Virtual assisted lung mapping: navigational thoracoscopic lung resection

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Abstract
Virtual assisted lung mapping (VAL-MAP) is a new technique for bronchoscopic lung marking developed to assist in navigational lung resection. Unlike conventional marking techniques using a single marking to identify an intrapulmonary tumor, VAL-MAP utilizes multiple dye-mediated markings, providing “geometric information” on the lung surface. The purpose of the technique is to identify a tumor and obtain sufficient resection margins, either in wedge resection or segmentectomies. Computer-based virtual bronchoscopy is used to design the lung map and to identify target bronchi for each marking. The dye injection procedure is conducted using a regular bronchoscope under fluoroscopy followed by a CT scan, which is then reconstructed into 3D images for intraoperative navigation. The advantages of VAL-MAP include: it is a reasonably safe procedure based on experience from approximately 1,300 markings undertaken in >430 patients; the dye lasts without significant fading for 2–3 days; the technique has good reproducibility; and multiple markings and adjustment using post-mapping CT result in the procedure being highly resistant to technical failure. VAL-MAP is likely to benefit many patients and surgeons in the era of minimally invasive navigational-based thoracic surgery. The technique has scope for further development, making it an exciting new field of research in thoracic surgery.

Keywords:
lung cancer, metastatic lung tumor, VATS, navigation, workstation, virtual bronchoscopy, lung marking, ground glass nodule

Introduction
The improved resolution of CT scanning has led to the detection of an increasing number of small lung nodules including ground glass nodules (GGNs), which are anticipated to be barely palpable if lung resection is conducted. Expansion of the use of thoracoscopic and video-assisted thoracic surgery has facilitated less invasive lung resection; however, palpation of lung tumors has become much more challenging because of limited manual access to the lung. These trends over the last two decades have made it necessary for thoracic surgeons to devise various types of lung marking approaches.

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 (1). VAL-MAP not only overcomes multiple limitations of conventional marking techniques but to extend the application as an aid for navigation during operation. In this review article, indications, details of methods, tips and pitfalls concerning the techniques are discussed, as are the future directions this new technique would reveal in the field of thoracic surgery.

Some of the data presented in this article are based on the preliminary results of the ongoing prospective multi-center clinical study examining VAL-MAP. In short, this is a single-arm study intended to examine the safety, efficacy and reproducibility of VAL-MAP. By December 2015, >400 patients had participated in this study involving 17 centers across Japan (clinical trial ID: UMIN000008031). Patients with a pulmonary lesions or lesions suspicious of malignancy were eligible for the study if: 1) the lesion was anticipated to be barely palpable during surgery; and/or 2) the resection margins needed to be carefully determined. Further details of the study are available at http://www.umin.ac.jp/ctr/index.htm

Marking and mapping for lung resection

Necessity for lung marking techniques

Expansion of the use of video-assisted thoracic surgery has made palpation of small lung tumors much more challenging. These trends over the last two decades have made it necessary for thoracic surgeons to devise various types of lung marking approaches, such as CT-guided needle-mediated placement of markings including a hook-wire (2), a microcoil (3, 4) dye injection (5, 6), or technetium 99m macro-aggregated albumin (7, 8). Another approach is to use a bronchoscope to place a marking such as a microcoil (9), or to inject dye (10, 11) or radiopaque materials (12, 13). Other non-invasive techniques such as intraoperative ultrasound (14, 15) or “endofinger” touch sensing of the lung surface (16) have been reported. However, there are advantages and disadvantages to these techniques. Although the non-invasive techniques are intriguing, the reported lesions are mostly solid nodules (14-16) and the usefulness of these techniques for GGNs is unclear.

Complications tend to be the major limiting factor for the CT-guided needle-mediated methods, and pneumothorax and bleeding are seen relatively frequently; the most feared complication is air embolism leading to cerebral infarction and/or myocardial infarction (17-22) that could even be fatal (18). The incidence of air embolism related to the CT-guided methods is reported to be as high as 1–2% (23, 24). Air embolism related to lung marking has been attributed to communication between airways and the pulmonary vein, or injection of air directly into the pulmonary vein; similar mechanisms concerning air embolism have been experienced in CT-guided lung biopsy (25). Particularly in Japan, where the surgical mortality associated with lung cancer surgery is very low (30-day mortality rate for lobectomy, 0.6% (26)), such morbidity and mortality related to markings used for even tiny lung nodules is considered unacceptable. Bronchoscopic-mediated techniques have been reportedly and theoretically safer; however, the technique has not been well accepted because real-time CT guidance is required for accurate marking (11).

Advances in radiology workstations and the resulting emergence of virtual bronchoscopy have made the use of bronchoscopy-mediated markings practical. Now virtual bronchoscopy is easily constructed from thin-slice CT images and subsequently transferred to a bronchoscopy suite, where the virtual bronchoscopic images are utilized to facilitate accurate navigation for bronchoscopic procedures. Virtual bronchoscopy has made bronchoscopy-mediated lung marking possible without the need for real-time CT imaging (12, 13).

From marking to mapping

We have recently developed an important new approach termed virtual assisted lung marking, or VAL-MAP; multiple markings provide “geometric information” concerning the lung surface, and thus this modality can be used to aid navigation during an operation (1). Because of the low risk of pneumothorax in bronchoscopy-mediated lung marking, it is easy to simultaneously conduct multiple markings. Initially multiple markings were
Table 1: Comparison between conventional CT-guided percutaneous marking, bronchoscopic marking techniques and VAL-MAP

<table>
<thead>
<tr>
<th></th>
<th>Conventional CT-guided needle percutaneous marking</th>
<th>Bronchoscopic marking</th>
<th>VAL-MAP</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Hookwire, microcoil, dye injection</td>
<td>Dye, radiopaque material, microcoil</td>
<td>Multiple bronchoscopic dye injection</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>Localization of a target lesion</td>
<td>Localization of a target lesion</td>
<td>Determination of appropriate resection lines with safe surgical margin</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>Primarily wedge resection</td>
<td>Primarily wedge resection</td>
<td>Wedge resection, segmentectomy (especially complex extended segmentectomy)</td>
</tr>
<tr>
<td><strong>Anatomical limitations</strong></td>
<td>Inaccessible areas: diaphragm side, mediastinal side, apex, interlobar fissure</td>
<td>Depends on bronchial anatomy</td>
<td>Depends on bronchial anatomy but multiple markings, anatomical landmarks and/or auxiliary lines are complementary</td>
</tr>
<tr>
<td><strong>Number of markings</strong></td>
<td>Usually one</td>
<td>Usually one</td>
<td>Multiple</td>
</tr>
<tr>
<td><strong>Success ratio</strong></td>
<td>92–100%</td>
<td>96–100%</td>
<td>Each marking 90%; multiple markings as a whole 98–99%</td>
</tr>
<tr>
<td><strong>Outcome of marking failure</strong></td>
<td>Planned resection becomes extremely difficult or impossible</td>
<td>Planned resection becomes extremely difficult or impossible</td>
<td>Resection is usually still possible because multiple markings complement each other</td>
</tr>
<tr>
<td><strong>Outcome of displaced marking</strong></td>
<td>Planned resection becomes extremely difficult or impossible</td>
<td>Planned resection becomes extremely difficult or impossible</td>
<td>Resection is usually still possible because the actual location of the marking is confirmed using post-mapping CT, based on which 3D images are reconstructed preoperatively. The operation plan (i.e., planned resection lines) is adjusted before surgery.</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Pneumothorax (30–50%), bleeding, air embolism (up to 1–2% in hookwire)</td>
<td>Rare (reported case number limited)</td>
<td>Minor pneumothorax (3–4%), pneumomediastinum (&lt;1%), pneumonia (&lt;1%)</td>
</tr>
<tr>
<td><strong>References</strong></td>
<td>2-8, 17-24</td>
<td>9-13</td>
<td>1, 27, 29, 30</td>
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</table>

* Described thoracoscopic identification and resection of a tumor. The definitions of “success” of markings, the number of patients and characteristics of targeted lesions are quite variable among reports; the success ratio is not simply comparable for each report.
considered to be backups for each other in the event that a single marking failed. Indeed, this approach has worked very well, making the procedure much more resistant to technical errors. Furthermore, it was evident that multiple markings on the lung surface were useful not only in the identification of a lung tumor but also in providing geometric information regarding the lung surface (1). For example, if a single marking is made close to a tumor, the surgeon needs to estimate the location of the tumor based on the position of the marking and then image the appropriate resection lines (Fig. 1A). However, if multiple markings are made around the tumor, the surgeon does not have to worry about its position, because he or she knows that it is located among the markings (Fig. 1B). In addition, the relative relationship between the multiple markings allows surgeons to determine oncologically appropriate resection lines with sufficient resection margins. This unique characteristic of VAL-MAP has extended its application to segmentectomies, in which VAL-MAP is used to assist in the determination of the appropriate intersegmental resection lines (Fig. 1C).

Notably, the markings do not need to be located along the resection lines. Indeed, bronchial anatomy does not always allow for such ideal mapping. As mentioned, an important concept regarding VAL-MAP is that multiple markings provide “geometric information” concerning the lung surface and navigation during an operation. Multiple markings are used to determine appropriate resection lines not only by directly indicating the resection lines but also by allowing auxiliary lines to be drawn, and/or by being combined with anatomical landmarks (Fig. 1D). The details of these techniques have been described previously (27).

The current VAL-MAP technique was originally established in Kyoto University, Japan (1). Data regarding CT-guided needle-mediated percutaneous marking techniques, bronchoscopic marking techniques and VAL-MAP are detailed by way of comparison in Table 1. Currently a multi-institutional lung mapping study (MIL-MAP study) is ongoing across Japan. A total of >430 patients have been enrolled in the study, and >1,300 markings have been made. Although the final outcome of the study is yet to be summarized, the interim findings adequately support the safety and reproducibility of the technique. Based on the accumulated experience, indications, details of methods, tips and pitfalls concerning the techniques are discussed as follows.

### Indications for VAL-MAP

The multiple markings used in VAL-MAP provide geometric information on the lung surface and, thus, enable surgeons not only to identify the tumor but also to obtain secure resection margins. As such, VAL-MAP is indicated when a lesion requiring resection is anticipated to be hardly identifiable during surgery and/or the resection margins need to be carefully determined because of the characteristics of the lesion or the underlying lung.

GGNs. Small pure GGNs, especially those that are <10 mm in diameter are good indications for VAL-MAP (Fig. 2A(i)). These lesions are often barely identifiable during surgery; in addition, sublobar resection such as wedge resection and segmentectomy tends to be selected for both diagnostic and curative purpose even if lung cancer is suspected. In the interim analysis of our ongoing multicenter study, VAL-MAP was found to contribute most to the operation if the tumor is pure GGN in the CT scan. Mixed GGNs (GGNs that contain solid components) or relatively larger pure GGNs (Fig. 2A(ii)) may be easier to identify during surgery than pure GGNs. However, if sublobar resection is selected, the resection margins need to be carefully determined because of the extension of the ground glass component that is still hardly identifiable.

**Solid nodules.** Solid nodules subjected to sublobar lung resection are most typically metastatic lung tumors. The interim analysis of our ongoing multicenter study, VAL-MAP was found to contribute most to the operation if the tumor is less than 10 mm (particularly less than 5 mm) in the CT scan. Failure of localization under direct vision and/or instrumental palpation has been reported to be significantly correlated with nodules of size <10 mm, and their distance from visceral pleura >10 mm (28). Indeed, palpability of a pulmonary nodule is a
**Figure 1:** Comparison between the conventional marking technique and VAL-MAP. (A) A conventional marking. The location of a hard to identify tumor is estimated based on the marking, and then the resection line is determined. (B) VAL-MAP-assisted wedge resection. Multiple markings using VAL-MAP indicate not only the location of the tumor but oncologically appropriate resection lines. (C) VAL-MAP-assisted segmentectomy. Multiple markings made using VAL-MAP indicate the resection lines along the anatomical segments. (D) Use of auxiliary lines and anatomical landmarks in combination with VAL-MAP. A ground glass nodule (GGN) lesion 5 mm in diameter was found close to the minor fissure in the right middle lobe (*). The patient also had another large GGN requiring segmentectomy in the right upper lobe. No bronchus extends close enough to the GGN. A three dimensional image (ii) and intraoperative view (iii) showing a marking made at the edge of the middle lobe (*). An auxiliary line (interrupted line) was drawn between the marking and an anatomical landmark (connection of interlobar fissures; black arrow). The tumor (white arrow) was located at the middle point of the auxiliary line. The tumor was successfully resected with the final pathology confirming an adenocarcinoma in situ. UL, upper lobe; ML, middle lobe; LL, lower lobe.
subjective issue depending on multiple factors such as the surgeon’s experience and accessibility to the lesion (anatomy, depth, and size of the thoracotomy that may allow for only one-finger palpation or “pinching” by two fingers). For solid nodules, we generally apply the following rule: VAL-MAP should be considered if the diameter of the lesion is <1 cm (Fig. 2B(i)) and/or the depth (distance from the visceral pleura) is greater than the diameter (Fig. 2B(ii)).

**Underlying lung**. The underlying conditions of the lung are another important factor that can be used to determine the indication for VAL-MAP. Pleural adhesion makes identification of a lung nodule difficult. Markings made using VAL-MAP are still identifiable if pleural adhesion is dissected though the intrapleural layer (Fig. 2C(i)). Pre-existing benign nodules caused by previous inflammatory diseases such as silicosis and tuberculosis may also make identification of a lesion challenging. Conversely, anthracotic lungs (Fig. 2C(ii)) that are predicted using a Brinkman index ≥500, and probably severe emphysema, are much more challenging (although not impossible to deal with) regarding clear visualization of markings made using VAL-MAP than clean non-emphysematous lungs (29).

### Table 2: Steps, tips and pitfalls regarding VAL-MAP

<table>
<thead>
<tr>
<th>Steps</th>
<th>Tips and pitfalls</th>
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<tr>
<td><strong>Mapping design/planning</strong></td>
<td>● Design depends on the operation plan. Surgeon(s) should be involved</td>
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<td></td>
<td>● Fluoroscopic view is simulated by means of a coronal/sagittal CT view or using an ray-sum picture</td>
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<td></td>
<td>● Track as much peripheral bronchus as possible in planning</td>
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<td><strong>Preparation</strong></td>
<td>● Plan mapping at &lt;3 days before the operation; mapping carried out on the same day or 1 day before mapping delivers better visualization</td>
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<td>● Use atropine and sedation before mapping and consider antibiotic prophylaxis (option)</td>
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<td></td>
<td>● Check the air tightness of the catheter system after loading the dye</td>
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<td><strong>Bronchoscopic procedure</strong></td>
<td>● Gently suction and clean the target bronchus, drawback to the central airway to achieve air-suction and cleaning of the bronchoscope working channel, and then insert the catheter and return to the target bronchus</td>
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<td>● Gently manipulate the catheter, watch the catheter tip and confirm the subpleural location</td>
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<td>● Slowly withdraw the catheter by only 1–2 mm while watching the fluoroscope monitor</td>
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<td>● Never forcefully push air</td>
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<td></td>
<td>● For posterior marking, rotate the patient (operation side up), not the fluoroscope, to inflate the collapsed lung</td>
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<td><strong>Post-VAL-MAP CT and 3D reconstruction</strong></td>
<td>● Take the CT scan within 2–3 hours after VAL-MAP</td>
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<td></td>
<td>● Routinely take the CT scan in the decubitus position (operation side up)</td>
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<td></td>
<td>● If markings are difficult to identify on the CT scan, compare it with the previous CT scan</td>
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<td></td>
<td>● Track the bronchus that should have been used for dye injection</td>
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<td></td>
<td>● Reconstruct the 3D image including markings and the tumor, and then make the final resection plan</td>
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<td>● Continuously display the final 3D image during the operation as a reference</td>
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As such, indications for VAL-MAP should be determined by taking multiple factors into consideration, such as the characteristics of the lesion, the condition of underlying lung tissue, experience of the team and operation types, which will be discussed later in the article. Figure 2D shows the relationship between the necessity and difficulty, based on our experience involving hundreds of cases of VAL-MAP. The right lower corner in Figure 2D 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 technical challenges of VAL-MAP (Figure 2D) mostly involve two issues, namely hindered visualization of dye markings and limited bronchial anatomy.

Underlying conditions such as pleural adhesion (Fig. 2C(i)) and anthracotic (Fig. 2C(ii)) or severely emphysematous lungs tend to hinder visualization of markings. If such conditions are anticipated preoperatively, bronchoscopic dye injection is recommended to be scheduled as close to the operation as possible, ideally on the same day. The dye is gradually absorbed and tends to become faint over time. Although it is clearly visible on a clean pink lung even at 2 days after injection, to increase the chance to identifying the markings in such challenging cases, the timing of dye injection should be taken into consideration. Technical tips are described in the next section; we tend to inject dye with somewhat greater force than usual to ensure better development of the marking on the visceral pleura. As mentioned above, in cases of pleural adhesion, markings can be visualized by dissecting the intra-pleural layer rather than the extra pleural space; thick parietal pleura adherent to the visceral pleural make markings invisible. Conversely, in our experience, markings are still visible if the visceral pleural is damaged because the dye stains not only the visceral pleura but also the underlying lung parenchyma to some extent.
Figure 2: Indication for VAL-MAP. (A) Typical ground glass nodules (GGNs) indicated for VAL-MAP. A small peripheral GGN (i) and a relatively large GGN (ii). (B) Typical solid lung nodules indicated for VAL-MAP. A small nodular lesion suspected of a metastatic tumor located peripherally (i) and relatively centrally with the distance from the visceral pleura greater than the diameter of the lesion (ii). (C) Visibility of markings can be affected by underlying conditions of the lung such as severe pleural adhesion (i) and severe anthracosis (ii). Blue arrows indicate markings. Note that in a case of pleural adhesion, dissection along the intra-pleural layer allows for visualization of markings. (D) Matrix showing the relationship between necessity and difficulty regarding VAL-MAP among variable cases. The lower right corner is the best indication, while the upper left corner is not a good indication. The lower left corner is suitable for beginners, while the upper right corner is suitable for an experienced team.
Figure 3: Preparation for VAL-MAP. (A) The “mapping mode” of the Synapse Vincent® software used to calculate all of the candidate markings. (B) A panel of snap shots obtained using virtual bronchoscopy as a reference for a bronchoscopist. One panel shows the route taken to reach one marking point. The letters, “X”, “Y”, “Z” and “a” indicate the bronchial septum or branching. It is important to keep information overlapped between adjacent snap shots (e.g., “X” is shown in both the top middle and top right pictures). The right lower snapshot is taken as a ray-sum picture, simulating how the root looks on fluoroscopy. (C) The injection catheter is constructed with two three-way stopcocks, a 1 ml syringe for dye loading and a 10 ml syringe for air injection. Now the stylet is removed for safety reason and then the part is capped. (D) The injection catheter loaded with indigo carmine. The dye should travel approximately 10–20 ml from the catheter tip (arrow head, catheter tip; blue arrow, top of the loaded dye). If the dye moves excessively in the catheter when the catheter is lifted (as shown in the picture), the system is unlikely to be air tight. Airtightness needs to be checked before the next step.
Regarding bronchial anatomy, interlobar fissures, portions facing the diaphragm and the mediastinum generally have a limited number of good bronchi that can be reached. Even if a good bronchus is identified in virtual bronchoscopy, it is often difficult to insert a catheter because of the branching angles. Experience in bronchoscopy appears to be important in bringing the catheter to the ideal portion. Another important strategy is to make the most of anatomical landmarks and auxiliary lines (27) to complement the limitation of bronchial anatomy as described above, and also shown in Fig. 1D.

In general, the success ratio for markings is operator dependent, as was reported recently (29). Previous experience in transbronchial lung biopsy was suggested to be a reasonable predictor of the outcome; this is because the maneuver in VAL-MAP, particularly the process of gently advancing the catheter to reach the visceral pleura, followed by slow withdrawal, is almost identical to that involved in transbronchial lung biopsy (29). Instructional videos as previously published (30) or the one accompanying the current article (additional file 1: Movie steps of VAL-MAP) are useful tools for learning the technique (29).

Techniques, tips and pitfalls of VAL-MAP
Steps, technical tips and pitfalls involved in the use of VAL-MAP are summarized in Table 2. The steps involved in VAL-MAP are also explained using a supplementary video (additional file 1: Movie steps of VAL-MAP). Instruments and equipment used in VAL-MAP are summarized in Table 3.

Mapping design, planning and preparation
The general principles of mapping are presented in Figure 1 and are as follows: the tumor is surrounded by two to four markings for wedge resection, and three to five markings are placed along the resection lines for segmentectomy. The mapping design entirely depends on the operation plan. Thus, the surgeon should consider what kind of map would most effectively enhance the performance of the operation. Ideally the surgeon should design the map by himself/herself, or at least be involved in the design process. In other words, unlike conventional marking techniques, surgeons should not leave VAL-MAP to a third party with the brief of marking the tumor. Mapping is not a simple marking procedure, but an essential component of the operation.

Target bronchi that reach the ideal marking points are determined using virtual bronchoscopy based on thin-slice CT scans. Nowadays, virtual endoscopy images can easily be built using radiology workstations. A target bronchus can be selected by tracking candidate bronchi manually one by one using virtual bronchoscopy to determine which point on the lung surface the selected bronchus reaches. Alternatively, several programs allow for the selection of candidate bronchi based on the target point (the ideal marking in this case). Usually the route selected using a computer terminates at the end of the tracked airways (i.e., the route does not reach the lung surface where an actual marking is placed). The most recent application that has been integrated into the Synapse Vincent® (Fujifilm Medical, Tokyo, Japan) bronchoscopy simulator is what is called “mapping mode”; this involves the computer calculating the extension of each bronchi to the lung surface and then displaying all of the anatomically possible marking candidates (Fig. 3A).

Virtual bronchoscopy is an evolutional tool used to navigate the bronchoscope to the target point. However, with the exception of a real-time navigation system using a magnetic field (31), virtual bronchoscopy on a computer is not linked to the actual bronchoscopy. Recorded video of virtual bronchoscopy is not so useful because it operates independently regardless of actual bronchoscopy; to simultaneously move virtual bronchoscopy on a computer with actual bronchoscopy, an additional person is needed. Our recommendation is to prepare a panel composed of snap shots of virtual bronchoscopy, as shown in Figure 3B. We usually take snap shots and paste them into Microsoft PowerPoint® as a reference at the time of bronchoscopy. In each snap shot, it is important to mark the bronchial branching(s) to show the relationship with the next snap shot. The peripheral bronchus should be tracked as far as possible, even beyond the reach of a regular bronchoscope (the reason for this is explained later in the section.
describing dye injection). We usually aim at the 7th to 11th branching. In addition, it is important to place a sagittal or coronal view of the CT scan or a ray-sum picture to indicate the fluoroscopic view at the time of bronchoscopy (Fig. 3B, right lower corner).

**Preparation for bronchoscopic mapping**

The bronchoscopic mapping procedures are conducted within 2–3 days before surgery. Because the dye is absorbed over time, dense clear markings are likely to be visible if the mapping procedure is conducted on the same day or a day before the operation. The mapping procedure is undertaken in a bronchoscopy suite equipped with a fluoroscope, similar to regular bronchoscopic examination in accordance with the institutional protocol. For example, laryngopharyngeal local anesthesia is established using 4% lidocaine spray, and this is followed by intravenous sedation with 2–3 mg of midazolam. Intramuscular administration of atropine is also strongly recommended to reduce airway secretion. Antibiotics can also be used to prevent septic fever, which is a relatively common complication associated with the bronchoscopic procedure. A regular flexible bronchoscope equipped with a working channel of 2 mm in diameter (e.g., BF-260 or BF-P260; Olympus, Tokyo, Japan) should be selected. A metal-tip bronchoscopic spray catheter (PW-6C-1; Olympus) is connected to 3-way stopcocks, and the stylet of the catheter is removed for safety. The catheter setup is shown in Figure 3C. It should be noted that this catheter is reusable; attention needs to be paid to retaining the catheter after the procedure.

To decrease dead space in the catheter, 1 ml of indigo carmine (Daiichi-Sankyo Inc., Tokyo, Japan) is loaded into the catheter first. The tip of the dye should extend approximately 10–20 cm from the tip of the catheter. If necessary, some air should be pushed in to progress the dye. Once the dye reaches the target point, the three-way stopcocks should be locked. If the system is not airtight, the dye will move in the catheter when it is lifted (Fig. 3D). If this happens, it is important to check all of the connections and stopcocks; otherwise, the dye drips during the procedure and impedes bronchoscopic vision.

**Initiation of the bronchoscopic procedure**

A bronchoscope is orally inserted and the route for reaching the target bronchus is identified using virtual bronchoscopic guidance. Subsequently, the peripheral airway should be cleaned by suctioning secretions. The bronchoscope should be withdrawn once, back to the proximal airways (around the second carina) and then the suction is turned on in the airway for ≥5 seconds. This maneuver cleans up the working channel of the bronchoscope, thorough which the catheter is next inserted; otherwise airway secretion and/or dye left in the channel is pushed out to impede bronchoscopic vision. Notably, if required, the peripheral airways should be suctioned very carefully because negative pressure on the peripheral bronchial mucosa can easily cause edema, which interferes with good visualization of the peripheral bronchus.

**Insertion of preloaded catheter**

Finally, the preloaded catheter is inserted into the bronchoscope through the working channel. During catheter insertion, attention needs to be paid to avoid sucking the dye out of the catheter. If this happens, it is necessary to remove the catheter and reload it with new indigo carmine. Once the catheter tip reaches the tip of bronchoscope, the bronchoscope should be progressed towards the target bronchus.

Sometimes the target bronchus is too peripheral for the scope to reach. However, it is still important to know the branching of the bronchus beyond the reach of the scope in order to better direct the catheter for accurate marking. Occasionally the peripheral airway is too dark for the identification of the peripheral target bronchus. The target bronchus may be visualized by increasing the light intensity (if it is set to the automatic mode, it can be switched to the manual mode). Sometimes the angle of the bronchus does not allow for visualization of the target bronchus. In such cases, insertion of the catheter in proximity to the target bronchus may slightly change the scope-bronchus angle enabling
Figure 4: Post-VAL-MAP CT scan and following 3D reconstruction. (A) Representative findings from a post-VAL-MAP CT scan include ground glass shadow (i) and airway dilation in the subpleural area (ii). (B) Typical failed or inappropriate markings. Subpleural “crawling” of the injection catheter (i) can be caused by careless manipulation of the injection catheter. Pneumothorax (ii) can be caused by too forceful an air injection, although usually it is minor pneumothorax that does not need any additional treatment. What is called “central injection” (iii: black arrow) is the most frequent cause of technical failure. The white arrow, an appropriate marking; T, tumor. (C) Adjustment of operation plan by post-VAL-MAP 3D images. (i) Pre-VAL-MAP 3D image showing the planning of VAL-MAP using Synapse Vincent® mapping mode. The yellow ball indicates the tumor. The red balls indicate planned markings. All the other white balls indicate anatomically possible marking candidates in the left lower lobe. (ii) Post-VAL-MAP 3D image reconstructed from post-VAL-MAP CT images. The purple dot indicates the tumor and the blue dots indicate actual markings. Note the difference from (i). (iii) Thoracoscopic view showing three markings. Note that the intraoperative view is almost identical to the post-VAL-MAP 3D image in (ii), demonstrating that technical errors (misplacement of markings in this case) can be corrected by post-VAL-MAP CT before surgery. (D) Gravity effect concerning VAL-MAP shown on CT scans. (i) Post-VAL-MAP CT scan taken with the patient in the supine position. The posterior marking (arrow) is mixed with the gravity effect (collapsed lung caused by gravity) and is hardly distinguishable. (ii) Post-VAL-MAP CT scan taken with the patient in the decubitus position (marking side up). The posterior region of the lung is well inflated, and the marking (arrow) is clearly visible.
visualization of the target bronchus. In most cases, the target bronchus (7th to 11th branching levels) is beyond the range of regular bronchoscopy, but, once again, it is important to try to insert the catheter as accurately as possible.

Dye injection

After catheter insertion, the fluoroscope is turned on to reveal the tip of the catheter; then the catheter is gently progressed. The catheter tip is blunt, similar to that of closed biopsy forceps used for transbronchial lung biopsy. Thus, the catheter can easily be progressed through the peripheral lung tissue to the visceral pleura (Fig. 3C). The direction of the catheter is confirmed fluoroscopically, and the catheter is further advanced to reach the visceral pleura, which can be felt through the catheter and is visible under fluoroscopy. Rotation of the fluoroscope or the patient is useful in confirming the location of the catheter tip; unless the catheter reaches the diaphragm, interlobar fissure or mediastinal side, its tip should be visualized touching the chest wall.

Once the catheter tip is considered to have reached the visceral pleura, the three-way stopcock connecting the catheter and a 10-ml syringe containing air is opened. At this moment, the catheter tip is usually wedged, and resistance is felt through the plunger if it is gently pushed. The plunger should never be forcefully pushed further. The catheter is slowly withdrawn by 1–2 mm while watching the fluoroscope and feeling the resistance on the plunger, until the point at which the resistance suddenly decreases and the plunger can be easily pushed. Then, the fluoroscope is turned off and 10 ml of additional air is gently injected to completely eject the dye. The fluoroscopic radiation exposure time is usually 20–45 seconds per mark, and the total radiation time was limited to 1–2 minutes per patient (1). For bronchoscopists and patients, this amount of radiation exposure is considered to be acceptable as compared with other procedures such as coronary intervention or CT-guided marking techniques. The catheter is then withdrawn. This process is repeated for all targeted bronchi. A video showing the overall processes of bronchoscopic dye injection is accessible online through one of our previous publications (30).

Tips and pitfalls of dye injection

The injection procedure is not technically difficult but there are several tips and pitfalls. As is discussed later, a typical successful markings are usually identifiable on a post-VAL-MAP CT scan as ground glass attenuation (Fig. 4A(i)) and/or some bronchial dilation (Fig. 4A(ii)). Failed or inappropriate markings can also be identifiable in CT scan (30). First, the catheter should not be progressed roughly or forcefully; this can cause bleeding or bulla formation. In particular, attention should be paid to the movement of the catheter tip. If it bends beneath the chest wall or around an interlobar fissure, the catheter is likely to be crawling beneath the visceral pleura. Air injection always accompanies some resistance, but too forceful an injection causes barotrauma. Damage to the visceral pleura and pneumothorax can be identified in post-VAL-MAP CT scans (Fig. 4B(i) and (ii)). Conversely, the catheter can be withdrawn over too great a distance at the time of injection, which causes what is known as “central injection” (Fig. 4B(iii)). Central injection appears to be the most common cause of marking failure in VAL-MAP (30). To prevent central injection, the catheter should be withdrawn little by little (1–2 mm at a time, and then injection should be attempted by pushing the plunger). It is important to keep watching the catheter tip on the fluoroscope screen. If it is >1 cm from the chest wall (or the initial wedged portion if the catheter tip is located on the fissure or the diaphragm), it is likely to be too central to deliver an appropriate injection; if this is the case then the procedure should be repeated. Although the resistance against the plunger decreases once the catheter tip becomes unwedged, movement of the dye in the catheter is observed slightly earlier. Thus, not to miss anything, we usually watch the fluoroscopy monitor while withdrawing the catheter at intervals of 1–2 mm; then the catheter is observed while holding it to check if the dye inside it moves while pushing the plunger. Once the dye starts to be injected, the catheter should be slightly (about 1–2 mm) progressed. A video offering advice regarding
the prevention of central injection is available through one of our previous online publications (30).

Importantly, when a marking is made on the posterior side, it tends to be more successful if a patient is placed in a decubitus position with the marking side up. This is probably because once a patient is rotated the posterior region of the lung, which is collapsed in the supine position, becomes more inflated.

**Post-VAL-MAP CT scans**

The role of post-VAL-MAP CT is highly important because bronchoscopic markings are not always placed at the exact location that was initially 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)).

After bronchoscopic marking, thin-slice CT is performed within 2–3 hours to examine the localization of the actual markings. Although indigo carmine is not radiopaque, the markings are usually identifiable on a CT scan as ground glass attenuation (Fig.4A(ii)) and/or bronchial dilation (Fig. 4A (ii)); this is presumably because of the creation of an artifact similar to that observed after bronchoalveolar lavage (i.e., water in the lung parenchyma). Similar to dye injection, markings placed in the dorsal region of the lung have greater visibility if the CT scan is taken with the patient in the decubitus position (marked side up), avoiding the gravity effect (Fig. 4D). Regardless of the location of the markings, post-VAL-MAP CT scans are routinely taken in the decubitus position.

Sometimes identification of a marking is difficult. If this is the case, it may be helpful to compare the CT scan with the previous one. With regard to locating a marking on CT, one of the tips is to track the bronchus that was used for dye injection. Notably, markings that are visible on CT scans and are located in contact with the pleura are usually visible during the operation (30). Conversely, markings that are not identifiable on CT scans or markings (ground glass attenuation) that are located at a distance from the pleura (Fig. 4B(iii)) are barely identifiable during the operation (30). Likely explanations for invisibility during the operation are central injection as mentioned above, emphysema and anthracosis (30). Especially in patients with a history of heavy smoking and/or emphysematous lung on CT scans, the visibility of the markings may be improved if the mapping procedure is conducted on the same day as the operation.

It should be noted that markings are sometimes invisible on post-VAL-MAP CT scans, although they are clearly visible during the operation. In our experience, this tends to happen once the dye injection technique becomes too sophisticated. If the timing of dye injection is perfect, the dye may be completely ejected towards the pleura without disseminating in the lung parenchyma; in addition, all of the extra air may escape from the side of the catheter without dilating the airway. If this starts to happen, the speed of air injection may be slightly increased to intentionally disseminate the dye and also to induce some airway dilation.

**Three-dimensional image reconstruction for the final planning of the operation**

Three-dimensional lung images are constructed based on the post-VAL-MAP CT scan. These post-VAL-MAP images include “actual” markings and a target lesion; thus, the 3D image should look exactly the same as the operation field, and be directly usable in the operation as an aid to navigation (Fig. 4C). This 3D image can differ somewhat from the original plan (compare Fig. 4C(ii) and (iii)). On the one hand, this is a limitation of the current VAL-MAP technique, in which the direction of the catheter is not completely controllable. On the other hand, adjustment using a post-VAL-MAP CT scan is considered a strength of VAL-MAP in overcoming technical errors. Indeed, the purpose of VAL-MAP is to provide “geometric information” on the lung surface; it provides coordinates and allows surgeons to draw auxiliary lines based on multiple markings, as long as information on the relative localization of the markings, tumor and the lung anatomy (such as segments) is collected from the lung “map”.

**Results of VAL-MAP**

We have previously reported the data from the initial
Figure 5: Principles of VAL-MAP-assisted segmentectomy. (A) A good marking stains a single secondary lobule. The staining should not disseminate across the intersegmental plane. (B) A marking placed close to the intersegmental line (bordered by inter-segmental veins). The target segment is shown as a shadowed area. In general, a marking is placed from a bronchus located inside the target segment (i). If there is no good bronchus extending close to the intersegmental line from the target segment, a bronchus in the adjacent segment can also be used (ii). (C) A case of ground glass nodule (GGN) that required S8+9 anatomical segmentectomy of the right lower lobe. A CT image showing the GGN (arrow) (i) and corresponding three-dimensional images showing five markings placed along the resection lines, particularly at the corner (ii). The target segment (S8+9) is shown in gray. (D) VAL-MAP-assisted segmentectomy beyond conventional anatomical segmentectomy. Designs of conventional anatomical segmentectomy (i), extended segmentectomy (ii), and combined subsegmentectomy (iii) are shown. Compared with conventional anatomical segmentectomy in which the resection is “unbalanced,” extended segmentectomy and combined subsegmentectomy allow for obtaining sufficient resection margins.
100 consecutive cases of VAL-MAP conducted in Kyoto University (30). Interim analysis of the ongoing multi-center study indicated that the results were consistent with those of the previous study, suggesting good reproducibility of VAL-MAP. In short, marking failure (i.e., invisible marking) occurs in approximately 10% of all the markings and this number is highly reproducible across centers participating in the ongoing multi-center study. However, the actual successful resection ratio regarding the intended sublobar lung resection was 98–99% in both the previous report (30) and the current multi-center study. This high success ratio is explained by the multiple markings used in VAL-MAP that work as a “backup” to each other. We do not repeat the marking procedure even if it is found to have failed in the post-VAL-MAP CT scan, but in most cases failure of a single marking or two among 3–4 markings does not hinder accurate lung resection.

Complications associated with VAL-MAP

In an ongoing multi-center study, VAL-MAP has been demonstrated to be a highly safe procedure. Complications that require additional treatment appear to be very rare (<0.5%) including fever and pneumonia. Minor complications include pneumothorax (3–4%) and pneumomediastinum (<1%), which are usually barely identifiable in post-VAL-MAP CT and no treatment is needed. Comparative data regarding complications and success ratio for VAL-MAP and the conventional needle-mediated percutaneous CT-guided marking techniques are detailed in Table 1.

Operation techniques using VAL-MAP

Wedge resection

The most important feature of thoracoscopic wedge lung resection using VAL-MAP is the “reproducibility” of the procedure. Usually 2–3 markings on the lung surface assist not only in intraoperative identification of small tumors, but also in acquisition of adequate resection margins (Fig. 1B). As mentioned earlier, anatomical landmarks and auxiliary lines can also be used as parts of the lung map (Fig. 1C). These techniques enable surgeons to plan and simulate the procedure preoperatively, and to complete ideal lung resection in a reproducible way.

One of the limitations of the current VAL-MAP technique is its inability to display a sufficiently “deep margin”. The extension of the dye in the vertical direction is hardly controllable and is not visible from the lung surface. As an alternative, we have developed a technique that involves the use of a lateral margin to indicate how much tissue should be grasped in the lateral direction to obtain a sufficiently deep margin (27). When there is any concern regarding achieving a satisfactorily deep margin, we select segmentectomy; in general, if the depth of the lesion is >1/3 of the lung in CT scans segmentectomy is applied. A new strategy under development to overcome the limitation regarding the extent of the application of wedge resection will be discussed later in relation to future directions.

Segmentectomy and variations

Segmentectomy can be applied to pure or mixed GGNs suspicious of lung cancer, for which wedge resection is considered oncologically insufficient, but for which lobectomy can be reserved. In particular, when extension of the GGN component raises concern about the surgical margin, this is a good indication for the use of VAL-MAP. Another indication for VAL-MAP concerning segmentectomy is a relatively centrally located nodular lesion suspicious of being a metastatic lung tumor. In such a case, pure anatomical segmentectomy is not oncologically necessary; resection of central structures in combination with “wide wedge” resection that guarantees the resection margin may be sufficient.

If an appropriate marking technique is applied, VAL-MAP results in the clear staining of a single secondary lobule without crossing the border between segments (Fig. 5A). Utilizing this characteristic, multiple markings for VAL-MAP can be positioned along the intersegmental resection lines for a segmentectomy. If a bronchus that reaches the edge of the target segment is selected, the marking is likely to be very close to the intersegmental line. Thus, if such a marking is made from inside of the target segment, the outside margin of the staining should represent the exact anatomical
intersegmental line (Fig. 5B(ii)). Conversely, if such a good bronchus reaching close to the intersegmental line is not found, a bronchus coming from the adjacent segment can be used instead. In this case, the inside of the staining is the intersegmental line (Fig. 5B(iii)). Usually three to five markings along the intersegmental line provide sufficient geometric information to complete anatomical segmentectomy (Fig. 5C). This technique eliminates the necessity for producing inflation/deflation lines, which often interferes with the visualization of the surgical field in thoracoscopic surgery.

One of the potential problems in applying conventional anatomical segmentectomy to cancer surgery is that cancer is a disease that occurs and extends regardless of anatomical segments. Thus, conventional anatomical segmentectomy, which was originally developed as a therapeutic option of mycobacterial infection (a disease that extends along the anatomy) may result in failure to achieve oncologically satisfactory resection (Fig. 5D(i)). Instead of adherence to pure anatomical segments, extension of the resection area beyond an anatomical segment is a more favorable strategy; this strategy has been called “extended segmentectomy” (32) and may involve the combination of an anatomical segment with part of an adjacent segment or a whole subsegment (Fig. 5D(ii)). Similarly, combination of subsegments may result in a satisfactory resection margin without taking extra tissue (Fig. 5D(iii)).

Current limitations and future directions of VAL-MAP

Although the techniques involved in VAL-MAP have been refined over time, this remains a technique that has scope for further development. Indeed, its potential for improvement makes VAL-MAP an exciting area of research. Here are several examples of future directions regarding VAL-MAP development. First, selection of target bronchi is a somewhat time-consuming step in VAL-MAP. Once again, virtual bronchoscopy is widely available using practically any recent radiology workstation, or even free software such as OsiriX imaging software. However, the “mapping mode” developed in Synapse Vincent® software (Fig. 3A) has dramatically facilitated the process. Additionally, the “mapping mode” is still in the process of refinement regarding algorithms for the prediction of the marking point on the lung surface. Similar programs may also be developed in other workstations in the near future to further facilitate accessibility to VAL-MAP.

Second, a deep margin at the tip of the wedge resection always raises a question. Indeed, in most cases, the deep margin is secured by taking sufficient lateral margin (27); however, this depends on the surgeon’s judgment. There has been a report that has described transbronchial placement of a microcoil, which was used for tumor identification (9). Although fluoroscopy is required during an operation, by combining it with the current VAL-MAP, it may be possible to realize true three-dimensional lung mapping.

Third, the conditions of underlying lungs such as anthracosis or severe emphysema may hinder the visibility of indigocarmine on the lung surface. If such as condition is expected from smoking history or CT scan, another option might be the use of microcoils placed in the subpleural area instead of the use of dye. Indeed, we are preparing the next clinical trial using bronchoscopic placement of microcoils in combination with bronchoscopic dye injection, to overcome the second and third limitations of current techniques of VAL-MAP detailed above.

Fourth, as mentioned above, markings are sometimes difficult to identify in a post-VAL-MAP CT scan, even if “central injection” is avoided. It might be a good idea to mix the dye with a contrast medium, although the potential risk of a chemical reaction between the dye and the contrast medium needs to be clarified.

Another important future direction of VAL-MAP is the field of diagnostic thoracoscopic lung resection. In relation to the rapid progression of molecular-targeted chemotherapy and immunotherapy for malignant diseases, an interesting application of VAL-MAP is biological characterization of small lung tumors. For example, a third generation of epidermal growth factor receptor-tyrosine kinase inhibitors is emerging as a treatment option. For appropriate use of these new medications, re-biopsy of the tumor...
and confirmation of genetic mutations such as T790M is likely to be required more frequently (33). If appropriate lesions are not accessible using other modalities (e.g., mediastinal lymph nodes usually accessible using endobronchial ultrasound transbronchial aspiration) and peripheral small pulmonary lesions are the primary option for re-biopsy, then VAL-MAP would play an important role as a part of integrated multi-modality approach for lung cancer; this is because it enables minimally invasive “pin-point” thoracoscopic operations even in the case of a tumor with a diameter of 2–3 mm.

**Conclusions**
VAL-MAP has been demonstrated to be an effective, safe and highly reproducible procedure (30). The evidence supporting its use is being further reinforced through our ongoing multi-center clinical trial. The technique has been shown to benefit many patients and surgeons in the era of navigational minimal-invasive thoracic surgery. The VAL-MAP technique still has considerable scope for advancement, and thus is an exciting area of future research.

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**Abbreviations:**

- CT: computed tomography
- GGN: ground glass nodule
- VAL-MAP: virtual-assisted lung mapping
- VATS: video-assisted thoracic surgery
References


