Dear Dr. Yang:

According to the reviewers’ comments and suggestions, I have revised the manuscript as follows. Indeed, I believe the process has strengthened the manuscript. Also, following the reviewer 2’s suggestion, I have uploaded a video showing the overall concept and techniques of VAL-MAP. I profoundly thank the two reviewers for spending time on the manuscript. I hope it meets the quality required by the journal.

Best Regards,

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Reviewer 1:


Again, the author should consider also the application of ultrasound during VATS procedure, that avoid the patient’s and surgeon’s exposure to radiation. Transthoracic endosonography for the intraoperative localization of the lung nodules. Ann Thorc Surg 2005;79:443-9; Minimally invasive thoracoscopic ultrasound for localization of pulmonary nodules 2008 J Ped Surg

R: I thank the reviewer for the suggestion to make the article more comprehensive. Following this suggestion, other techniques of lung marking have been included in the introduction of the manuscript (P4 Ln10-17).
There are two different subtitles called “indications for VAL-MAP” on page 6 and page 8. The author should summarise these pages, removing the redundant parts, focusing on the indication/necessity of the mapping procedure (as reported in the abstract, the aim of this paper was to discuss about the indications, details of method of the VAL-MAP technique), rather than on the indications for a wedge resection or a segmentectomy or other than curative surgery.

Such as reported on page 8, indications for a mapping procedure should be based on lesion features (GGN, solid nodule, diameter and depth of the lesion).

An interesting paper analysed the necessity to submit the patients to a preoperative labeling process of lung nodule, trying to avoid unnecessary procedure without reduce the success rate of VATS identification (A Strategy for thoracoscopic resection of small lung nodules 2005 Surg Endosc; 19:1644-7).

Page 8: Indication by legion characteristics and operations /Indication by lesion.....

R: I thank the reviewer for the useful suggestion regarding organization of the indications for VAL-MAP. Now this part have been better organized primarily based on lesion characteristics (P7 Ln8-P10 Ln9). Accordingly, original Figure 3 has been moved up to Figure 2. Discussion about segmentectomy and resection other than curative intent are rather “Operation techniques using VAL-MAP” from surgical and oncological viewpoints. These parts have been moved down to the section after complication of VAL-MAP (P20 Ln20 – P23 Ln4). Original Figure 2 has also moved to Figure 5. Original Figures 4 is now Figure 3.

Technique, tips and pitfalls of VAL-MAP

Page 11-14 should be more synthetic and schematic.

R: This has also been pointed out by the reviewer 2. Thus, following the suggestion of the reviewer 2, supplementary video has been edited and cited in the text to show the steps of VAL-MAP procedure.

The fact that the catheter could reach the visceral pleura or touch the chest wall is perplexing.

R: I thank the reviewer for pointing the confusion. The catheter is similar to a biopsy forceps for TBLB in the size so that it can reach the visceral pleura without any
problem. To avoid such confusion, we have added explanation (P15 Ln6-8) and also added a picture of the catheter tip in Figure 3C (original Fig. 4C) as an inset. Also as a reference, Table 3 listing necessary instruments and equipment including the catheter PW-6C-1 (Olympus) has been added (P35).

It is not clear why a post-VAL-MAP CT scan is performed, if the dye (indigo carmine) is not radiopaque and is visible as a ground glass area, if it is. It is not clear if the primary end-point of this mapping technique is the 3D reconstruction of CT scan after marking procedure, or the intraoperative findings.

R: Once again, I thank the reviewer for pointing out the shortness of explanation.

Post-VAL-MAP CT scan plays a critical role in accurate intraoperative navigation of VAL-MAP. The following explanation has been added at the top of the “post-VAL-MAP” section (P17 Ln19-23).

The role of post-VAL-MAP CT is highly important because bronchoscopic markings are not always placed at the exactly same location as was planned using virtual bronchoscopy. Thus, adjustment of the lung map at this stage enhances the accuracy of the technique (compare pre- and post-VAL-MAP 3D images and an intraoperative view in Fig. 4C (i), (ii), and (iii)).

Although indigocarmine per se is not radiopaque, the marking is visible under CT scan for the water density. This phenomenon is similar to the artifact after BAL. This has already been explained in the section of post-VAL-MAP CT (P18 Ln2-6; no correction made).

For lesion sited deep in the parenchyma,

- The first stapler firing is performed on the pre-operative CT imaging, when the dye is not visible on pleural surface, isn’t it?
- the surgeon has to find marked areas during stapler firing progression, isn’t it?

The author should describe also the operative technique.

R: Following the reviewer’s suggestion, a new section of the operative technique has been added (P20 Ln20-). As mentioned above, explanation on segmentectomy (original Fig. 2) was integrated into this part.
Regarding wedge resection for a deep lesion, the technique has also been described in this section. In short, dye markings of VAL-MAP are made only on the lung surface --- it could be made in the lung parenchyma by mistake (i.e., central injection), it is not visible and useless. Thus, we place markings laterally indicating how much lung tissue needs to be grasped to go sufficiently deep. On the other hand, this is one of the limitations of current technique of VAL-MAP. The discussion has also been extended in the limitation and future directions (P24 Ln6-9).

The author should report also the disadvantages of this procedure, such as the difficult identification of the marked area such as for methylene blue (anthracosis...), or the necessity of a fluoroscope during bronchoscopic mapping (exposition to radiation for patients and surgeons)

R: Following the reviewer’s suggestion, the discussion about anthracosis and other conditions that hinder visibility of dye marking has been extended (P8 Ln14-23). We have also added pictures of pleural adhesion and anthracosis (new Figure 2C). In addition, a new strategy to overcome the challenge has been discussed in the “limitation and future direction” section (P24 Ln6-9).

Radiation exposure is a good point of discussion. This has been added to (P15 Ln22 – P16 Ln3).

For the completeness of the study, the author should report also the success rate of this and other different labelling procedures reported in the literature (in terms of identified lesions/total number of lesions or necessity to conversion to open thoracotomy from a VATS procedure). A table should be helpful.

R: Although the definition of “success” as well as targeted lesions (solid vs. GGO) are quite variable among reports, success rates of different procedures (thoracoscopic identification of tumors) have been added to Table 1. Difficulty in fair comparison has also been commented in the note of the table. Indeed, because of these challenges, we are currently doing a retrospective analysis comparing different marking procedures using the same definition of successful resection within the same center.

Reviewer 2:
It's a well-written manuscript, containing a rather new technique for intraoperative guidance to pulmonary ground glass opacities as well as summarizing the current pros and cons of competing methods for this purpose.

After some following minor comments the manuscript can be considered for publication:

First at all I will mention that it is difficult to understand how the technique entirely works from the text and the figures alone. I think it would be applicable to add a video, containing the steps and an expert explanation of VAL-MAP (from the initial CT scan to the pulmonary wedge resection or segmentectomy), for supplement if the journal accepts it. Although the author cross-references an article containing a video of VAL-MAP, not every reader of this article will be able to open the video-file in the given reference and thus a supplemented video will make this article much more impactful.

R: I thank the reviewer for the excellent idea. Indeed, according to the author guideline of the journal, a supplementary video up to 34MB is allowed. A video clip summarizing the steps of VAL-MAP showing how it works has been edited, added, and cited in the text (P10 Ln14, P10 Ln21).

In the second part of the introduction section of the manuscript references are missing ("Beyond these marking techniques, we have recently developed a technique termed virtual assisted lung mapping (VAL-MAP), a bronchoscopic multi-spot dye-marking technique utilizing 3D-virtual imaging.").

R: Following the reviewer’s suggestion, we have added the first paper describing VAL-MAP as a reference (P3 Ln12).

The indications and pitfalls are nicely depicted in the manuscript, but the author should clarify the fact that some parts of the lung are better and others are no good indications for VAL-MAP! ("The right lower corner is the best indication; the left upper corner is not a good indication. The left lower corner is a good indication for beginners in using VAL-MAP because even if VAL-MAP fails, the operation can be completed using other methods. The right upper corner is the most challenging indication and is more suitable for a highly experienced team."). The author should describe it from a technical and experiential point of view. Is there a learning curve in VAL-MAP available?

R: I thank the reviewer for indicating the important point. We have added paragraphs at the end of the “indications for VAL-MAP” section (P9 Ln10 – P10 Ln16). In short, the
challenges are separated into two; 1) lung conditions (anthracosis, emphysema, adhesion) and 2) bronchial anatomy. Technical tips to overcome these challenges have been described.

Learning curve in VAL-MAP has also been discussed; a recently published paper has described operator dependency of VAL-MAP (Yamanashi K, et al.). Although there is no solid data regarding learning curve, the same paper suggested that the use of instruction videos and experience of TBLB contribute to developing a steep learning curve of the technique.

The author describes in the manuscript some products, e.g. Synapse Vincent (R) from Fujifim. The author should clearly depict his conflicts of interest and his relationships to the named companies. Are there products available from other companies?

R: There is no conflict of interest and this has been clearly described at the end of the manuscript. The “mapping mode” is now available only from Fujifilm, although another company is also developing a similar thing. On the other hand, VAL-MAP is doable without using the mapping mode. This is an important thing and has been re-emphasized in the text (P23 Ln11 – Ln13) and Table 3 showing necessary instruments and equipment has been added (P35).

What is the rate of marking failure in VAL-MAP, based on the preliminary results of your multi-center study? Is it possible to repeat the marking procedure after failed marking determined by CT-scan or does a failed landmark hinder good intraoperative results?

R: Marking failure (i.e., invisible marking) occurs in approximately 10% of markings and this number is quite reproducible across centers participating in the study. However, actual successful resection ratio with intended sublobar lung resection is around 99% mostly due to the multiple markings that are complementary to each other. In other words, multiple markings work as a backup to each other. This feature makes the system error-resistant.

We do not repeat the marking procedure but in most cases failure in a single marking among 3-4 markings do not hinder accurate lung resection. This has been commented in the new section of “Results of VAL-MAP” (P19 Ln20 – P20 Ln9).
Is there a study-protocol available for the multi-center study examining VAL-MAP, the author mentioned? Please reference it because some evidence from the manuscript is based on its preliminary results. Otherwise some more information should be given to the mentioned study. Is it a RCT comparing VAL-MAP with other methods?

**R:** Following the reviewer’s suggestion, the following information has been added (P3 Ln17- P4Ln2).

This is a single-arm study intended to examine safety, efficacy and reproducibility of VAL-MAP. By December 2015, more than 400 patients have been participated in this study in 17 centers across Japan (clinical trial ID: UMIN000008031). Patients with a pulmonary lesion or lesions suspicious of malignancy and 1) the lesion is anticipated to be hardly palpable during operation and/or 2) the resection margins need to be carefully determined are eligible for the study. Further details of the study is available at [http://www.umin.ac.jp/ctr/index.htm](http://www.umin.ac.jp/ctr/index.htm).

Regarding table 1: what does the "?" mean in CT-guided needle marking complications? Please specify "rare" in VAL-MAP complications?

**R:** Following the reviewer’s suggestion, table 1 has been updated as follows:

CT-guided needle marking: air embolism (up to 1.5-2% in hookwire)

VAL-MAP: pneumomediastinum (<1%), pneumonia (<1%)

Regarding the "steps, tips and pitfalls" of VAL-MAP: why do you not mix the dye with a contrast-medium for CT to better detect the markings?

**R:** I thank the reviewer for pointing this out. Indeed, there has always been the discussion about mixing a contrast medium for better visualization in CT scan. Probably it works while a potential concern about mixing two solutions is unexpected chemical reaction that may hinder the safety even if the original two solutions are known to be safe. To overcome this potential problem, we have to undergo special examinations and clear regulations. This is certainly something we are intending in the future and, as such, this idea has been mentioned in the “future directions” (P24 Ln12-13).

Regarding "Difficulties" in figure 3: Does extendes adhesiolysis with damages of the visceral pleura hinder a sufficient visualization of the markings within the operation?
In cases of pleural adhesion, an important technical key is to dissect the intra-pleural layer rather than extra pleural dissection. Thick parietal pleura adherent to the visceral pleural makes markings invisible. However, in our experience, markings are still visible if visceral pleural is damaged because the dye stains not only the visceral pleura but also the underlying lung parenchyma to some extent. This has been commented in the text (P9 Ln23).