **suggested** the safety of VAL-MAP DS.

Comment 4: In the materials and methods, there should a statement that the nodules are assumed non-palpable before surgery otherwise guidance techniques are not mandatory.

Reply 4: Following the reviewer's suggestion, we have added the sentence as follows (see Page 6, line 78-80).

Changes in the text:

Before changes:

The eligibility criteria for VAL-MAP DS are summarized in Table 1.

After changes:

The eligibility criteria for VAL-MAP DS are summarized in Table 1. **As shown in Table 1, the indications were nodules which assumed non-palpable or required marking for other reasons.**

Comment 5: Concerning the evaluation of grading of marking, the purpose of the marking is to guide surgery and spare lung parenchyma for small peripheral nodules. The grading used I propose to use a grading that evaluate the usefulness of the marking to guide the surgeon. In the same study that you cited (ref N°4 16. Sato M, Yamada T, Menju T, Aoyama A, Sato T, Chen F et al. Virtual-assisted lung mapping: outcome of 100 consecutive cases in a single institute. Eur J Cardiothorac Surg 2015;47:e131-e139.) they used a grading A, B and C (Grade A, the same level of operative precision was considered to be impossible without dye marking; Grade B, a similar level of precision was considered possible but dye marking improved confident performance of the operation; and Grade C, the same operation was considered possible without dye marking) which is more useful in the real life.

Reply 5: We appreciate the reviewer's comment. We strongly agreed with the idea that usefulness of markings should have been evaluated as the reviewer suggested. However, we were not able to investigate contribution of VAL-MAP DS to operation as the previous report due to its retrospective nature. This is one of major limitations of this study. Following the reviewer's comment, we have added sentences as follows (see Page 19-20, line 297-300).

Changes in the text:

Before changes:

Second, evaluation of each marking grade might be biased. Because the two dyes

complemented each other to identify markings, the ICG marking rate might be overestimated because of indigo carmine marking.

After changes:

Second, evaluation of each marking grade might be biased. Because the two dyes complemented each other to identify markings, the ICG marking rate might be overestimated because of indigo carmine marking. **Third, unlike the previous report (4), contribution of VAL-MAP DS to operation could not be evaluated due to its retrospective nature. Further studies should investigate the actual usefulness of markings.**

Comment 6: As IC and ICG are complementary is there a place to compare them and there is no significant difference between them?

Reply 6: Following the reviewer's suggestion, we have added the result as follows (see Page 13, line 193-194).

Changes in the text:

Before changes:

Comparing the overall detectable marking rate and indigo carmine visible marking rate, the chi-squared value (calculated chi-squared test with Yate's continuity correction) was 3.08. The effect size (phi) was 0.21.

After changes:

Comparing the overall detectable marking rate and indigo carmine visible marking rate, the chi-squared value (calculated chi-squared test with Yate's continuity correction) was 3.08. The effect size (phi) was 0.21. **There was no significant difference between the indigo carmine visible marking rate and ICG visible marking rate.**

Comment 7: How many patients were smokers or past smokers. As smoking history seems to have an influence on the marking, smoking history of the patients should be more detailed. If there is a low proportion of smokers (frequent in east asian countries) it should be stated in the limitations as it is different from Europe or North America.

Reply 7: We greatly thank the reviewer for a good question. In this study, 10 patients (50%) were ever smokers. We have added the result in Table 2. We also have corrected the sentences as follows (see Page 11, line 157-158).

Changes in the text:

Before changes:

Ten patients (50%) had a history of smoking.

After changes:

Ten patients (50%) had a history of smoking and detailed pack-year smoking history was summarized in Table 2.

Reviewer C

Comment 1: The localization of the pulmonary nodules is still a hotspot for thoracic surgeons. Accuracy, precision, minimal invasiveness, less complications, and operational convenience are the major concerns of such technique. The authors present a dual staining with two different dye via a bronchoscopy, which is very similar to the electromagnetic navigation bronchoscopy. However, the authors indicated that the location tip would be confirmed via a X-ray fluoroscopy and the marking would be rechecked with the CT scan after localization, which made this procedure complicated and time-consuming. Besides, the patients would have to receive more X-ray radiation. Could the authors reconsider the feasibility and convenience of such method?

Reply 1: We appreciate the reviewer's comment. Our institute has experienced and published a marking method using electromagnetic navigation bronchoscopy (Sato M, et al. Gen Thorac Cardiovasc Surg. 2019; 67: 1062-1069.). We believed that VAL-MAP DS using electromagnetic navigation bronchoscopy would be feasible and practical. However, due to limited availability of electromagnetic navigation bronchoscopy in our institute and in Japan in general due to an issue around public health insurance, the current study did not demonstrate such a method. More recently, we have done a few cases of ENB-VAL-MAP DS without any problem, although the case was beyond the scope of the study. We have added sentences as follows (see Page 19, line 282-287).

Changes in the text:

Before changes:

As a result, we did not experience grade 5 markings (bulla formation), which would be a great risk factor for pneumothorax. Grade 5 markings reportedly occurred in about 3% of patients (2).

After changes:

As a result, we did not experience grade 5 markings (bulla formation), which would be a great risk factor for pneumothorax. Grade 5 markings reportedly occurred in about 3% of patients (2).

Our modified method still has room for improvement. X-ray fluoroscopy and post-

procedural CT scan would provide patients X-ray radiation and be time-consuming. More recently, we have also successfully conducted VAL-MAP DS using electromagnetic navigation bronchoscopy as an extension of the technique we have previously reported (14). We believed that VAL-MAP DS using electromagnetic navigation bronchoscopy would be a feasible and practical option.

Comment 2: The authors reported the overall detectable rate and the visible marking rate of each dye to demonstrate the superiority of the dual-staining. However, the data showed that the detectable rate of dual-staining was 96%, which was just a little higher than ICG alone (93%). Regardless of the statistical significance, only 3% higher rate in less than 30 cases does not seem to be convincing enough.

Reply 2: We thank the reviewer for the comment. We agreed with the idea that only 3% higher rate was not convincing enough. We have attenuated the conclusions as follows (see Page 20, line 301-302).

Changes in the text:

Before changes:

In summary, VAL-MAP DS would improve the detectable marking rate because of dual staining with both ICG and indigo carmine.

After changes:

In summary, VAL-MAP DS **could** improve the detectable marking rate because of dual staining with both ICG and indigo carmine.

Comment 3: The authors used indigo carmine as the complementary dye. However, such dye could interfere the frozen section observation, of which the circumstance is similar in using methylene blue. Therefore, the necessity of using indigo carmine should be reconsidered.

Reply 3: We appreciate the reviewer's suggestion. Although we had used indigo carmine as a dye in VAL-MAP for more than 700 patients, we have never encountered the problem of interfering the frozen section pathological observation. Moreover, indigo carmine has been widely used as an instilled material in bronchoscopic marking (Yanagiya M, et al. Eur J Cardiothorac Surg 2020;58:40-50.). Although we were truly not sure if indigo carmine could affect frozen section pathology, one of the characteristics of VAL-MAP has been to place marks to surround the targeted lesion to indicate resection margins, which may have potentially avoided the problem. However, if the lesion per se needs to be marked for any lesion and frozen section is needed,

attention would be needed in selection of dyes. We have added the sentence as follows (see Page 19, line 287-291).

Changes in the text:

Before changes:

We believed that VAL-MAP DS using electromagnetic navigation bronchoscopy would be a feasible and practical option.

After changes:

We believed that VAL-MAP DS using electromagnetic navigation bronchoscopy would be a feasible and practical option. **In addition, although one of the characteristics of VAL-MAP is to place marks to surround the targeted lesion to indicate resection margins, considering the possibility of dye to interfere with frozen section, if the lesion per se needs to be marked for any lesion and frozen section is needed, attention should be needed in selection of dyes (12, 15).**

Comment 4: The present study is retrospective with a relatively small sample size. Meanwhile, the authors failed to indicate that whether the lung marking procedures were performed by the same surgeon or different surgeons. We believed the operators had inevitable contributions to the accuracy of the marking.

Reply 4: The marking procedures were performed by different surgeons. We have added the sentence as follow (see Page 7, line 95-96).

Changes in the text:

Before changes:

The post-VAL-MAP CT images were created in three dimensions for surgery.

After changes:

The post-VAL-MAP CT images were created in three dimensions for surgery. **The bronchoscopic procedures were conducted by different surgeons.**