Preoperative lung surface localization for pulmonary wedge resection: a single-center experience

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Background: Preoperative lung surface localization is effective in sublobar resection for small lung nodules. However, the efficacy may vary depending on the underlying conditions of the lung and tumor, as well as the technique. This study aimed to evaluate the efficacy and limitations of preoperative lung surface localization for wedge resection by analyzing the outcomes of computed tomography (CT)-guided percutaneous marking and virtual-assisted lung mapping (VAL-MAP).

Methods: We investigated 215 patients who underwent curative wedge resection for malignant tumors using CT-guided localization or VAL-MAP from 1998 to 2018 in our institute. Each resected nodule was assessed for successful resection, which was defined as complete resection with adequate margins.

Results: One-hundred-and-nineteen patients with 153 nodules were included. The overall successful resection rate was 87.6%. The successful resection rate was significantly lower for nodules with intraoperative adhesion than those without intraoperative adhesion (75.0% *vs.* 90.1%; P=0.034), and for tumors requiring deep resection margins (>31 mm) than those requiring shallow margins (≤31 mm) (76.7% *vs.* 94.6%; P=0.002). Although the successful resection rate for nodules resected using CT-guided localization was significantly lower in cases with versus without intraoperative adhesion (54.5% *vs.* 86.7%; P=0.048), the successful resection rate for nodules resected using VAL-MAP was not influenced by the presence or absence of adhesion (85.7% *vs.* 93.4%; P=0.491).

Conclusions: A requirement for deeper resection and the presence of intraoperative adhesion were limitations of preoperative lung surface localization for curative pulmonary wedge resection.

Keywords: Thoracic surgery; marking; lung cancer; metastatic lung tumor; ground-glass opacity

Introduction

Recent advances in computed tomography (CT) screening mean that many small lung tumors can be detected at early stages (1,2). Although early detection of small lung nodules improves the prognosis (1), thoracic surgeons sometimes find it challenging to localize small pulmonary nodules intraoperatively (3,4).

To overcome the difficulties encountered in the surgical resection of tiny pulmonary nodules, we conducted preoperative CT-guided percutaneous marking until 2016, as reported previously (5). However, due to concerns regarding fatal complications such as air embolism (6-8), we recently started using a preoperative marking technique known

as virtual-assisted lung mapping (VAL-MAP), which is a novel bronchoscopic dye marking technique (9-12). VAL-MAP comprises multi-spot dye marking performed under virtual bronchoscopy (9-14). A prospective multi-center trial showed that VAL-MAP has reproducible efficacy (13). However, another prospective multi-center study reported that about 12% of sublobar lung resections performed using VAL-MAP failed to acquire adequate resection margins larger than the tumor diameter or 2 cm (14). As VAL-MAP is a lung surface marking technique, the deep resection margin is the most significant factor affecting successful resection with sufficient resection margins.

The present study evaluated the efficacy and limitations of two lung surface marking techniques: CT-guided percutaneous marking and VAL-MAP. We analyzed the surgical outcomes of both procedures and evaluated the risk factors for resection failure.

Methods

Patients and main endpoint

The present single-center retrospective study included patients who underwent CT-guided percutaneous needle marking (CT-guided localization) or VAL-MAP from October 1998 to April 2018 at The University of Tokyo Hospital. The inclusion criteria were patients who underwent pulmonary wedge resection with curative intent for malignant lung tumors after a preoperative localization procedure. The exclusion criterion was missing data. Both procedures were indicated for patients with pulmonary nodules that were challenging to identify intraoperatively.

The primary endpoint was the rate of successful resection. Successful resection was defined as complete resection of target tumors with resection margins larger than or equal to the lesion diameter, or ≥2 cm if the tumor was larger than 2 cm (14). Unsuccessful resection was defined as either resection with insufficient margins or the performance of additional resection to obtain adequate margins to achieve curative wedge resection. The successful resection rate was calculated as the number of successfully resected nodules divided by the total number of nodules resected.

CT-guided percutaneous needle marking procedure

CT-guided localization was performed as previously described (5). In brief, a 21-gauge hookwire marker (Hakko

Medical, Tokyo, Japan) was placed near the nodule under CT guidance after administration of local anesthesia by board-certified radiologists on the day of surgery. Another chest CT scan was performed immediately after the procedure to confirm that the marker was appropriately placed.

VAL-MAP procedure

The VAL-MAP procedure was conducted on the day of surgery or 1–2 days before surgery as previously described (9,13). While the patient was under local anesthesia and mild sedation, clinicians performed the bronchoscopic procedure using a bronchoscope (BF-260F or BF-P260F; Olympus, Tokyo, Japan). Using virtual bronchoscopic images, a metal-tipped catheter (PW-6C-1; Olympus) preloaded with 1 mL of indigo carmine was inserted through the working channel of the bronchoscope into the target bronchus. Clinicians injected indigo carmine into the target bronchus after confirmation of the appropriate location of the catheter tip under X-ray fluoroscopy. This procedure was repeated multiple times for multiple markings. After the dye injections, a chest CT scan was performed to reconstruct three-dimensional images that showed the actual locations of the markings and the target nodules.

Data collection

All hospital records were retrospectively reviewed. The patients' demographic data and main outcomes were assessed and confirmed by board-certified surgeons (K Nagayama, T Yoshioka, T Yotsumoto, and KJ Fukumoto). Two board-certificated surgeons (K Nagayama and S Kawashima) assessed the resection margins based on either the operative notes or pathological reports.

Statistical analysis

Continuous variables are reported as mean and standard deviation, while categorical variables are reported as frequency and percentage. The two-sample t-test and the chi-squared test were used to compare the frequencies of continuous and categorical variables, respectively.

Logistic regression analyses were conducted to assess the factors associated with successful resection, considering the preoperative marking technique, characteristics of target nodules, and intraoperative adhesion (15,16). The required
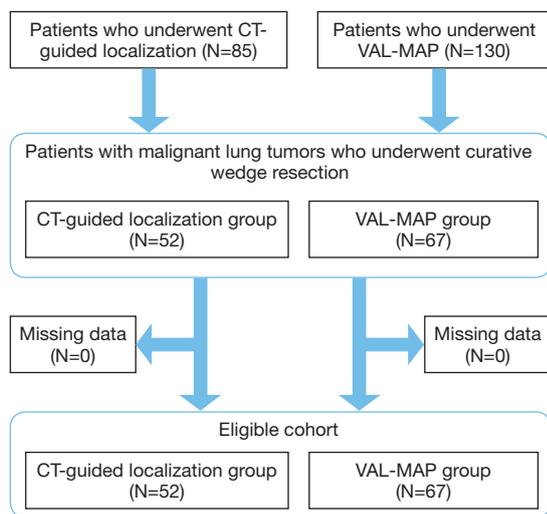
Figure 1 Study flow diagram. CT, computed tomography; VAL-MAP, virtual-assisted lung mapping.

resection depth was also assessed, as the successful resection rate reportedly decreases in tandem with increased required resection depth (14). The required resection depth was defined as the minimum depth of the resection line required to achieve successful resection and was calculated as: Required resection depth (mm) = depth (distance from the closest pleura) + {[lesion size × 2 (tumor <2 cm)] or [lesion size + 20 (tumor ≥2 cm)]} (14).

The receiver operating characteristics (ROCs) curve was plotted to determine the optimal cutoff point of the required resection depth for the prediction of successful resection. The ROC curve was obtained by calculating the sensitivity and specificity at every possible cutoff point. The optimal cutoff point was determined as the point that was closest to the upper left-hand corner (17).

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan, 2012) (18). The level of significance was set at P<0.05.

Ethical issues

This observational study was approved by the Ethics Committee of The University of Tokyo (approval number 2406-5). The requirement for written informed consent was waived because of the retrospective nature of this chart review.

Results

Patient and lesion characteristics

CT-guided localization was performed in 85 patients from October 1998 to July 2016, whereas VAL-MAP was performed in 130 patients from January 2014 to April 2018. Of these, 119 patients with 153 nodules met the eligibility criteria (*Figure 1*). The characteristics of the patients and resected nodules in the CT-guided localization group and VAL-MAP group were summarized in *Table 1*. The two groups significantly differed regarding patient age, lesion size, required resection depth, appearance of nodules, and pathological diagnosis (*Table 1*).

Factors affecting successful resection

Univariate analysis revealed that the VAL-MAP procedure was significantly associated with successful resection [odds ratio (OR): 2.72, 95% confidence interval (CI): 1.02–7.24; P=0.045], while the required resection depth (OR: 0.50, 95% CI: 0.33–0.77; P=0.002) and intraoperative adhesion (OR: 0.30, 95% CI: 0.11–0.83; P=0.020) were significantly related to unsuccessful resection (*Table 2*). Multivariate analysis revealed that the required resection depth was the only significant independent risk factor for unsuccessful resection (OR: 0.55, 95% CI: 0.35–0.87; P=0.011) (*Table 2*).

Optimal cutoff value for the required resection depth

As shown above, the required resection depth was a significant independent predictive factor for successful resection. The ROC curve identified the optimal cutoff value of the required resection depth for successful resection as 31 mm (*Figure 2*). This cutoff value had a sensitivity of 65.7% (95% CI: 57.0–73.7), specificity of 73.7% (95% CI: 48.8–90.9), positive predictive value of 94.6% (95% CI: 87.9–98.2), and negative predictive value of 23.3% (95% CI: 13.4–36.0).

Successful resection rate in accordance with the localization procedure, intraoperative adhesion, and required resection depth

In the overall cohort, the successful resection rate was 87.6% (134 of 153 lesions). Although the successful

Table 1 Characteristics of the patients and resected nodules

Characteristic	CT-guided localization	VAL-MAP	P value
Number of patients	52	67	–
Number of nodules	56	97	–
Age	61.1±12.8	66.3±9.7	0.014
Sex (male: female)	29: 23	33: 34	0.719
Lesion size (mm)	10.2±4.7	8.4±4.2	0.013
Depth (mm)	12.4±8.7	10.1±9.6	0.139
Required resection depth (mm)	32.8±10.4	26.8±12.0	0.002
Appearance of nodules			<0.001
Ground-glass opacity	32 (57.1)	26 (26.8)	
Solid	24 (42.9)	71 (73.2)	
Pathological diagnosis			0.006
Primary lung cancer	32 (57.1)	31 (32.0)	
Metastatic lung tumor	24 (42.9)	66 (68.0)	

Data are presented as mean ± standard deviation or n (%). Required resection depth (mm) = depth (distance from the closest pleura) + {[diameter × 2 (tumor <2 cm)] or [diameter + 20 (tumor ≥2 cm)]}. CT, computed tomography; VAL-MAP, virtual-assisted lung mapping.

Table 2 Uni- and multivariate logistic regression analyses to identify factors associated with successful resection

Factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Procedure, VAL-MAP *vs.* CT-guided localization	2.72	1.02–7.24	0.045	2.22	0.78–6.30	0.134
Required resection depth (cm)	0.50	0.33–0.77	0.002	0.55	0.35–0.87	0.011
Appearance of nodules, solid *vs.* ground-glass opacity	1.56	0.59–4.10	0.366	–	–	–
Intraoperative adhesion, present *vs.* absent	0.30	0.11–0.83	0.020	0.35	0.12–1.03	0.055

VAL-MAP, virtual-assisted lung mapping; CT, computed tomography; OR, odds ratio; CI, confidence interval.

resection rate did not significantly differ between the two groups, VAL-MAP tended to result in a higher successful resection rate than CT-guided localization (91.8% *vs.* 80.4%; P=0.071) (*Figure 3A*). The successful resection rate was significantly worse in the presence of adhesion than in the absence of adhesion (75.0% *vs.* 90.1%; P=0.034) (*Figure 3B*). The successful resection rate was significantly worse for nodules with a greater required resection depth (>31 mm) than those with a smaller required resection depth (≤31 mm) (76.7% *vs.* 94.6%; P=0.002) (*Figure 3C*).

Post-hoc analysis of the effects of intraoperative adhesion and required resection depth on the successful resection rate for each localization procedure

The presence of intraoperative adhesion and greater required resection depth (>31 mm) were significant negative factors affecting successful resection (*Table 2*).

In the CT-guided localization group, the successful resection rate was significantly worse for nodules with versus without intraoperative adhesion (54.5% *vs.* 86.7%; P=0.048; *Figure 4A*). In the VAL-MAP group, the successful

resection rate did not significantly differ for nodules with versus without adhesion (85.7% *vs.* 93.4%; P=0.491; *Figure 4B*).

Although the differences were not significant, the successful resection rate for nodules with a greater required resection depth (>31 mm) tended to be worse than that for those with a smaller required resection depth in both the CT-guided localization group (70.0% *vs.* 92.3%; P=0.079; *Figure S1A*) and the VAL-MAP group (83.3% *vs.* 95.5%; P=0.106; *Figure S1B*).

Discussion

A greater required resection depth was a significant risk factor for resection failure, regardless of preoperative localization technique (*Table 2*, *Figures 3C,S1*). As both CT-guided localization and VAL-MAP only enable the placement of markings on the lung surface, uncertainty regarding the deep resection margin has been assumed to be a potential limitation, and the present findings confirmed that this was an actual problem. The present study revealed that a required resection depth of 31 mm may be the threshold value for predicting the success of curative pulmonary wedge resection assisted by lung surface preoperative localization. Our results suggest that care is needed when choosing the surgical approach for nodules that require a resection depth of more than 31 mm, and surgeons should consider selecting segmentectomy or lobectomy instead of wedge resection assisted by a preoperative localization technique.

An interesting new approach to overcome the challenge of determining the deep resection margin is to place a fiducial marker in the deep lung parenchyma to indicate the optimal deep resection lines. Our pilot study combining VAL-MAP and bronchoscopic microcoil placement to indicate the deep resection line demonstrated a promising outcome (19), and we are currently evaluating this technique in a prospective multicenter study in Japan.

The present study revealed that intraoperative adhesion negatively affected curative wedge resection of small pulmonary nodules (*Table 2*, *Figure 3B*). The negative effects of intraoperative adhesion were especially notable
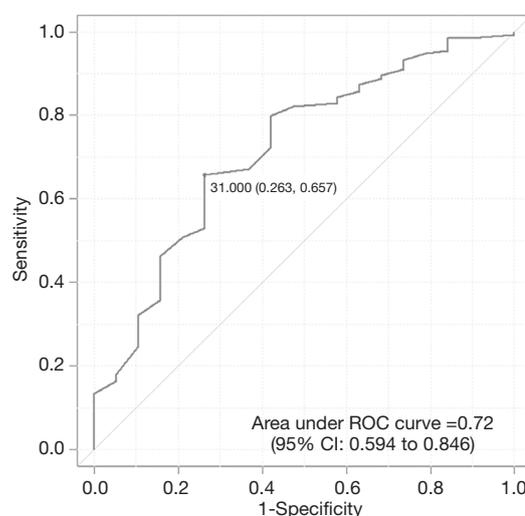

Figure 2 ROC curve for required resection depth as a predictor of successful resection. The optimal cutoff depth was identified as 31 mm, with a 1-specificity of 26.3% and sensitivity of 65.7%. ROC, receiver operating characteristic; CI, confidence interval.
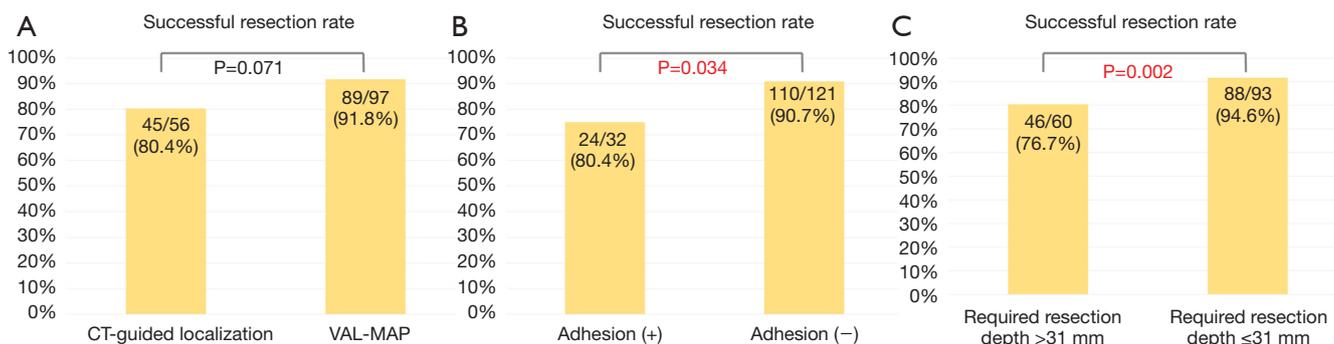

Figure 3 Successful resection rate in accordance with the localization procedure, intraoperative adhesion, and required resection depth. Successful resection was defined as complete resection with resection margins larger than or equal to the lesion diameter or 2 cm. (A) Localization procedure; (B) intraoperative adhesion; (C) required resection depth. CT, computed tomography; VAL-MAP, virtual-assisted lung mapping.
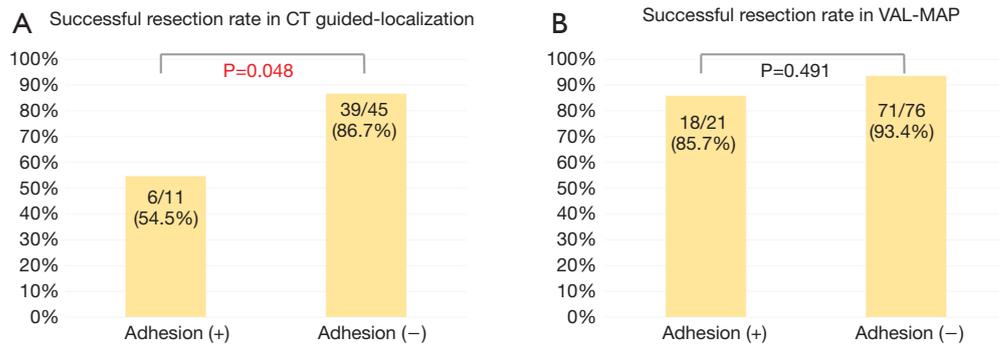
Figure 4 Influence of intraoperative adhesion on the successful resection rates of subgroups created for each localization procedure. Successful resection was defined as complete resection with resection margins larger than or equal to the lesion diameter or 2 cm. (A) The successful resection rate was significantly lower in the presence of adhesion than in the absence of adhesion in the CT-guided localization group (54.5% *vs.* 86.7%; P=0.048); (B) there was no significant difference in the successful resection rate in accordance with the presence of adhesion in the VAL-MAP group (85.7% *vs.* 93.4%; P=0.491). CT, computed tomography; VAL-MAP, virtual-assisted lung mapping.

when CT-guided localization was used (*Figure 4A*), while VAL-MAP was less influenced by intraoperative adhesion (*Figure 4B*). This may be because VAL-MAP provides multiple-spot marking and mapping for each nodule, while CT-guided localization only provides one marking for each nodule. Even if one VAL-MAP marking is not visible due to adhesion, the surgeon may be able to use other visible markings to successfully localize the target nodule (7). This advantage of VAL-MAP may have led to the relatively high successful resection rates regardless of the presence of adhesion (*Figures 3A,4B*).

The present study did not draw a definitive conclusion regarding the difference in the efficacy of CT-guided localization versus VAL-MAP. Although univariate analysis showed a significant association between VAL-MAP and successful resection (*Table 2*), surgeons tended to use CT-guided localization for nodules with a greater required resection depth (*Table 1*), and this confounding factor would have contributed to the relatively low successful resection rate (*Table 2, Figure 3A*). However, considering the relative resistance to intraoperative adhesion (*Figure 4B*) and the safety profile (15,20,21), we consider VAL-MAP the preferred method for preoperative lung marking for curative wedge resection.

The present study had some limitations. First, it was a small single-institutional retrospective study. Because of the retrospective nature, it would be challenging to compare the two marking techniques appropriately in the present study. Second, the constancy assumption may have been violated, as surgeons' concerns about the resection margins and the quality of markings would have greatly changed

over the decades included in the study period. In our institute, indication of lung surface markings and planned surgical procedure has been preoperatively discussed for each nodule among certificated surgeons. However, actual design of wedge resection considering surgical margin for each nodule has depended on each certificated surgeon. Surgeon's bias could not be avoided.

In conclusion, intraoperative adhesion and greater required resection depth were limitations of preoperative lung surface localization for curative pulmonary wedge resection. Intraoperative adhesion negatively affected the resection status, especially in CT-guided localization. Considering the relative resistance to intraoperative adhesion, VAL-MAP might be a better preoperative lung surface marking technique than CT-guided localization. Further studies are needed to improve the preoperative localization technique for small lung nodules.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.04.43). JN reports grants from Astellas, grants from Taiho Pharma, outside the submitted

work. MS serves as an unpaid editorial board member of *Journal of Thoracic Disease* from Oct 2018 to Sep 2020. 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. This observational study was approved by the Ethics Committee of The University of Tokyo (approval number 2406-5), and was conducted in compliance with the Declaration of Helsinki.

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A Successful resection rate in CT guided-localization
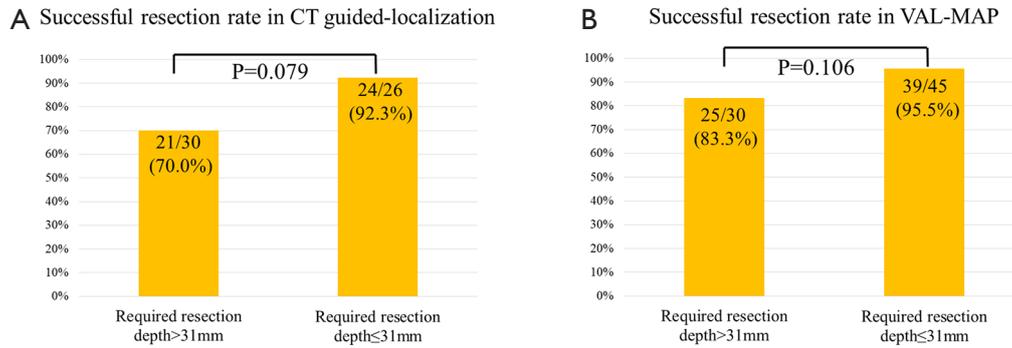

B Successful resection rate in VAL-MAP

Figure S1 Influence of required resection depth on successful resection rates using each localization procedure. Successful resection was defined as complete resection with resection margins larger than or equal to the lesion diameter or 2 cm. (A) The successful resection rate for nodules with a greater required resection depth (>31 mm) tended to be worse than that for those with a smaller required resection depth in the CT-guided localization group (70.0% *vs.* 92.3%; P=0.079) and (B) the VAL-MAP group (83.3% *vs.* 95.5%; P=0.106). CT, computed tomography; VAL-MAP, virtual-assisted lung mapping.