Original Article

Virtual-assisted lung mapping using dual staining with indocyanine green and indigo carmine enhanced marking detectability

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Background: Virtual-assisted lung mapping (VAL-MAP) is a preoperative bronchoscopic multispot dye-marking procedure to facilitate sublobar lung resection for unidentifiable lung nodules. To increase detectable markings, we performed VAL-MAP using dual staining (VAL-MAP DS) with indocyanine green (ICG) and indigo carmine. This study was designed to evaluate the efficacy and safety of the modified technique.

Methods: We retrospectively reviewed the records of patients who underwent VAL-MAP DS. Twenty patients with 27 lesions underwent 72 VAL-MAP DS markings. We investigated the overall detectable marking rate, visible marking rate, successful resection rate, and complications.

Results: The overall detectable marking rate, thanks to both ICG and indigo carmine, tended to be higher than the indigo carmine visible marking rate (95.7% *vs.* 85.5%, P=0.08). The successful resection rate with sufficient margins was 92.0%. There were no adverse events related to the use of ICG. ICG markings of the lungs of patients with a history of smoking more than 50 pack-years tended to be visible, but the staining was too extensive compared with the staining in patients who smoked less or not at all (58.8% *vs.* 0.0%, P<0.001).

Conclusions: VAL-MAP DS is likely be efficacious and safe in enhancing the detectability of markings. This bronchoscopic technique should be considered as one of the optimal preoperative marking methods in thoracic surgery.

Keywords: Indocyanine green (ICG); thoracic surgery; virtual-assisted lung mapping (VAL-MAP)

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Introduction

Virtual-assisted lung mapping (VAL-MAP) is a preoperative bronchoscopic multiple-spot dye-marking technique that aids intraoperative virtual bronchoscopic navigation to localize unidentifiable pulmonary nodules (1,2). VAL-MAP's multiple markings (lung mapping) assist in identifying pulmonary nodules and drawing resection lines for sublobar lung resections. VAL-MAP could greatly contribute to achieving ideal sublobar lung resections.

Although VAL-MAP is efficacious and safe, approximately 10% of markings are invisible and unidentifiable because of either patient factors or technical issues (1,2). To overcome this problem, we developed VAL-MAP using dual staining (VAL-MAP DS) with indocyanine green (ICG) and indigo carmine (3). ICG fluorescence is visualized with a near-infrared thoracoscope and is expected to provide better marking quality (3). Our preliminary report presented promising results for VAL-MAP DS (3).

The current study assessed the efficacy and safety of

Table 1 Eligibility criteria for VAL-MAP DS with ICG and indigo carmine

Inclusion criteria
(I) A case in which pulmonary malignancy is suspected or diagnosed and the establishment of resection lines other than the typical interlobar fissure is required
(II) A case that requires careful determination of resection lines to ensure resection margins because of difficult intraoperative tumor localization. It falls under any of the following:
• Lesions that are challenging to identify intraoperatively because of the lesion characteristics including:
(i) Lesions containing ground glass opacity in whole or in part
(ii) Lesions with a tumor diameter of 5 mm or less
(iii) Lesions whose distance from the visceral pleura is greater than the tumor diameter
• Lesions that are challenging to identify intraoperatively because of underlying lung conditions:
(i) Severe pleural adhesion or anthracosis is anticipated (e.g., past history of open chest surgery or heavy smoking history)
(ii) Pre-existing benign nodules that are confusing and misleading (e.g., silicosis, old tuberculosis)
• Lesions/conditions judged to require marking for other reasons
(III) The consent of the patient or substitute has been obtained
Exclusion criteria
(I) Allergy to indigo carmine or ICG
(II) Pregnancy
(III) Bronchoscopy and/or marking cannot be conducted because of existing complications
(IV) Other reasons that are judged to be inappropriate for inclusion by the corresponding or participating surgeons/physicians in the study

VAL-MAP DS, VAL-MAP using dual staining; ICG, indocyanine green.

this new technique. We recently introduced this modified technique and performed more than 50 marking procedures in 20 patients. Based on our experience, we reviewed the outcomes of VAL-MAP DS. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1829/rc).

Methods

Patients

The current single-center, retrospective study included patients who underwent VAL-MAP DS from November 2020 to September 2021 at The University of Tokyo Hospital. The indications for VAL-MAP DS were almost the same as for conventional VAL-MAP (1). From the first to fifth patients, VAL-MAP DS was conducted for patients who were likely to have anthracosis, pulmonary emphysema, or pleural adhesion. 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. 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.

Procedure

The mapping procedure was conducted 1 day before surgery because of availability of bronchoscopy and surgeons. The details of the VAL-MAP DS procedure were reported previously (3). Briefly, with the patient under mild sedation and local anesthesia, thoracic surgeons performed the bronchoscopic procedure using a bronchoscope (F-P260F; Olympus Corp., Tokyo, Japan). With the aid of virtual bronchoscopic images, a metal-tipped catheter (PW-6C-1; Olympus Corp.) preloaded with 0.1 mL of ICG and 1 mL of indigo

carmine was gently inserted through the working channel of the bronchoscope into the target bronchus (3). After confirming the location of the catheter tip under X-ray fluoroscopy, the mixture of ICG and indigo carmine was injected into the target bronchus (3). This procedure was repeated multiple times for all planned markings. After the bronchoscopic procedure and dye injections, a chest computed tomography (CT) scan was used to confirm the actual locations of the markings and the target nodules. The post-VAL-MAP CT images were created in three dimensions for surgery. The bronchoscopic procedures were conducted by different surgeons.

Surgery was conducted utilizing mapping images. In this current series, the surgical procedure was sublobar lung resection such as wedge resection or segmentectomy. The surgical approach was either video-assisted thoracic surgery (VATS) or open thoracotomy, based on the preference of the surgeon.

Evaluation and grading of markings

During surgery, the markings were initially evaluated based on indigo carmine dye marking as conducted in conventional VAL-MAP. Subsequently, we utilized the VISERA ELITE II system (Olympus Corp.) equipped with near-infrared fluorescence imaging capability to evaluate markings dyed with ICG.

For the evaluation of indigo carmine markings, we utilized a grading system described previously (4): grade 0, unidentifiable; grade 1, identifiable, but faint and hardly visible; grade 2, easily identifiable without a central red spot or target-like shape; grade 3, easily identifiable with a central red spot; grade 4, target-like appearance with or without a central red spot; and grade 5, bulla formation.

Regarding evaluation of ICG markings, we utilized the novel grading system shown in *Figure 1*: grade A, invisible; grade B, visible with a well-defined spot; grade C, visible but too extensive in coverage.

Primary and secondary endpoints

The primary endpoint was the rate of overall detectable marking based on the visible marking of both indigo carmine and ICG. We evaluated the visibility of markings as mentioned above. In the present study, indigo carmine visible marking was defined as markings graded 1 or more, whereas ICG visible marking was defined as markings graded B or C. Finally, "overall detectable marking" was defined as marking regarded as either indigo carmine or ICG visible marking. We estimated the rates of indigo carmine visible marking, ICG visible marking, and overall detectable marking for markings that had been evaluated intraoperatively.

The secondary endpoints were successful resection rate and complication rate. Successful resection was defined as complete resection of target tumors with resection margins larger than or equal to the lesion diameter, or ≥2 cm for a tumor larger than 2 cm (2). Unsuccessful resection was defined as either resection with insufficient margins or the performance of additional resection to obtain adequate margins to achieve curative resection (2). The successful resection rate was evaluated for resected nodules in which resection margins had been measured intraoperatively as described previously (2). A complication was defined as any adverse events related to the of VAL-MAP DS procedure.

Statistical analysis

The current study assessed patients' demographic data and outcomes based on medical records. Patients with missing data were excluded from this study. Data were expressed as the mean and standard deviation, if appropriate. The chi-squared test with Yate's continuity correction was conducted (5). Based on the chi-squared value, the effect size was calculated (6). The Bonferroni correction was used to adjust the P value in the multiple comparisons. Statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan, 2012) (7). The level of significance was set at $P<0.05$.

Ethics statement

This retrospective study used and analyzed the patient data. The present study was approved by the Ethics Committee of The University of Tokyo Hospital (approval No. 2406-6) and individual consent for this retrospective analysis was waived. The form of opting-out on the website was accessible to patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Patients, target lesions, and surgeries

Twenty patients with 27 lesions underwent VAL-MAP DS from November 2020 to September 2021. The patient

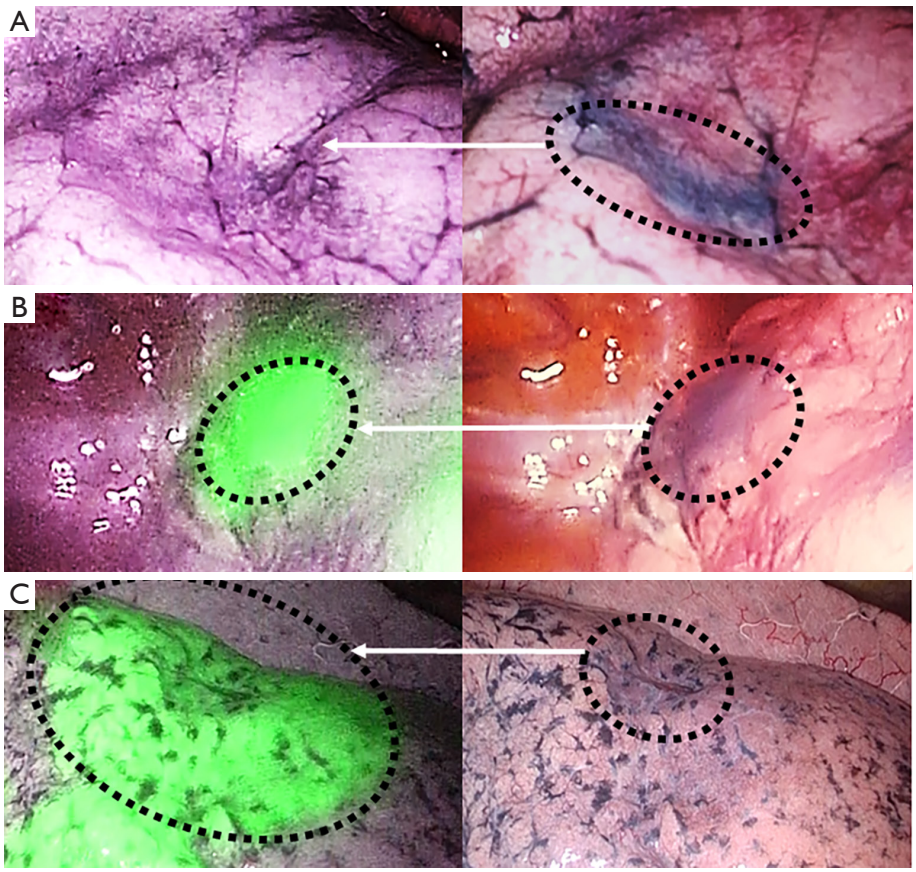

Figure 1 Grading system of intraoperative findings in ICG marking of VAL-MAP. (A) Grade A: invisible. (B) Grade B: visible with a well-defined spot. (C) Grade C: visible but too extensive in coverage. Indigo carmine marking was visible (black dotted circle); however, ICG marking was invisible (A). ICG marking and indigo carmine marking were visible in the same location (B). ICG marking was visible but too extensive (C), compared with indigo carmine marking. ICG, indocyanine green; VAL-MAP, virtual-assisted lung mapping.

Table 2 Baseline demographics of patients

Parameter	Data
Mean age (years)	64.0±12.3
Female sex	11 (55.0%)
Ever smoker	10 (50.0%)
Smoking history (pack-years)	28.2±48.3
Comorbidities	
Past history of coronary artery disease	3
Past history of stroke	1
Liver cirrhosis	1
Atrial fibrillation	1
Past history of nontuberculous mycobacteria	1
Diabetes mellitus	1
Autoimmune disease	1

demographics are shown in *Table 2*. Ten patients (50%) had a history of smoking and detailed pack-year smoking history was summarized in *Table 2*. Nine patients (45%) had comorbidities such as cardiovascular disease. Among them, five patients with a history of cardiovascular diseases required stopping antithrombotic agents during the periprocedural period. One patient with liver cirrhosis required platelet transfusion after the surgery because of a decreased platelet count.

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*. Sixteen patients (80%) had one target lesion; the remainder had multiple lesions. Seven lesions (26%) were localized apically. Eleven lesions (41%) were histopathologically diagnosed as primary lung cancer, while the others were diagnosed as tumor metastatic to the

Table 3 Characteristics of lesions and surgeries

Characteristics	Data
Number of target lesions per patient	
1	16
2	2
3	1
4	1
Number of markings per patient	3.6±1.4
Number of actual markings	72
Number of markings evaluated intraoperatively	69
Appearance of lesions on chest CT	
Pure GGN	5
Partly solid GGN	6
Solid	15
Cavitary	1
Diameter of lesions (mm)	10.0±5.3
Depth from lesions to pleura (mm)	8.4±7.0
Histopathological diagnosis	
Primary lung cancer	11
Tumor metastatic to lung	16
Surgical procedure	
Wedge resection	25
Segmentectomy	2
Surgical approach	
VATS	19
Open thoracotomy	1

CT, computed tomography; GGN, ground-glass nodule; VATS, video-assisted thoracic surgery.

lung. 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. Nineteen patients (95%) underwent the VATS approach, while the others underwent open thoracotomy. There were no missing data regarding characteristics of the patients, lesions, and surgeries.

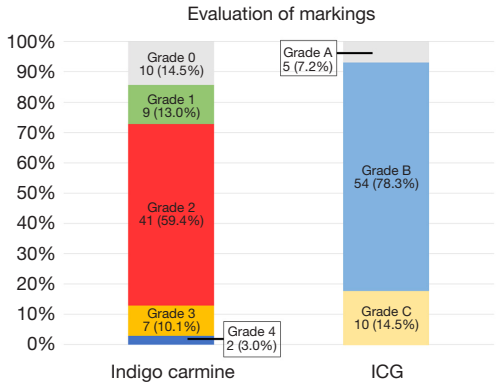

Figure 2 Summary of grading evaluation of markings. ICG, indocyanine green.

Table 4 Reasons for unidentifiable (grade 0) or faint (grade 1) markings

Reason	Grade 0	Grade 1
Central injection	6	0
Anthracosis	4	9

Markings

In this series, 72 markings were made in 20 patients (3.6±1.4 markings per patient). Of these, 69 markings were evaluated intraoperatively (*Table 3*). Three markings were not evaluated intraoperatively because the clinical assessment deemed that confirmation was unnecessary. Even though multiple markings had been created appropriately, some surgeons conducted pulmonary resection only with the aid of a portion of the multiple markings and, consequently, confirmation of the other markings was omitted.

The grades of each marking via indigo carmine or ICG are summarized in *Figure 2*. The reasons for grade 0 or 1 observed in indigo carmine marking are summarized in *Table 4*. Among these 19 indigo carmine marking failures, 16 markings were detectable as a result of the ICG markings (*Figure 3*).

Endpoints

The indigo carmine visible marking rate, ICG visible marking rate, and overall detectable marking rate were 85.5%, 92.8% and 95.7%, respectively. The overall

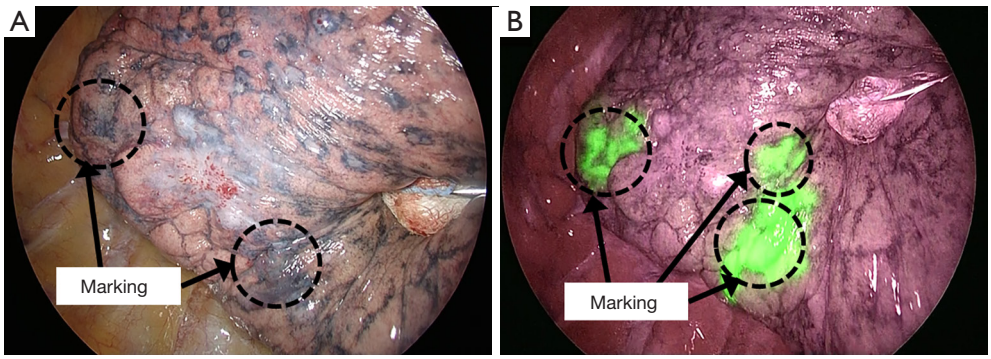

Figure 3 An intraoperative image in which indigo carmine markings were hardly identified, but ICG markings were easily identified. (A) Indigo carmine markings were indistinguishable or faint because of anthracosis. (B) ICG markings were clearly visible even with anthracosis. ICG, indocyanine green.

detectable marking rate tended to be higher than the indigo carmine visible marking rate (P=0.08). 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.

The successful resection rate with sufficient margins was 92.0% (23 of 25 patients). Among the surgeries for 27 lesions, curative resections were planned for 26 lesions. Of these, one lesion had not been identifiable in the resected specimen intraoperatively, although the target lesion turned out to be appropriately resected in the histopathological examination. For the remaining 25 lesions, 23 lesions were successfully resected; we have experienced two resection failures. 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. The other lesion was completely resected in the initial resection; however, the surgical margin was insufficient. We did not conduct an additional resection because the tumor was located unexpectedly close to the interlobar fissure, and completion lobectomy would be unacceptable because of the patient's poor respiratory function and comorbidities. The histopathological diagnosis in the second failure case was minimally invasive adenocarcinoma with invasive size of 3 mm and whole size of 30 mm. Because we had obtained a surgical margin of 10 mm in the second failed case, the surgery would be clinically acceptable for minimally invasive adenocarcinoma.

Regarding complications of the bronchoscopic procedure, airway bleeding was observed in one patient (5%), which did not require any intervention or treatment. In the current series, we never experienced pneumothorax, one of the most common complications of VAL-MAP. There were no adverse events related to the use of ICG.

Post-hoc analysis of the influence of smoking on ICG marking visibility

We assessed the relationship between smoking status and the visibility of ICG marking because smoking status might influence marking visibility (8). The results are summarized in *Figure 4*. The distribution of grades of ICG marking differed significantly between the lungs of patients with a smoking history equal to or less than 50 pack-years and those with more than 50 pack-years (P<0.001). Chi-squared tests with the Bonferroni adjustment showed that the frequency of grade C markings was significantly higher in the lungs of those with a smoking history of more than 50 pack-years than in those with equal or less than 50 pack-years, comparing the frequency of grade B marking (P<0.001). Markings made on the lungs of patients with a smoking history of more than 50 pack-years developed grade C significantly more frequently, compared with those having a history equal to or less than 50 pack-years (58.8% *vs.* 0.0%, P<0.001).

Discussion

We demonstrated that the overall detectable marking rate defined by the visibility of either ICG or indigo carmine marking was approximately 96%. The effect size calculated

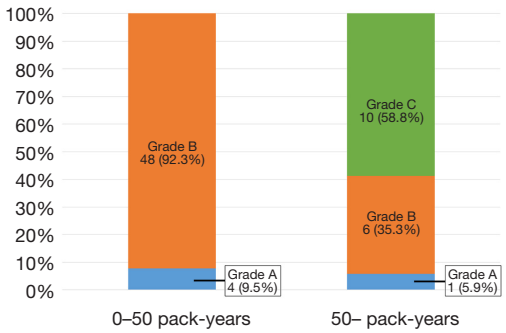

Figure 4 Influence of smoking status on ICG marking quality. The distribution of grades of ICG marking significantly differed between lungs with smoking history equal or less than 50 pack-years and those with more than 50 pack-years (P<0.001). ICG, indocyanine green.

by the comparison between the overall detectable marking rate and indigo carmine visible marking rate was about 0.2, which would be considered a small to medium effect according to Cohen's guideline (9). Considering these outcomes, the use of ICG and near-infrared fluorescence imaging contributes to the improvement of VAL-MAP marking detection efficacy.

Our modified method has a great advantage in terms of the capability to assess markings via two types of dyes. As *Figure 3* shows, the ICG visible marking rate was approximately 93%, which was not as high as we expected. However, with the aid of conventional indigo carmine marking, we were able to confidently identify 96% of the markings. Indigo carmine and ICG do not conflict, but rather complement each other to lead to successful markings. A previous report also demonstrated modified VAL-MAP technique using ICG (10). Unlike our method, they only utilized ICG to identify marking intraoperatively. Although we appreciate the report and their method, grade C markings (visible, but too extensive in coverage) might be problematic if markings were evaluated by only one dye (*Figure 1*). In addition, their method utilized contrast agents to make it easier to identify actual markings on preoperative CT images (10). The contrast agents could be harmful to patients allergic to the agents (11). Our method should be preferably used especially for patients allergic to contrast agents. Based on these reasons, we recommend the combined use of ICG and indigo carmine.

The present study suggested the safety of VAL-MAP DS. Previous reports revealed a rate of approximately 6% for pneumothorax and 1% for pulmonary hemorrhage observed in VAL-MAP (12). In this series, we did not experience pneumothorax because there would be no need to inject forcibly, thanks to the visibility of ICG marking. The previous study reported that ICG marking would be resistant to marking failure because of central injection (3). Because surgeons know of this issue, forcible dye injection decreased, and thus no pneumothorax occurred. While the present series included many patients with comorbidities such as cardiovascular diseases, we were able to minimize the occurrence of complications because of the use of ICG.

Interestingly, we found that smoking status may influence ICG marking visibility. A previous report demonstrated that the Brinkman index calculated by smoking history significantly negatively affected the visibility of conventional VAL-MAP marking (8). Contrary to the previous report, our result suggested that a heavy smoking history might increase ICG markings too extensively (*Figure 4*). In short, a heavy smoking history would make indigo carmine marking faint or unidentifiable, but ICG marking is visible with an unclear border in an extensive area. 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.

The rationale for the relationship between smoking status and ICG marking visibility might be the alveolar wall destruction observed in pulmonary emphysema (13). Because the alveolar fenestrae created by the small ruptures appearing in emphysema associated with heavy smoking, ICG would be sprayed more extensively than expected. As ICG was more sensitive than indigo carmine, ICG marking would then be visualized too extensively.

In our series, the indigo carmine visible marking rate was relatively low, compared with previous reports (1,2). The main reason for this result was that we did not inject forcibly because of the ICG marking visibility. 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. 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).

The present study has several limitations. 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. 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.

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. The multi-center prospective study would be needed to prove efficacy and safety of VAL-MAP DS.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1829/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1829/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1829/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1829/coif). MS reports a grant from the Japan Agency for Medical Research and Development, related to the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of The University of Tokyo Hospital (approval No. 2406-6) and individual consent for this retrospective analysis was waived. The form of opting-out on the website was accessible to patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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