Safety and efficacy of computed tomography-guided dye localization using patent blue V for single lung nodule for video-assisted thoracoscopic surgery: a retrospective study

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Background: For invisible or impalpable lung nodules, video-assisted thoracoscopic surgery (VATS) has some limitations; some preoperative localization has been developed to overcome this limitation. This study aimed to assess the safety and efficacy of preoperative computed tomography (CT)-guided localization with patent blue V dye.

Methods: In this retrospective study, we examined patients with solitary pulmonary nodule undergoing preoperative CT-guided patent blue V dye localization from 2013 to 2015. We analyzed patients' demographic data, nodular features, and procedures undergone.

Results: We enrolled 282 patients (282 lung nodules; mean age: 56.6±11.6 years, with female preponderance) in this study. The mean size of nodules was 0.9±0.5 cm, and mean time of localization was 24 min. The leading complications after localization were asymptomatic pneumothorax (48 patients, 17%) and localized pulmonary hemorrhage (51 patients, 18%). Other rare complications included subcutaneous emphysema and hematoma. We noted two cases with intraoperative poor or fail dye localization. Most patients underwent wedge resection (221 patients, 78.4%) and segmentectomy (36 patients, 12.8%), whereas 25 patients underwent lobectomy (8.9%) after the intraoperative frozen histopathological study confirmed malignancy. Furthermore, postoperative hospital stay was 4.8±2.0 days. Few patients experienced postoperative complications such as empyema (n=1), air leakage (n=3), and chylothorax (n=1).

Conclusions: This study establishes that CT-guided dye localization is a safe and efficient method with rare severe complications and high success rate.

Keywords: Computer-assisted surgery; lung neoplasms; radiology; technology; trityl compounds; video-assisted thoracic surgery (VATS)

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Introduction

In 2017, lung cancer was one of the leading causes of cancer-related mortality in the United States, accounting for up to 26% cases (1). The National Lung Screening Trial Research Team reported that the use of low-dose computed tomography (LDCT) as a screening tool to detect early-stage lung cancer could reduce mortality up to 20% among smokers or ex-smokers (2). Compared with chest radiography and conventional CT, LDCT provided more detailed information about lung disease with less radiation dose. Of note, patients experiencing symptoms such as cough, hemoptysis, dyspnea, or chest pain and high-risk patients, such as smokers or those with a cancer history, are more likely to undergo CT scanning. Reportedly, the incidental pulmonary nodules could be classified as benign and malignant, such as lung cancer, metastases, carcinoid tumor, infectious granuloma, or benign tumor (3). If nodules exhibit suspicious image features or are indeterminate, nonsurgical biopsy or excision could be performed for the tissue diagnosis.

Surgical excision is the gold standard for diagnosis among the management options for cancer, also providing other benefits, such as diagnosis, tumor staging, lymph node sampling, and treatment within a single operative procedure. Additionally, minimally invasive thoracic surgery (MITS), including video- or robotic-assisted thoracoscopic surgery, offers advantages such as faster recovery time, shorter hospitalization, reduced postoperative pain, and smaller chest wall incision, making it a favorite option for surgeons compared with open thoracotomy (4-6). Nevertheless, MITS has some limitations. Tsai *et al.* reported the challenges in recognizing small, subsolid, or deeply-seated pulmonary nodules during video-assisted thoracoscopic surgery (VATS) (7); these pulmonary nodules were either invisible or impalpable. Previously, several localization methods have been developed to enhance the accuracy of resection; however, those methods with different localized material or modality exhibited variable complications, advantages, or drawbacks (8). For instance, the dislodgement rate was about 2.4–6.9% at the hookwire localization. Hence, this study aims to assess the safety and efficacy of the preoperative computed tomography (CT)-guided localization with patent blue V dye.

Methods

Study design and patients

In this retrospective study, we enrolled patients who had a lung nodule and underwent the preoperative CT-guided patent localization from March 2013 to March 2015. We obtained informed consent from all patients before the procedure. Of note, we excluded patients who had undergone other methods of localization (*Figure 1*).

Study procedure

In this study, dye localization was performed (*Figure 2*) under a 4- or 16-slice CT (HiSpeed CT/i or GE LightSpeed; GE Healthcare, Milwaukee, WI, USA). After confirming the location of the lung nodule with a surgeon, we planned a needle tract as short as possible to avoid transverse through a large vessel, bulla, or interlobar fissure. A 22-gage, 15-cm Chiba needle (PTC needle, Hakko, Nagano, Japan) was inserted into the target nodule under CT scan after sterilization and local anesthesia with 2% lidocaine. Next, 0.1–0.2 mL dye (patent blue V 2.5%; Guerbet, Aulnay-sous-Bois, France) was administered through a needle into the target lesion. If the lesion was far from the pleura, the dye was injected multiple times along the tract between the nodule and the subpleural region. We arranged the final CT to validate the result of the dye localization and postprocedural complication, including pneumothorax or hemorrhage. Then, patients were transferred to the operating room/ward for VATS, where a surgeon could resect the lesion along the trace of dye (*Figure 3*).

To simplify our comparison, we excluded patients with >1 nodule to preoperative localization or those who underwent additional procedure during operation from our study (*Figure 1*). We analyzed the image features of lung nodules, including the nodule size, attenuation, and distance to the nearest visceral pleural or fissure surface. Furthermore, we analyzed the details of surgery and localization, including the distance of needle transversing the lungs, procedural time, postprocedural complication, and postoperative hospital stay.

Results

In this study, we enrolled 518 nodules of 430 patients who had a lung nodule and underwent the preoperative CT-guided patent localization from March 2013 to March 2015. Of these, 422 patients underwent the dye localization with patent blue V, while the other 8 underwent the preoperative localization with patent dye blue V and hookwire owing to multiple lung nodules. Of the remaining patients, 66 patients with >1 nodule to the preoperative localization were excluded from the analysis. Furthermore, 74 patients with additional intraoperative procedure were excluded. Hence, we finally analyzed 282 patients in this study.

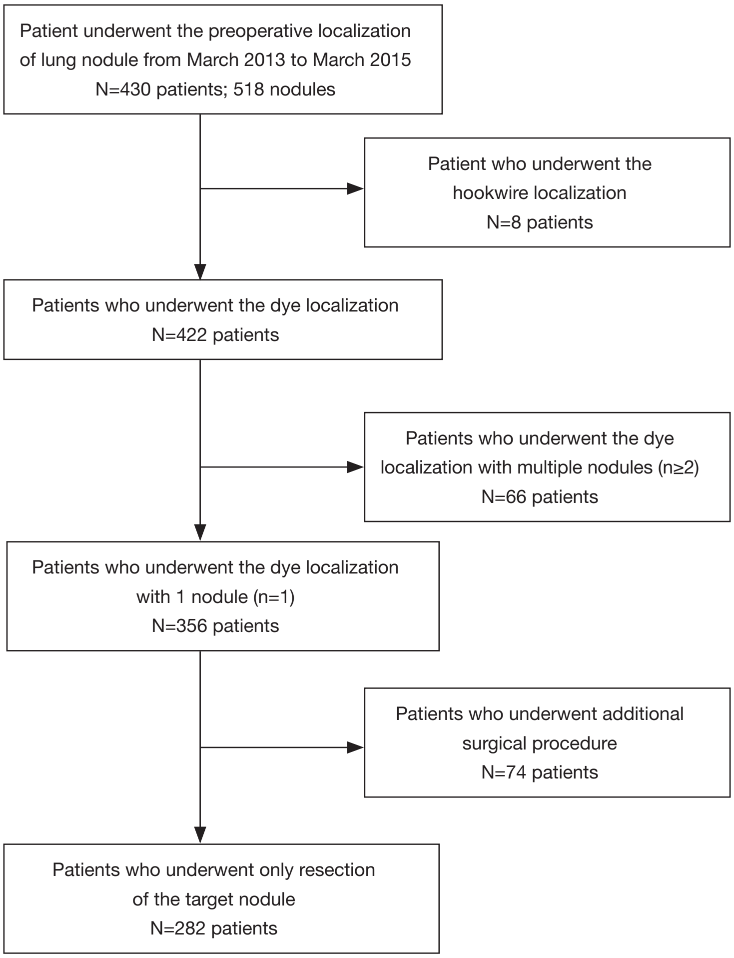

Figure 1 The patient selection algorithm.

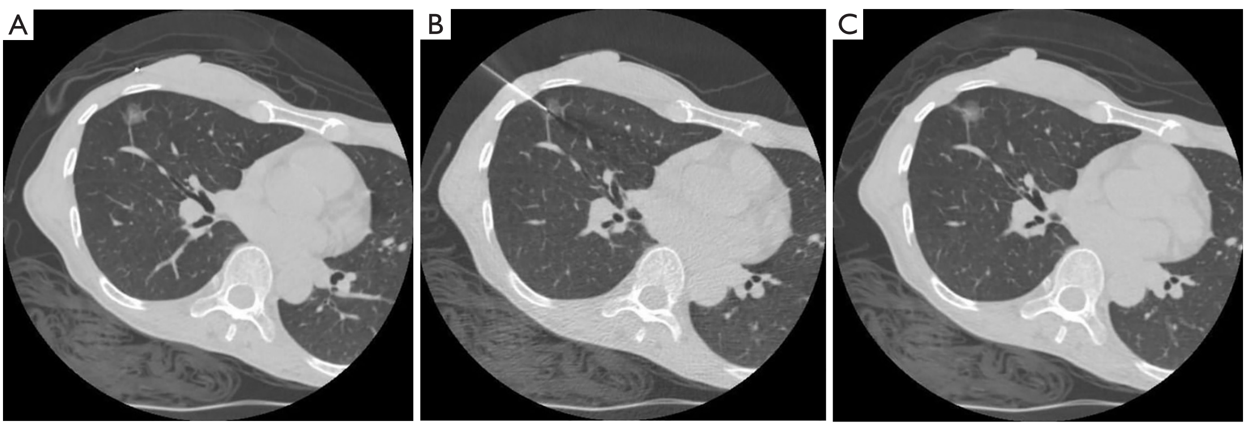

Figure 2 A 52-year-old female who had pure ground-glass nodule at the right middle lobe underwent the preoperative localization. The final pathological report confirmed adenocarcinoma. (A) The initial computed tomography (CT) revealed a ground-glass nodule at the right middle lobe of the lung; (B) the Chiba needle is inserted into or adjacent to the lung lesion; (C) after dye injection and removing the Chiba needle, the CT scan revealed the marked route of the localization. CT, computed tomography.

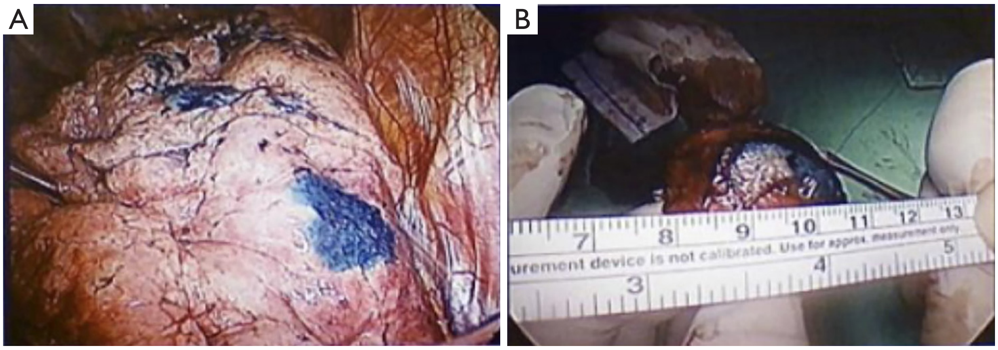

Figure 3 The thoracoscopic view of the same patient from *Figure 2*. The location of patent blue V dye is clearly visible at the lung surface during wedge resection.

Table 1 Patients' characteristics

Characteristics	Number
Age (years), mean [range]	56.6±11.6 [19–85]
Gender	
Female	187 (66.3%)
Male	95 (33.7%)
Cigarette smoking	33 (11.7%)
Prior lung surgery	38 (13.4%)
Cancer history	83 (29.4%)

Table 1 summarizes the patients' demographics. The mean age of our study sample was 56.6±11.6 (range, 19–85) years, with female preponderance (male/female, 95/187). Of all, 33 patients were either smokers or ex-smokers, and 83 had a cancer history. Furthermore, 38 patients had undergone lung surgery in the past, and CT revealed visible emphysema in 4 patients.

Table 2 presents the image features of nodules. The mean size of nodules was 0.9±0.5 (range, 0.3–3.2) cm. There were 67 solid nodules, 60 subsolid nodules, 151 pure ground-glass nodule, and 4 nodules with cavitation. In 41 patients, the nodule depth from the visceral pleural or interlobar fissure surface was >2 cm.

Table 3 presents each parameter of localization such as the depth of the needle transversing the lungs, procedural time, and complication rate. The mean depth of the needle transversing the lungs was 1.9±1.2 cm. Overall, 15 patients had a deep needle penetrating route with >4 cm length. The mean localization duration was 24 (range, 3–70) min. Except for two cases with the poor or fail dye localization, our localization procedures were performed successfully with minimal or acceptable complications; these two cases underwent successful resection after cautious palpation. In addition, four cases used two Chiba needles during the localization because the tip of the first needle was far away from the target lesion, whereas three cases reported the transfissural route of localization. In our localization, the leading complications were pneumothorax (48 patients,

Table 2 Image characteristics

Characteristics	Number
Location	
Left upper lobe	72 (25.5%)
Left lower lobe	47 (16.6%)
Right upper lobe	80 (28.4%)
Right middle lobe	14 (5.0%)
Right lower lobe	69 (24.5%)
Size (mm)	0.9±0.5 (0.3–3.2)
≤10	204 (72.3%)
>10	78 (27.7%)
Nodule characteristics	
Solid	67 (23.8%)
Part solid	60 (21.3%)
Nonsolid	151 (53.5%)
Cavitary	4 (1.4%)
Emphysema	4 (1.4%)
Location depth from pleura/fissure (cm)	1.0±0.9 (0–3.2)
≤2	241 (85.5%)
>2	41 (14.5%)

Table 3 Localization characteristics

Characteristics	Total
Needle transverse lung depth (cm)	1.9±1.2 (0.3–6.2)
≤1	69
>1, ≤2	113
>2, ≤3	60
>3, ≤4	25
>4, ≤5	7
>5, ≤6	6
>6	2
Duration of localization, mean [range] (min)	24 [3–70]
Complications	
Pneumothorax	48 (17%)
Hemorrhage	51 (18%)
Subcutaneous hematoma	2 (0.7%)
Subcutaneous emphysema	1 (0.35%)
Failure due to poor dye injection	2 (0.7%)
Use 2 Chiba needles	4 (1.4%)

Table 4 Surgery and pathology

Characteristics	Total
Type of surgery	
Wedge	221 (78.3%)
Segmentectomy	36 (12.8%)
Lobectomy	25 (8.9%)
Procedure time (min)	105 [35–325]
Pathology	
Primary lung cancer and premalignant lesions	209 (74.1%)
Adenocarcinoma	194
Squamous cell carcinoma	1
Mucoepidermoid carcinoma	1
Atypical adenomatous hyperplasia	13
Metastatic	18 (6.4%)
Lymphoma	1 (0.35%)
Benign nodule	54 (19.1%)

Table 5 Surgical outcomes

Characteristics	Total
Postoperative length of stay (days)	4.8±2.0 [3–19]
Complication	
Air leak	3
Chylothorax	1
Empyema	1
Stroke	1
Bloody sputum	1
Readmission	1
Mortality	1
Acute myocardial infarction	1

17%) and mild pulmonary hemorrhage (51 patients, 18%); all were asymptomatic under the oxygen supplement through a nasal cannula. Other rare complications were subcutaneous hematoma or subcutaneous emphysema, which spontaneously resolved without treatment.

Table 4 presents the type of surgery and pathological results. In this study, most patients underwent wedge resection (78.3%) and segmentectomy (12.8%); the remaining patients received lobectomy after intraoperative frozen-proven malignancy (25 patients, 8.9%). The mean duration of lung operation was 105 (range, 35–325) min. In addition, the leading pathology in this study was lung cancer and premalignant lesions (74.1%). The ratio of the benign nodule was about 19.1%. Residual nodules include metastases or lymphoma.

Table 5 summarizes the details of patients' outcomes. Of note, three patients reported air leak and one experienced chylothorax, receiving pleurodesis postoperatively. Additionally, one patient had empyema, receiving decortication and empiric antibiotics during readmission; one patient had postoperative left-side weakness, and the brain magnetic resonance imaging (MRI) revealed with right middle cerebral artery infarction. We noted no definite image evidence of embolic infarction in the brain MRI. Notably, one patient died due to the left ventricular rupture, probably because of acute myocardial infarction.

VATS is a minimally invasive procedure, which provides short recovery time and one-step diagnosis and

Table 6 Summary of computed tomography (CT)-guided patent blue vital dye localization of the lung nodule

Study	Patients/nodules number	Tumor size (mm)	Tumor depth (mm)	Procedure duration (min)	Fail case (%)	Complications
Our study	282/282	9.3	9.5	24.0	2 (0.7)	Pneumothorax: 17%; intrapulmonary focal hemorrhage: 18%; subcutaneous hematoma: 0.7%; subcutaneous emphysema: 0.4%
Lin *et al.* (24)	177/196	7.8	18.3	30.0	1 (0.5)	Pneumothorax: 29.4%; intrapulmonary focal hemorrhage: 54.2%; hemoptysis: 0.5%
Tseng *et al.* (25)	100/217	8.0	7.0	50.0	2 (0.9)	Pneumothorax: 40%; intrapulmonary focal hemorrhage: 24%; anaphylaxis:1%

treatment; hence, most surgeons preferred this procedure for treating indeterminate lung nodules. However, a study has reported small subsolid characteristics of VATS (9). Previously, several localization methods have been developed to enhance the accuracy of resection; however, those methods with different localized material or modality exhibited variable complications, advantages, or drawbacks. Arguably, hookwire localization is a safe and effective method; however, its limitation is dislodgement. Reportedly, the nodules near the hilum or scapula are also not suitable for the hookwire localization (10,11). In some studies, the intraoperative ultrasonography was highly operator-dependent and was not suitable for pure ground-glass nodule or lung(s) with emphysema (12,13). Some liquid contrast media, such as lipiodol or barium, have been applied for localization; however, they amplified the radiation exposure to surgeons, increasing the likelihood of errors in pathological results owing to the focal inflammation of specimens (14-17). Furthermore, some studies have provided details of other methods or materials, such as isotope, medical adhesive, methylene blue dye, microcoil, or electromagnetic navigation bronchoscopy (18-23) (*Tables 6,7*).

Patent blue V, a synthetic triphenylmethane dye, has been extensively used in sentinel lymph node mapping in patients with malignancy. Haque *et al.* reported six patients with an allergic reaction, such as hypotension, bronchoconstriction, erythema, urticaria, and angioedema, to patent blue V during sentinel lymph node mapping for breast cancer (29). Likewise, Mertes reported 14 cases of hypersensitivity reaction between 2004 and 2006; 6 patients had cardiovascular collapse (30). In this study, we noted no associated allergic reactions.

This study revealed that the CT-guided dye localization was a useful method to aid sublobar resection of lung nodules. Previously, we faced challenges in dealing with deep lung nodules owing to nonvisualization of the dye at the surface of the lung parenchyma. In this study, we injected the dye from the lung nodule to the subpleural region of the lungs when pulling the Chiba needle backward stepwise. The surgical outcome revealed that the CT-guided dye localization is a feasible technique for the preoperative localization of small deep lung nodules. The surgeon found the lung nodule along the trace of the dye at the lung surface, and the excision of the lung nodule at VATS could be performed smoothly. Moreover, the surgeon could make decisions about the need for additional surgery based on the results of frozen histopathology. Furthermore, the CT-guided dye localization could help avoid needless lobectomy.

Compared with other methods of localization, the advantage of the dye is the simplicity by using a 22-gauge Chiba needle and CT equipment, eliminating any need of receiving additional radiation dose for an operator during the procedure. In fact, multiple nodules localization could also be manipulated by the CT-guided dye localization simultaneously. In our procedure, the common complications were pneumothorax and focal lung hemorrhage; most patients were asymptomatic and only dealing with nasal cannula oxygenation. Few patients needed the insertion of a chest tube to drainage the air. In this study, two patients required insertion of the second Chiba needle because of malposition of the first Chiba needle with moderate pneumothorax. Choosing the small-diameter needle, avoiding transversing the pleura recurrently, and the transfissural route could minimize the

Table 7 Summary of different methods of localization

Study	Patients/nodules number	Tumor size (mm)	Tumor depth (mm)	Procedure duration (min)	Fail case (%)	Complications
Our study	282/282	9.3	9.5	24.0	2 (0.7)	Pneumothorax: 17%; intrapulmonary focal hemorrhage: 18%; subcutaneous hematoma: 0.7%; subcutaneous emphysema: 0.4%
Hookwire by Chen *et al.* (26)	43/43	17.2	18.5	NA	2 (4.6)	Pneumothorax: 23%
Hookwire by Li *et al.* (27)	86/86	14	7.3	19.1	0 (0)	Pneumothorax: 24%; focal pulmonary hemorrhage: 21%; hookwire dislodgement: 1.6%
Hookwire by Huang *et al.* (28)	273/273	12.4	11.3	8.6	0 (0)	Pneumothorax: 5.9%; needle track hemorrhage: 27.1%; hemoptysis: 0.4%
Barium suspension by Lee *et al.* (14)	10/10	7.6	8.4	25.6	0 (0)	Pneumothorax: 20%
Lipiodol by Miura *et al.* (15)	55/103	5.5	16	NA	0 (0)	Pneumothorax: 61%; pulmonary hemorrhage: 35%
Lipiodol by Watanabe *et al.* (17)	150/174	10	10	NA	0 (0)	chest pain: 11%, hemosputum: 6% pneumothorax:17% hemopneumothorax: 0.6%
Medical adhesive by Tao *et al.* (18)	41/44	9	10	16	0 (0)	Pneumothorax: 7%; parenchyma hemorrhage: 7%; irritable cough: 5%
Methylene-blue by Vandoni *et al.* (20)	51/54	NA	NA	75–270	4 (8.0)	Pneumothorax: 25.4%
Microcoil by Su *et al.* (21)	92/101	8.8	9.2	NA	2 (1.9)	Pneumothorax: 17.3%; mild pulmonary hemorrhage: 9.7% microcoil; dislodgement: 1.9%

NA, not available.

risk of pneumothorax or other complications. We did not observe rare complications or an anaphylactic reaction in our patients.

The disadvantages of the dye localization are poor visualization of the dye in severely anthracotic or pigmented lung. Other limitations of the dye localization are gradual absorbance and diffusion. Thus, the operation at the same day of localization is the ideal condition.

In this study, two cases exhibited nonvisualization or poor identification of the dye during VATS. The first case (*Figures 4,5*) with mild pneumothorax during the procedure and shallow needle insertion depth was found at the image; this could be attributed to the dislodgement of the needle into the pleural cavity during the dye injection. The injected dye was mixed with the pleural fluid and became invisible to the surgeon during VATS. The second case (*Figure 6*) had a deeper lung nodule at the image. The localization review revealed that the final site of the dye injection was far away from the subpleural region; the distance between the lung surface and the needle tip was >1 cm. Perhaps, the poor dye visualization at the lung surface was caused by the remote distance; the dye was injected too deep to be viewed from the lung surface. Other causes of failed dye localization might include moderate or

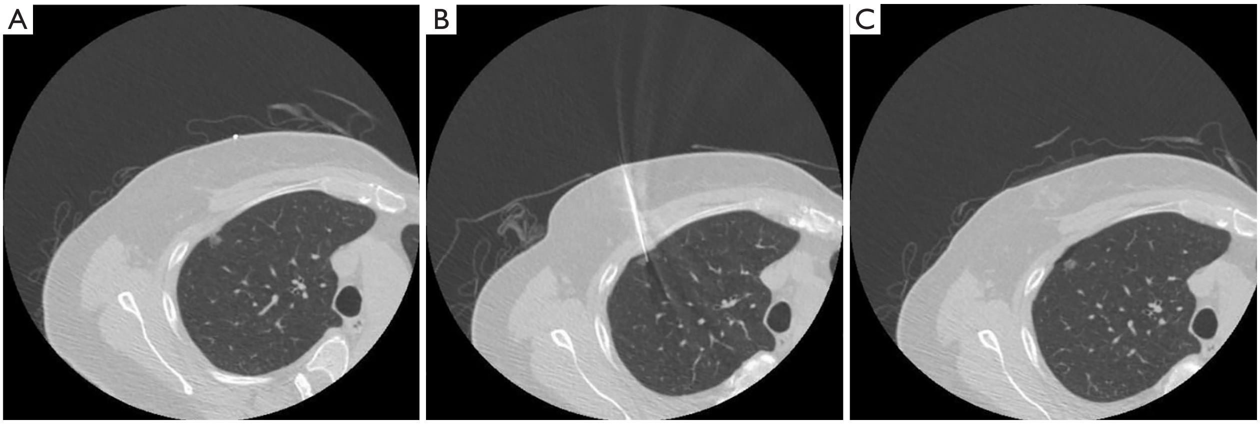

Figure 4 A 61-year-old female with a small nodule at the right upper lobe of the lung underwent the needle localization. (A) A small subpleural nodule at the right upper lobe of the lung at CT scan; (B) the depth of the Chiba needle transversing the lung is about 4 mm at the CT scan; (C) after dye injection and removing the Chiba needle, no tattoo visible adjacent to the target nodule at the CT scan; minimal pneumothorax was also noted. CT, computed tomography.

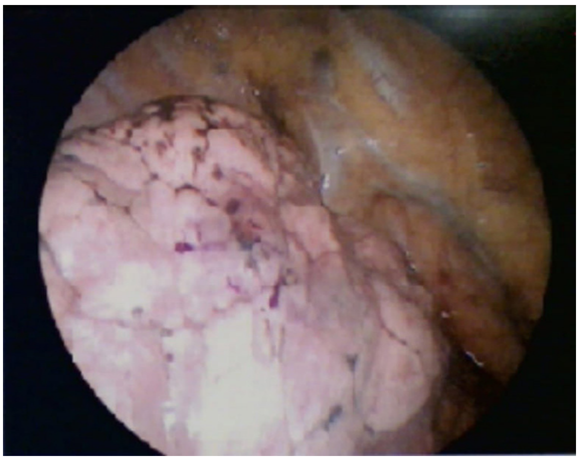

Figure 5 The thoracoscopic view of the same patient from *Figure 4*. No visible dye at the lung surface. The excision of the lung nodule was performed under the finger palpation of the surgeon. The final pathology revealed adenocarcinoma.

severe pneumothorax or uncooperative patients, making the lesion unapproachable or prolong the procedure duration during the localization.

This study has several limitations. First, it is a retrospective study conducted in a single center. Second, other variable factors could have affected the outcome of patients, including different surgical methods or underlying medical condition of patients. Third, we found few cases with other localization techniques at our institution, making it challenging to compare the pros and cons of different localization methods in this study. Finally, the study only reviewed patients with a single lung nodule. Hence, comprehensive studies with larger sample size are warranted.

Conclusions

This study reveals that the preoperative CT-guided dye localization of small deep lung lesion is a safe and effective method with acceptable mild complications and high success rate, making manipulating the sublobar resection smooth.

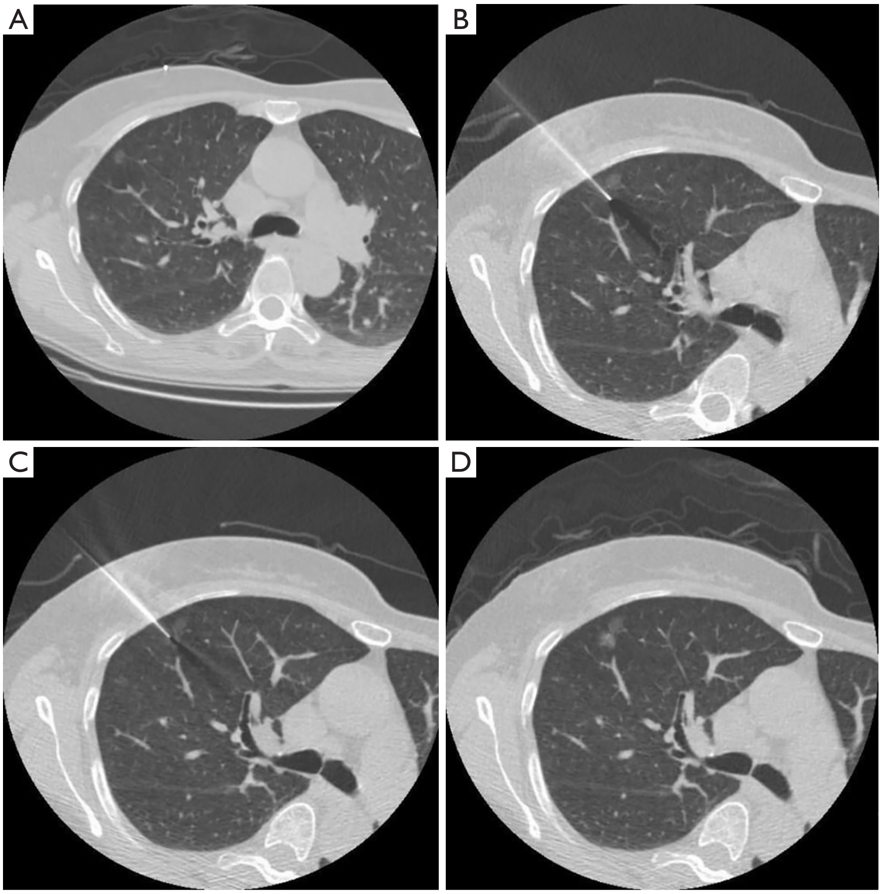

Figure 6 A 64-year-old female with a small pure ground-glass nodule at the right upper lobe of the lung. (A) A ground-glass nodule at the right upper lobe of the lung; (B) the Chiba needle is inserted adjacent to the target nodule with dye injection; (C) pulling back the Chiba needle with dye injection. The distance of the needle transversing the lung is 12 mm in depth; (D) the final CT scan revealed marked dye surrounding the target nodule but not at the subpleural region. The surgical report showed no obvious dye identification in the right pleural space during VATS. However, wedge resection was performed according to the presumed location of the target lesion from the anatomy. The pathology of the specimen showed adenocarcinoma. CT, computed tomography; VATS, video-assisted thoracoscopic surgery.

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None.

Footnote

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

Ethical Statement: This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki. All patients have provided written informed consent.

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