Review Article

The feasibility of electromagnetic navigational bronchoscopic localization with fluorescence and radiocontrast dyes for video-assisted thoracoscopic surgery resection

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Abstract: Recently, some groups have reported the utilization of electromagnetic navigational bronchoscopy (ENB) for localization of pulmonary lesion. Its application for intraoperative visual localization with dyes to determine the target area has been increasing. In this paper, we reviewed the feasibility of ENB utilization for video-assisted thoracoscopic surgery (VATS) or robotic sublobar resection as a localization tool, and its future application in minimally invasive thoracic surgery.

Keywords: Electromagnetic navigational bronchoscopy (ENB); video-assisted thoracoscopic surgery (VATS); robotic surgery; localization

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Introduction

In recent years, lung segmentectomy or wedge resection has been developed to offer better pulmonary preservation than lobectomy or pneumonectomy for lung malignancy (1,2). Sublobar resection has been used for the removal of inflammatory lung lesions or non-malignant lung masses (3,4); meanwhile, for early-stage lung malignancy (5-7), some groups have recommended the use of localization techniques to achieve a proper resection margin of more than 2 cm or the size of nodule (8-10).

Lobectomy remains the gold standard of treatment for early-stage lung cancer. Sometimes, we consider a sublobar resection in patients with poor cardiopulmonary reserve, which could be threatened by conventional lobectomy; another indication is preservation of normal pulmonary reserve in patients with very small lung malignancies. This corresponds to peripheral nodules smaller than 2 cm with a pure adenocarcinoma in-situ histology, more than 50% ground-glass portion on computed tomography (11) scan, and a long doubling time (>400 days) on radiologic imaging surveillance (12-14). In these cases, segmentectomy is preferred over wedge resection because of the high incidence of local recurrence with a wedge resection (15).

Further challenges are created by the single-port (16,17), subxiphoid (18) and robotic approaches (19,20) in lung cancer surgery. Technical issues regarding video-assisted thoracoscopic surgery (VATS) approaches for segmentectomy might be summarized as identification of the correct location of the target lesion and the proper sufficient resection margin for control of local recurrence (21,22). During open thoracotomy, surgeons can perform manual palpation of the target lesion and directly inspect the anatomic landmark for the intersegmental plane. On the other hand, the operative field might be limited for manual palpation and delineation of the intersegmental plane or for the identification of surgical anatomic landmarks. Thus, preoperative localization techniques were introduced to help locate non-palpable or deep-seated nodules at

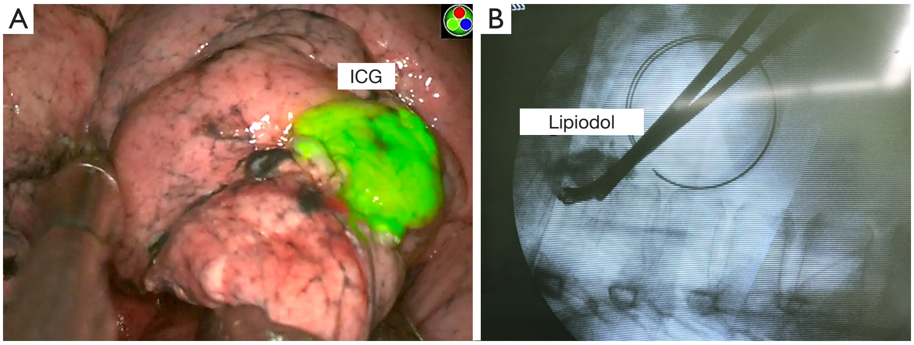

Figure 1 Electromagnetic navigational bronchoscopic localization with indocyanine green and lipiodol. (A) Fluorescent signal on intraoperative endoscopic fluorescence system; (B) lipiodol under C-arm fluoroscopy. ICG, indocyanine green.

the time of VATS. Dyes such as methylene blue (23,24) and indigo carmine (25,26), radiocontrast (lipiodol or iopamidol) (27,28), metallic markers such as hook-wire (29) or fiducials (30), and radioisotopes (31,32) were used for locating the lesions. These techniques, however, require preoperative percutaneous transthoracic intervention with CT scan, and occasionally, these techniques might be harmful for patients, as they may develop complications, particularly pneumothorax, hemothorax or embolization.

Recently, electromagnetic navigational bronchoscopy (ENB) has been applied to help localize the target lesion prior to surgical resection (26). ENB utilizes electromagnetic technology to guide the bronchoscope and the catheter using a three-dimensional (3D) virtual map from thin-section CT scan images. Historically, ENB was developed as a minimally invasive diagnostic tool for detection of lung lesions. The system consisted of a computer software for three-dimensional CT reconstruction used for planning, a positional sensor and magnetic generator in bed, and a navigational system for bronchoscopic guidance. For diagnostic purposes, ENB showed similar or superior diagnostic yield with regard to peripheral lung lesions compared to another diagnostic modality (transthoracic needle aspiration), with less procedure-related complications (33,34).

Experience of ENB localization for VATS sublobar resection

ENB was first introduced in our center in 2017 and we used ENB localization with fluorescent dye for VATS or robotic-assisted sublobar resection in ten patients. The superDimension system version 7 (Medtronic, Minneapolis, MN, USA) was used in our clinical experience. During that time, we concurrently performed multiple localization techniques for VATS or RATS resection, using CT-guided transthoracic injection of indocyanine green (ICG) with lipiodol, and hook-wire localization with or without lipiodol. We used the ICG dye for ENB localization with an endoscopic fluorescence imaging system (Pinpoint; Novadaq, Kalamazoo, MI, USA), which uses near infrared (NIR) imaging, for VATS. Additional lipiodol was mixed to the ICG dye to evaluate the surgical resection margin and to identify the appropriate intersegmental plane during sublobar resection (*Figure 1*).

In our study population (n=10), six patients underwent planned VATS segmentectomy for whom we performed intraoperative ENB localization with ICG and lipiodol to evaluate the location of the nodule and the appropriate intersegmental plane. Three patients underwent planned VATS wedge resection for an indeterminate pulmonary nodule without tissue diagnosis. The last patient had interstitial lung disease with mixed ground glass opacity (GGO) on CT scan, in whom we performed ENB localization to determine the accurate location of areas with higher malignant potential (*Table 1*).

For ENB localization with dye injection, we first need a CT scan with thin-section images to reconstruct a 3D map of the virtual airway and multiplanar views to create the pathway to the target lesion (*Figure 2*).

A 3D reconstruction software embedded on a laptop system was used to generate 3D mapping. In the operating room, the location board was placed on the operative bed to create an electromagnetic field and magnetic sensors for tracking were placed on the patient's anterior chest wall to show the real-time position of the locatable catheter tip.

We then performed endotracheal (ET) intubation with a single lumen ET tube with an 8.0 internal diameter using

Table 1 Cases of electromagnetic navigational bronchoscopic localization with indocyanine green and lipiodol—our experiences

No	Sex	Age (years)	Diagnosis	Lobe	Size (mm)	Depth (mm)	Procedure time (min)	Operation	Operation time (min)
1	Female	33	Benign	LLL	12	12	20	Segmentectomy	50
2	Female	68	Lung cancer	RLL	15	34	21	Segmentectomy	222
3	Female	57	Lung cancer	LLL	16	5	25	Segmentectomy	195
4	Male	69	Lung cancer	LLL	9.1	10	19	Segmentectomy	165
5	Male	73	Lung cancer	LLL	12	0	16	Segmentectomy	133
6	Male	60	Lung cancer	RUL	13	15	15	Lobectomy	160
7	Female	53	Lung cancer	LUL, LLL	Diffuse GGO	0	24	Wedge resection	40
8	Male	59	Metastatic cancer	RML, LUL	10	10	17	Wedge resection → RML lobectomy	72
9	Female	62	Lung cancer	RLL	12	5	7	Segmentectomy	150
10	Male	67	Lung cancer	RML	5	5	18	Wedge resection	130

LLL, left lower lobe; RLL, right lower lobe; RUL, right upper lobe; RML, right middle lobe; LUL, left upper lobe; GGO, ground glass opacity.

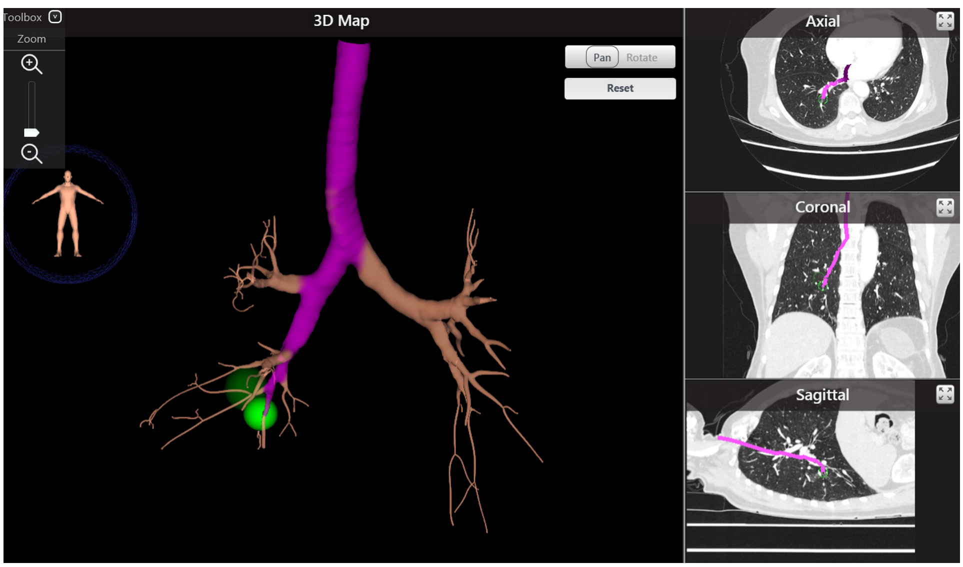

Figure 2 Three-dimensional reconstruction of virtual airway map to target lesion.

a 6-mm bronchoscope, BF-1T260 with a 2.8-mm working channel (Olympus, Tokyo, Japan) for the ENB localization. A steerable navigation catheter with a location sensor tip was inserted in the working channel of the bronchoscope. We then inserted the bronchoscope to examine the airway and proceeded with the registration sequence to synchronize the virtual and actual anatomies of the patient (*Figure 3*).

After registration was completed, the main monitor began to show the virtual bronchoscopic view on the screen. As the bronchoscope was advanced to the target lesion, the navigation catheter was wedged into the subsegmental bronchus. From this point, a locator guide was moved toward the target, and the real-time location of the catheter tip was displayed on the monitor. The navigational catheter could approach the target lesion by rotating and advancing along the pathway generated through virtual bronchoscopic images. The target lesion appeared as a green sphere on the monitor and the distance from the catheter tip was

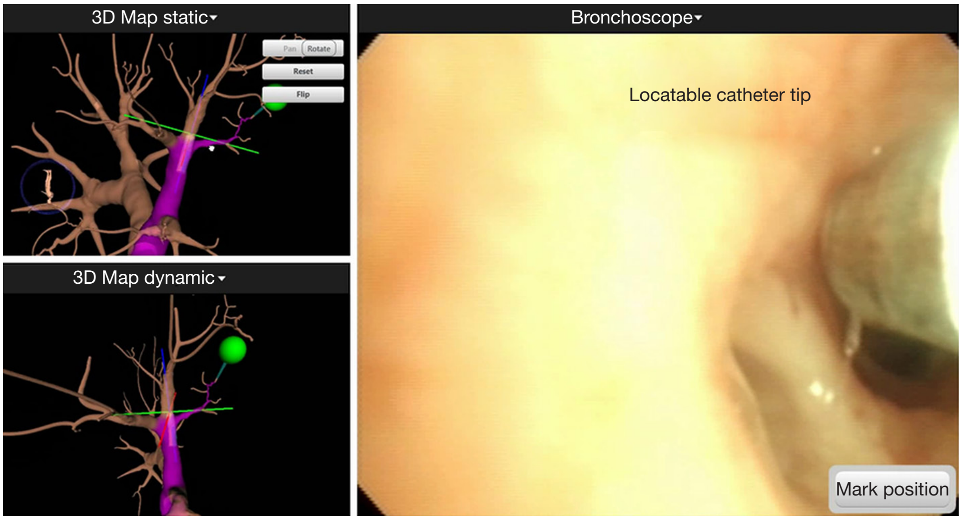

Figure 3 Bronchoscopic navigation with locatable guide catheter.

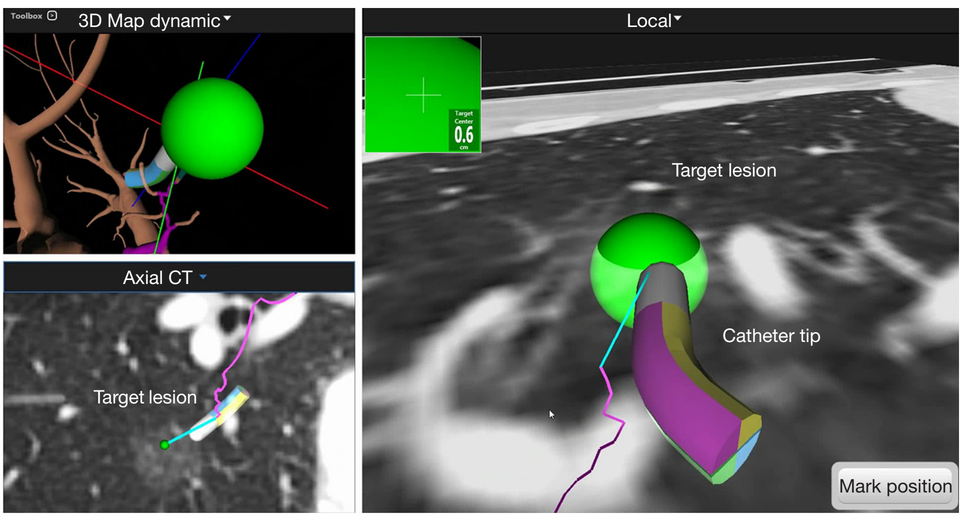

Figure 4 Peripheral navigation. Green sphere indicates target lesion.

simultaneously displayed (*Figure 4*). Once the catheter tip reached the target lesion, the catheter was fixed, and the locatable sensor tip removed. We then inserted a 25-gauge injection needle (diameter 1.9 mm) which has sufficient length (1.65 m) to reach the peripheral lesion through the catheter, and we injected 1 ml of mixed ICG dye and lipiodol (*Figure 5*).

To evaluate the real-time diffusion pattern of the injected dye, C-arm fluoroscopy was used to confirm the dye diffusion After the ENB localization with dye was completed, we removed the bronchoscope and changed the position of the patient to lateral decubitus for VATS or robotic resection. The mean procedure time was 18.2 minutes in our study. We used the endoscopic fluorescence imaging system for VATS and the SPY imaging system (*Figure 6*) embedded on the Da Vinci robotic system (Intuitive Surgical, Inc., Sunnyvale, CA, USA) during robotic lung resection. The outcomes are summarized in *Table 1*. The success rate was 90% and we failed only in a single case: the pure GGO lesion which was located 34-mm deep from the pleura. In this case, we planned the target location directly within the GGO lesion; however, we could not see the ICG

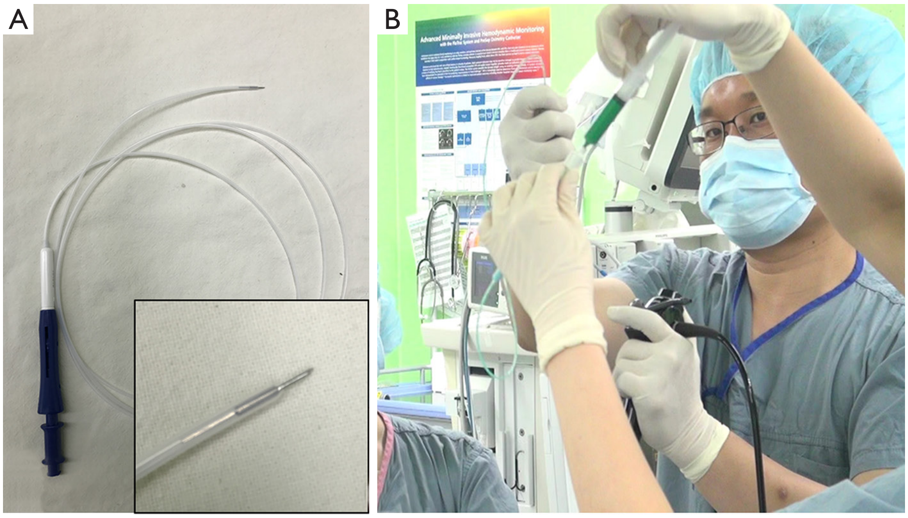

Figure 5 Dye injection with (A) a 25-gauge injection needle with 1.6 m length; (B) injection of combined indocyanine green and lipiodol through needle catheter

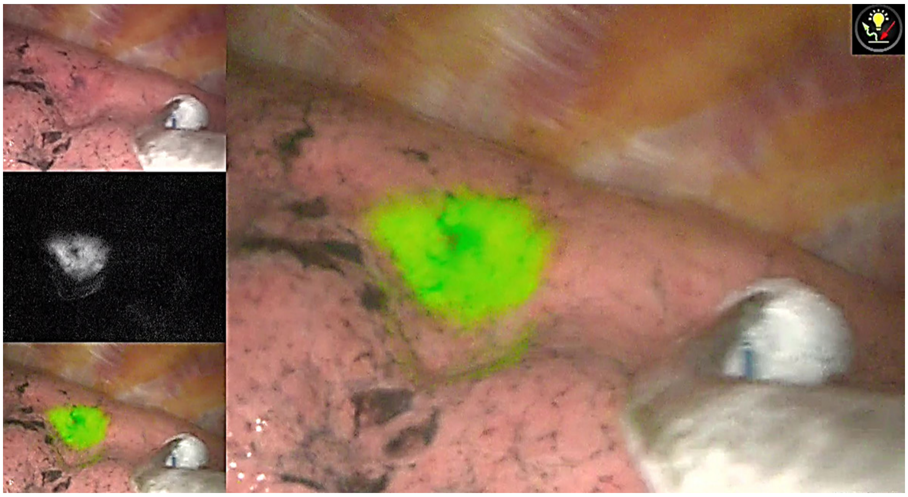

Figure 6 Operative finding after localization under endoscopic fluoroscopic camera.

signal on intraoperative SPY images. The ICG signal appeared after dissection deep in the lung segment. Of the nine malignancies, we achieved clear resection margins in eight cases for segmentectomy or wedge resection. We converted to VATS lobectomy in one case because the resection margin was positive on the intersegmental plane which fluorescent signal detected on fluorescent camera and we confirmed the positive margin on frozen biopsy. Minor endobronchial bleeding occurred during ENB localization, which stopped with compression. There was no adverse systemic event related with the ENB localization and dye injection.

Role of electromagnetic navigational bronchoscopy prior to VATS sublobar resection

There have been many attempts on localization of small pulmonary lesions to aid in improving visual identification and guidance for resection. Ideally, there is no need for devices and additional cost if the target lesion can be palpated by finger. However, for VATS sublobar resection without localization, 10–20% of cases have been reported to have missed nodules or have failed to achieve sufficient resection margins (35,36). Although percutaneous localization with dye (methylene blue) showed more than 80–90% success rate in published series (23,37), there have been unsolved problems, such as limited time interval between dye injection and operation (within 3 hours) to minimize dye diffusion, and lack of information about the accurate depth of the resection margin. CT-guided localization using hook wire or microcoils (38,39), radiolabeled aggregates (40,41), and lipiodol (42,43) also showed approximately 90–100% success rate with acceptable outcomes in randomized trials; however, these procedures are associated with a risk of procedure-related complications, namely pneumothorax, hemothorax, or for lipiodol, embolism. Microcoils or hook wires might also be displaced or dislodged in about 2–10% of cases (44). These localization procedures requisitely need the help of a radiologist or nuclear medicine specialist. Intraoperative ultrasonography might be a good option for identification of a solid pulmonary lesion, with a 93% success rate (45). However, the success of this technique depends on the surgeon's experience and the results may not be accurate if the lung is emphysematous (46). In addition, with the development of 3D multi-detector CT, some groups have used 3D reconstruction with different color mapping for arteries and veins, and lung segmental anatomy for surgical planning (47,48). This image-guided technique with 3D reconstruction might be helpful in the performance of lung segmentectomy, however, this has not been widely adapted at present.

The available evidence supporting the clinical efficacy of ENB as a localization tool for surgical resection is currently weak, with no randomized trials. However, the use of the ENB has been increasing, with the potential benefits of simplifying the current localization procedure, since this may be directly performed by the surgeon in the operating room, as well as extremely low rates of procedure-related complications. Multiple groups have described the use of ENB as a localization tool with methylene blue or ICG for the resection of lung nodules. Bolton *et al.* used ENB with methylene blue dye for localization of lung nodules in 19 patients who underwent robotic surgery (26). The mean tumor size was 18 (range, 8–40) mm and procedure time was 28 (range, 17–40) minutes. Using this method, they reported a 100% success rate, with no adverse event or conversion to open thoracotomy. Krimsky *et al.* also reported on ENB localization with methylene blue and ICG dye in 21 patients (49). The mean tumor size was 13.4 (range, 7–29) mm and ICG dye was used in ten patients. The success rate was 81% (17/21); there was no visible dye in three cases and the dye extravasated in one case, which made the mass impossible to identify. Marino *et al.* reported the largest case series using methylene blue dye for ENB localization in 70 patients (50). The mean tumor size was 8 (range, 4–17) mm and the mean distance from the pleura was 6 (range, 1–19) mm. By using this method, they reported a 97.2% success rate, with two cases of dye extravasation. Awais *et al.* also described the use of ENB localization using methylene blue in 29 patients (51). They performed 33 localization procedures for lung lesions with a mean nodule size of 10 (range, 4–27) mm and depth from the pleura of 13 (range, 3–44) mm. They reported a 100% success rate with the use of additional intraoperative CT scan to achieve adequate surgical resection margins. Abbas *et al.* used ENB localization with methylene blue, either alone or with ICG and iopamidol, or fiducial marker in two cases (28). They performed VATS resection in two patients and robotic resection in 47 patients. Two patients required thoracotomy for severe adhesions. They used additional ICG to use the NIR SPY images by robotic endoscope during the procedure. Iopamidol was also used to inspect the real-time flow pattern of the methylene blue dye by intraoperative fluoroscopy. The success rate was 98.1% in 54 localization procedures.

As a localization tool for ENB with dye in this reported case series, ENB is a safe and feasible modality for intraoperative localization during VATS or robotic sublobar resection. The reported success rate of ENB localization ranged from 80% to 100%, but was generally more than 95% in most case series. In literature review, the success rate of ENB localization for surgical resection appears to be acceptable, compared with other localization techniques; however, this should be evaluated in large series or randomized studies (*Table 2*).

There was no adverse systemic event related with bronchoscopic dye injection. The ENB localization technique for surgical resection has potential benefits compared to the current established localization techniques. Transthoracic procedures such as CT-guided injection of marker, metallic hook wire, or microcoils were associated with development of pneumothorax, hemothorax, displacement of metallic markers, embolism, and parenchymal hematoma. Furthermore, there have been safety concerns with regard to the time delay from the localization procedure to the operation, and discomfort and inconveniences for the patients with an additional procedure. Usually, ENB localization could be performed directly in the operating room by the surgeon or the bronchoscopist, with or without ET intubation under

Table 2 Review of electromagnetic navigational bronchoscopic localization for VATS or robotic resection

Authors	No of nodule	Size of nodule (mm)	Distance from pleura (mm)	Marker	Procedure time (minutes)	Success rate (%)
Bolton *et al.* [2014]	19	18 [8–40]	–	Methylene blue	28 [17-40]	19/19 (100.0)
Krimsky *et al.* [2014]	21	13.4 [7–29]	–	11 Methylene blue; 10 ICG	–	17/21 (81.0)
Tay *et al.* [2015]	6	21.2 [15–25]	2.2	5 ICG/1 methylene blue	–	6/6 (100.0)
Marino *et al.* [2016]	72	8 [4–17]	6 [1–19]	Methylene blue	–	70/72 (97.2)
Awais *et al.* [2016]	33	10 [4–27]	13 [3–44]	Methylene blue	9.7	33/33 (100.0)
Abbas *et al.* [2017]	54	13.3 [4–44]	22 [4–38]	Methylene blue +/– ICG or Isovue	–	53/54 (98.1)
Juan *et al.* [2017]	19	9 [4–32]	9.5 [1–40]	Methylene blue	–	15/19 (79.0)

VATS, video-assisted thoracoscopic surgery; ICG, indocyanine green.

general anesthesia. In addition, we could proceed with the planned operation without transport of the patient, which means this technique could minimize the waiting time between localization and operation to within 10 to 20 minutes, enabling the surgeon to use rapidly diffusible dyes such as methylene blue. However, ENB localization with dye injection alone might not be useful for target lesions in deep locations. For the deeply-seated pulmonary lesion, the usual target location of CT planning should be placed at the nearest pleura to visualize the dye color. The penetration power of the dye might sometimes be limited if the target location is too far away from the pleura. There have been no studies regarding the optimal distance for dye injection from the pleura to the mass during ENB marking (52). In such cases, the additional mixing of radiocontrast dye and intraoperative cone beam CT or fluoroscopy might help evaluate the deep resection margin or intersegmental plane during segmentectomy. ENB-guided deployment of additional fiducial markers might also be an option.

Thus, ENB localization with dye injection might be a feasible option for minimally invasive resection of small pulmonary nodules without tissue diagnosis. This method might also help identify the location with visual identification and can be performed safely in the operating room without delay. Furthermore, ENB could minimize the procedure-related complications frequently occurring with the currently performed transthoracic localization techniques.

Summary

From our preliminary experiences of ENB localization for VATS or robotic surgical resection, the entire localization procedure could be performed in the operating room without the help of a radiologist or bronchoscopist. The ENB localization procedure did not excessively extend the operation time. With high success rates of up to 90% and few procedure-related complications frequently associated with transthoracic intervention, such as pneumothorax or hemothorax, ENB localization might be a safe and feasible localization technique in the near future. In our technique, the use of ICG could provide more colorful images compared to methylene blue, which frequently produces diffuse staining. Potentially, additional radiocontrast such as lipiodol might prevent the dye diffusion, which should be evaluated in future studies. To overcome the insufficient resection margins for curative sublobar resection or deep-seated lesions that might not be visible even with localization, intraoperative cone-beam CT or C-arm fluoroscopy with the use of radiocontrast dye or fiducial markers can be useful to identify the deep location.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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