

Cardiothoracic Imaging

A simple and efficient method to perform preoperative pulmonary nodule localization: CT-guided patent blue dye injection

Kai-Hsiung Ko^a, Tsai-Wang Huang^b, Shih-Chun Lee^b, Wei-Chou Chang^a, Hong-Wei Gao^c, Hsian-He Hsu^{a,*}^a Department of Radiology, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan, Republic of China^b Department of Thoracic Surgery, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan, Republic of China^c Department of Pathology, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan, Republic of China

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ABSTRACT

Objective: To assess the efficacy of computed tomography (CT)-guided localization with the injection of a low dose of patent blue dye (PBD) for the thoracoscopic resection of pulmonary nodules.

Materials and methods: Overall, 125 consecutive patients underwent CT-guided localization with injection of a lower dose of PBD between June 2015 and June 2016. The total injection dose relative to the distance between nodules and the visceral pleura was recorded. The clinical and radiological characteristics, technical details, pathological results and procedure-related complications were reviewed.

Results: A total of 137 indeterminate pulmonary nodules were identified. The mean nodule size was 9.5 (3.0–22.0) mm. The mean injection dose of PBD relative to the distance between nodules and the visceral pleura was classified as follows: 0.07 ml: < 1 cm, 0.1 ml: 1–2 cm and 0.18 ml: > 2 cm. The mean time of CT-guided localization was 16.5 (10–50) min. The mean time interval from localization to surgery was 188 (24–1440) min. Pneumothorax developed in 50 patients (40%), and focal parenchymal hemorrhage occurred in 16 patients (12.8%) after localization. No patient required chest tube placement or emergent resuscitation. The success rate of dye marking was 98.5% (135/137). Malignancies, including 82 lung cancers, were diagnosed in 97 nodules (70.8%).

Conclusion: The injection of a lower dose PBD based on the distance to the visceral pleura can be successful with nodular localization and may facilitate thoracoscopic surgery, even in cases with a long interval from localization to surgery.

1. Introduction

With improvements in surgical intervention, video-assisted thoracoscopic surgery (VATS) has become the mainstream method for the diagnosis and therapy of pulmonary nodules because it reduces the rate of complications and shortens hospitalization time, which benefits patients [1]. However, several factors may influence the intraoperative identification of the nodule when it is deep relative to the visceral pleura (> 1 cm), is smaller in size, or has a predominantly ground-glass matrix appearance or is associated with pleural adhesion [2]. Therefore, precise preoperative nodular localization is crucial.

Many different techniques can localize nodules, including CT-guided insertion of hook wires; deployment of metallic coils; and injection of methylene blue dye (MBD), indigo carmine, barium or radiotracer [3–13]. Each method has its pros and cons. In clinical practice, an ideal method should be simple, safe and efficient and should not require additional specialized equipment. Injection of MBD is a relatively simple way to perform the localization. However, the utility of this technique is limited by a major drawback in the diffusion potential of MBD, which rapidly stains a larger portion of visceral pleural surface and hampers nodular identification. At our institute, patent blue dye (PBD) is readily available for nodular localization

Abbreviations: CT, computed tomography; PBD, patent blue dye; MBD, methylene blue dye; SLN, sentinel lymph node; VATS, video-assisted thoracoscopic surgery; GGO, ground-glass opacity; MIA, minimally invasive adenocarcinoma; AIS, adenocarcinoma in situ; AAH, atypical adenomatous hyperplasia; LCH, langerhans cell histiocytosis

* Corresponding author at: Department of Radiology, Tri-Service General Hospital, National Defense Medical Center, 325, Section 2, Cheng-Gong Road, Nei-Hu, Taipei 114, Taiwan, Republic of China.

E-mail address: m860818@ndmctsgh.edu.tw (H.-H. Hsu).

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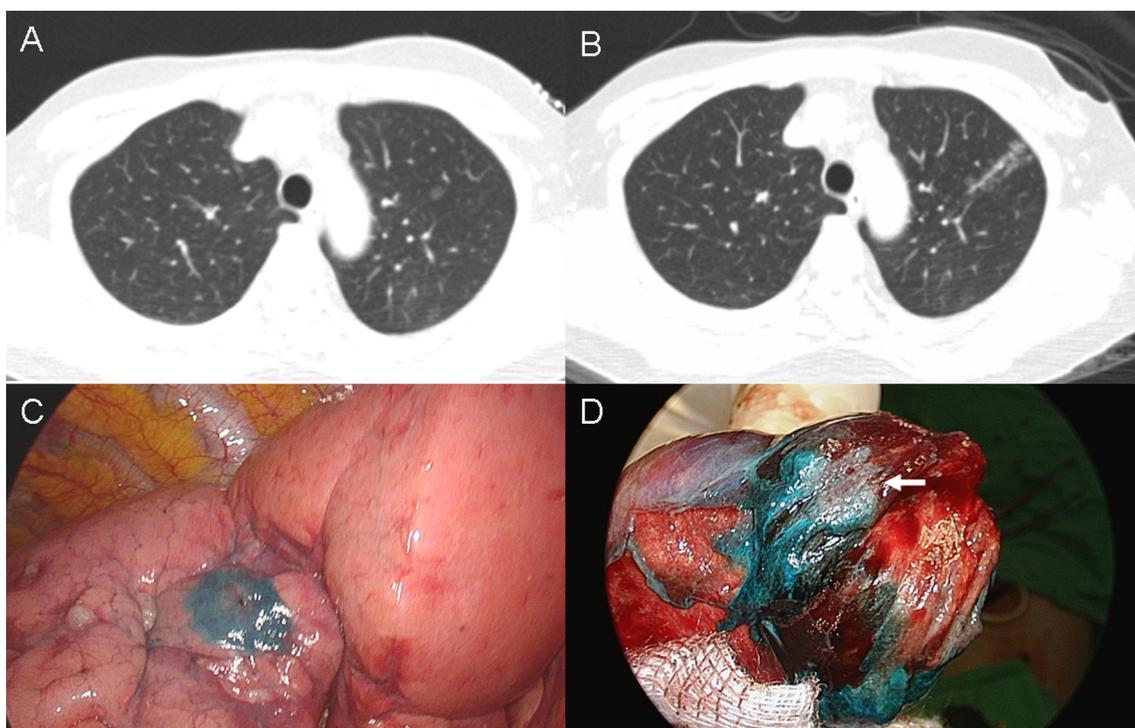


Fig. 1. A. An 8-mm ground-glass nodule was located in the left upper lobe with a 2.7-cm depth from the pleura. B. Patent blue dye (PBD) was injected in the deepest site near the nodule and along the path until the subpleural area (< 1 cm from the visceral pleura). C. The stained area on the visceral pleura was obvious. D. The tumor (arrow) was easily identified in the resected specimen, and the pathological result indicated adenocarcinoma in situ.

because we routinely use PBD to identify the sentinel lymph node (SLN) in breast cancer patients. Although the properties of the MBD and PBD are exactly the same, in our early experience, marked dye diffusion frequently occurred when we applied the same dose of PBD, ranging from 0.3 to 3 ml based on previous studies [7–10]. This problem might be attributed to an inadequate injection dose without considering nodular depth, and we presume that those doses of the dye used in previous studies were relatively high, especially for more peripheral nodules. Furthermore, the injection dose should vary based of the nodule depth. After a comprehensive literature search, the ideal dose is still unclear, and references for setting the amount of dye according to lesion depth are lacking. Therefore, we modified CT-guided lung nodule localization with an injection of a lower dose of PBD for this purpose and retrospectively evaluate its efficacy and safety for VATS.

2. Materials and methods

This retrospective study was approved by the institutional review board for human investigation and informed consent was waived. In the period between June 2015 and June 2016, 125 consecutive patients who underwent CT-guided localization with injection of PBD were enrolled. Preoperative localization was indicated when the following criteria were met: (1) nodules were < 3 cm in size, (2) nodules were not directly in contact with the visceral pleura and (3) both radiologists and surgeons thought that the nodule could not easily be identified during the operation. Indications for surgical intervention included (1) nodules with increasing size, (2) nodules with increasing solid components or (3) indeterminate nodules suggested by multidisciplinary discussion. In some cases of stationary subsolid nodules with a maximal diameter or solid component < 5 mm, surgery was requested by patients who were anxious about the possibility of cancer. Clinical parameters, including age, sex, smoking status and type of surgical intervention (i.e., wedge resection, segmentectomy or lobectomy), were recorded for each patient. The CT findings of each lesion were measured to determine (1) lesion size, (2) pulmonary lobe, (3) attenuation and (4) the distance

between the nodule and the visceral pleura. Several technical details of the localization, including the injection dose of PBD, distance between the nodule and dye, procedure time, and localization time, were recorded. The time interval from dye injection to the operation and any associated complications including pneumothorax (asymptomatic or symptomatic: an asymptomatic case means pneumothorax without respiratory symptoms such as substantial pain, dyspnea, or oxygen desaturation; a symptomatic case means pneumothorax that requires interventions before surgery), parenchymal hemorrhage, hemothorax or allergic reaction to PBD were also recorded. All images, including preprocedural, procedural and postprocedural CT scans were reviewed independently and discussed to achieve a consensus by two chest radiologists (H.H.H. and K.H.K.) with 27 years and 12 years of experience, respectively.

2.1. CT-guided dye localization procedure

All CT-guided localization procedures were performed by two experienced radiologists (H.H.H. and K.H.K.) before surgery. First, a non-contrast-enhanced CT scan [64-detector row scanner (Brilliance; Philips Medical Systems, Cleveland, OH, USA)] was performed using a low-dose setting (110 kVp, 30 mA, 1.25 pitch and 0.8-s tube rotation) to confirm the location of the nodules prior to the localization procedure. Next, we chose the optimal route for insertion of the puncture needle. After 2% lidocaine (TAI YU, Hsinchu, Taiwan) was injected into the puncture site of the chest wall, a 22-gauge Chiba needle (Cook Medical, Bloomington, Indiana, USA) was inserted under CT guidance. CT fluoroscopy was not used. Instead, the operator advanced the needle smoothly and assessed the needle position with interval images that were viewed on a console outside the examination room. When the needle tip was within 1 cm of the nodule, we began to inject PBD (patent blue V 2.5%; Guerbet, Aulnay-sous-Bois, France) with a 1-ml syringe. Dye was injected through the needle pathway until the subpleural area (< 1 cm from the pleura) while the needle was withdrawn (Fig. 1). The total injection dose was recorded as the total aspirated

dose minus the residual dose in the syringe. According to our early experience, pleural marking can be successfully identified with an injection of at least 0.05-ml PBD for the nodular depth < 1 cm from the visceral pleura. In order to realize the relationship between the mean injection dose and different nodular depths, the distances between the nodule and the visceral pleura were classified into < 1 cm, 1–2 cm and > 2 cm because of injecting a lower dose of PBD. During and after the procedure, CT scans were required to not only confirm the staining condition, which presents as focal ground-glass opacities near nodules and the subpleural region but also identify associated complications (e.g., pneumothorax or parenchymal hemorrhage). The procedure time was defined as the time interval between the first and last CT scans. After the localization procedure, the patient returned to the ward and waited to be transferred to the operating room.

2.2. VATS

VATS was performed for each patient with the same standard procedure. When the dyed area of the visceral pleura was identified, we performed a wedge resection with an Endo-GIA™ Universal Stapler. The resected specimen was immediately examined as a frozen section by a pathologist. If the pathological results showed that the nodule was benign, the surgery was terminated. Conversely, when lung cancer was confirmed, anatomic resection and mediastinal lymph node dissection were performed. A successful case was recognized when the dye marking on the visceral pleura could be identified and follow-up CT images confirmed complete resection of the nodule. In contrast, an unsuccessful case was defined by no marking observed on the visceral pleura. Additionally, to examine the staining condition of PBD and ensure the surgical margin, the diameter of the dyed area on the visceral pleura and the margin from the tumor to the resected specimen were assessed based on surgical videos and images.

2.3. Statistical analysis

The descriptive data for continuous variables are presented as the mean \pm standard deviation. A categorical comparison was performed using the chi-squared test. A multivariate logistic regression analysis was used to determine risk factors for postlocalization pneumothorax. *P* values < 0.05 were considered significant. All statistical analyses were performed using SPSS software (version 17.0; SPSS, Chicago, IL, USA).

3. Results

3.1. Clinical and imaging characteristics

The characteristics of the 125 enrolled patients with 137 indeterminate pulmonary nodules are shown in Table 1. Female patients (*n* = 75; 56.8%) and nonsmokers (*n* = 87; 65.9%) were predominant in this study. The mean size of the nodules was 9.5 mm (range, 3.0–22.0 mm). Most of the nodules (*n* = 87; 63.5%) presented with a pure ground-glass appearance and part-solid attenuation.

3.2. CT-guided patent blue dye localization

Most nodules (112/137, 81.7%) were < 2 cm from the pleura, and the mean distance between the nodule and the pleural surface was 12.1 mm (range, 2.0–42.1 mm). The mean injection dose of PBD corresponding to the distance between nodules and the visceral pleura was classified as follows: 0.07 ml dye was injected for a distance < 1 cm, 0.1 ml dye was injected for a distance between 1 and 2 cm, and 0.18 ml dye was injected for a distance of > 2 cm (Table 2). To inject the dye along the shortest path between the visceral pleura and the nodule, localization via transfissural puncture was performed for 15 nodules, which were deep in the lung parenchyma, near the fissure (Fig. 2). Twelve patients with two indeterminate nodules simultaneously

Table 1
Clinical and CT imaging characteristics of 137 nodules in 125 patients.

Characteristics	Value
Age (y), Mean (range)	61 (26–82)
Sex	
Male	44 (43.2%)
Female	81 (56.8%)
Smoking status	
Never	99 (79.2%)
Current or former	26 (20.8%)
Nodule size (mm), Mean (range)	9.5 (3.0–22.0)
< 10	80 (58.4%)
10–20	55 (40.1%)
\geq 20	2 (1.5%)
Pulmonary lobe	
RUL	39 (28.5%)
RML	16 (11.7%)
RLL	26 (18.9%)
LUL	38 (27.8%)
LLL	18 (13.1%)
Attenuation of nodules	
Pure GGO	46 (33.6%)
Part solid	41 (29.9%)
Solid	50 (36.5%)
Surgical procedure	
Wedge resection	114 (83.2%)
Segmentectomy	17 (12.4%)
Lobectomy	6 (4.4%)

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

Table 2
Results and complications related to CT-guided localization.

	N (%) or mean (range)
Distance between the nodule and pleura (mm)	12.1 (2.0–42.1)
< 10 mm	64 (46.7)
10 mm–20 mm	48 (35.0)
\geq 20 mm	25 (18.3)
Injection dose of the dye (ml)	
Nodule < 10 mm from the pleura	0.07 (0.05–0.08)
Nodule within 10 mm–20 mm from the pleura	0.1 (0.07–0.12)
Nodule \geq 20 mm from the pleura	0.18 (0.14–0.20)
Transfissural puncture	15 (10.9)
Distance between the nodule and dye (mm)	0.6 (0.2–1.3)
Procedure time (min)	16.5 (10–50)
Localization times in each patient	
1	113 (90.4)
2	12 (9.6)
Time interval from localization to surgery (min)	188 (24–1440)
Complications	
Pneumothorax	50 (40)
Asymptomatic	50 (40)
Symptomatic	0
Focal parenchymal hemorrhage	16 (12.8)
Hemothorax	0
Hemoptysis	3 (2.1)
Allergic reaction	0
Operative findings	
Pleural adhesion	8 (6.4)
Anthracotic pigment	29 (23.2)
Failed marking on the visceral pleura	2 (1.5)

underwent 2 localization procedures. The mean procedure time, which was 16.5 min (range, 10–50 min), depended on the localization times. The mean time interval from dye injection to the operation was 188 min (range, 24–1440 min). Due to a changed operation schedule, a longer time interval between localization and surgery (15–24 h) was noted in 7 patients. In these patients, nodular sizes ranged from 0.5 to 1.2 cm and the depth from the pleura ranged from 0.8 to 2.3 cm. After localization, asymptomatic pneumothorax developed in 50 patients (40%), and focal parenchymal hemorrhage was identified in 16 patients (12.8%). No



Fig. 2. A. Localization via transfissural puncture was performed for the nodule in the left upper lobe near the fissure. B. Postprocedural computed tomography confirmed the marked spot (arrow) abutting the nodule and fissure. C. Video-assisted thoracoscopy clearly identified the stained area on the fissure side.

Table 3
Factors associated with pneumothorax.

	OR (95% CI)	p-value
Smoking status	1.48 (0.58–3.75)	0.407
Pulmonary lobes	1.11 (0.84–1.47)	0.453
Operators of localization	0.67 (0.29–1.56)	0.354
Localization times	4.67 (1.11–19.64)	0.035
Depth of nodules	1.47 (0.53–4.13)	0.457
Transfissural puncture	5.62 (1.39–22.8)	0.016
Attenuation of nodules	1.03 (0.64–1.66)	0.899

patient required chest tube drainage or emergency resuscitation. The risk factors for pneumothorax were also investigated by multivariate logistic regression analysis, which showed that two localization procedures ($p = 0.035$) and the approach of the transfissural puncture ($p = 0.016$) were significant risk factors (Table 3). Three patients experienced hemoptysis, but the symptoms were self-limited. According to the surgical videos and images, the staining effect of PBD was quite strong, and the injection of 0.07 ml dye was sufficient to achieve a dense blue area on the pleural surface for nodules that were located < 1 cm from the visceral pleura. Even if diffusion occurred, the staining area was still limited to an area smaller than 3 cm. In total, dye diffusion occurred in 33 cases, and the mean diffusion diameter was 2.5 cm (range, 1.7–2.8 cm). Additionally, intraoperative nodular detection was also excellent in some cases with anthracotic pigment on the visceral pleura ($n = 29$) or with pleural adhesion ($n = 8$) (Fig. 3). Overall, the success rate of dye marking was 98.5% (135/137); it failed in 2 nodules (2.7 and 3.2 cm from the pleura). Since the final injection point was quite deep (> 1 cm from the pleura), no staining area could be identified on the pleural surface. Fortunately, the puncture hole was still identifiable. All nodules were successfully resected by VATS without conversion to open thoracotomy.

3.3. Surgical and pathological results

Most patients underwent a wedge resection ($n = 114$; 83.2%).

Table 4
Pathological results of pulmonary nodules.

Variables	N (%)
Malignant and premalignant lesions	103 (75.1)
Invasive adenocarcinoma	60
MIA	13
AIS	5
Squamous cell carcinoma	4
AAH	6
Metastasis	15
Benign lesions	34 (24.9)
Chronic granulomatous inflammation	16
Fibrosis	10
Intrapulmonary lymph node	4
Hamartoma	2
LCH	1
Mycetoma	1

MIA = Minimal invasive adenocarcinoma; AIS = Adenocarcinoma in situ; AAH = Atypical adenomatous hyperplasia; LCH = Langerhans cell histiocytosis.

Ninety-seven nodules (70.8%) were confirmed to be malignant, including 82 primary lung cancers and 15 metastases (Table 4). All margins were negative, and the average distance of the margin from the tumor in resected specimens was 1.7 cm (range, 1.3–2.7 cm). The histological subtypes of the majority of the nodules were invasive adenocarcinomas ($n = 60$; 43.7%), followed by minimally invasive adenocarcinomas (MIA) ($n = 13$; 9.5%), adenocarcinoma in situ ($n = 5$; 3.6%) and squamous cell carcinoma ($n = 4$; 2.9%). The remaining nodules were benign ($n = 34$; 24.9%).

4. Discussion

It is sometimes challenging for surgeons to resect pulmonary nodules without preoperative localization, especially when the nodule is < 10 mm in size, has a dominant ground-glass component and is > 5 mm from the pleural surface. The failure rate of nodular detection

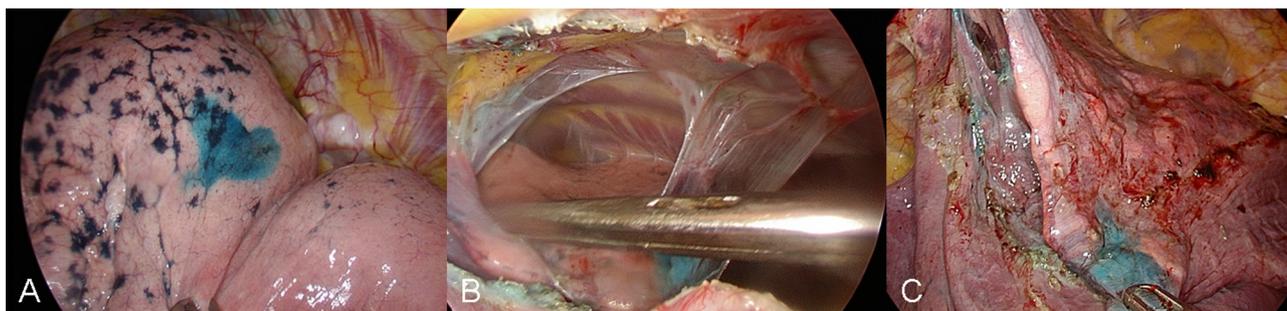


Fig. 3. A. The stained area was clearly identified regardless of the presence of anthracotic pigment. B. Pleural adhesion. C. Adhesiolysis.

can reach approximately 63% [2]. A variety of localization techniques have been developed to facilitate the intraoperative identification of nodules. Generally, the success rate of nodular detection with these techniques ranges from 58 to 100% [3–13]. The mean procedure time of each method varies from 12.5 to 150 min [6]. Although a simple comparison would not be appropriate because of differences among patient cohorts and approaches, our results show CT-guided localization with injection of PBD is a simple and efficient technique that not only requires a relatively short procedure time (16.5 min) but also achieves a high success rate (98.5%).

Regarding the localization of injected dye, the diffusion effect is always a major concern. In addition to the properties of the dye, the relationship between the injected dose and the nodular depth may be key for achieving good localization. However, previous studies demonstrated only a single or nonspecific range of dye injection doses [7–10]. Extensive dye diffusion may easily occur in more peripheral nodules when higher dye doses are injected because there are no definitive guidelines for dye injection. To the best of our knowledge, this is the first study to attempt to standardize dye localization with a lower dose of PBD injection according to nodule depth. The current results show that using even a lower dose (0.07 ml) of PBD injection for subpleural nodules (< 1 cm from the pleura) can result in excellent staining on the visceral pleura. For deeper nodules, injecting 0.15 ml of dye into the deepest area near the nodule and along the withdrawal path of the needle until the dye reaches the subpleural spot is sufficient to create a blue tract. Our approach not only facilitates an adequate resection margin but enables surgeons and pathologists to more efficiently identify nodules in resected specimens. Nevertheless, to avoid failure of dye marking on the pleural surface, the final injection in the subpleural area should be maintained at a depth of < 1 cm to the visceral pleura because a lower dose of PBD is used. Additionally, dye staining stability is also an important concern for lung localization. Nomori et al. reported that MBD mixed with collagen could achieve a long staining period, with a mean of 2.5 days, but no large-scale study has reported this information for PBD [14]. However, based on our study, a long staining effect lasting of 15 to 24 h was observed in 7 patients. The reason for this finding is not entirely clear, but we believe that PBD may be slowly absorbed into the lymphatics, bound to albumin and excreted into the urine and bile [15]. Although this result requires further validation because of the small sample size, PBD injection may allow for more flexibility in the surgical schedule.

Regarding complications, pneumothorax was the most common finding after a transpleural needle puncture procedure. The average incidence of pneumothorax is 20% [9,16]. Localization with hook wires has a higher rate of this complication (up to 68%) [5]. Our rate of pneumothorax occurrence (40%) was also higher than average because 12 patients underwent two localization procedures, and 15 nodules were located near a fissure. For nodules near a fissure, localization was usually performed via transfissural puncture to determine the shortest distance between the nodule and the visceral pleura. With this approach, the surgeon can easily and precisely identify the stained area on the fissure side. However, more puncture holes would be present on the visceral pleura. These two circumstances may explain why the multivariate analysis showed that localization times and transfissural puncture are significant risk factors for pneumothorax. This result is also consistent with previous reports [16,17]. Although all our cases with pneumothorax were asymptomatic and did not require the insertion of a chest tube, the results indicate that avoiding a long duration between localization and surgery might be ideal when a patient requires multiple or transfissural punctures. Parenchymal hemorrhage was usually focal, and minor hemoptysis occurred in only 3 patients who had nodules that were > 4 cm deep. Furthermore, in clinical applications, PBD is usually used for lymphangiography and identifying the SLN of breast cancer patients. The adverse effects are associated with allergic reactions ranging from urticarial rash to anaphylaxis and skin pigmentation [18]. Generally, the incidence of PBD allergy is lower than 2.7%

[15,19]. Although the exact allergic incidence of PBD injection for pulmonary localization remains uncertain, none of our patients experienced an allergic reaction, which may be related to the lower dose of PBD we used.

Currently, preoperative localization techniques can be classified into three categories: intraoperative modalities, injection of liquid materials and percutaneous placement of hook wires and microcoils. Considering the simplicity and cost effectiveness, we initially performed localization with CT-guided needle puncture which showed acceptable results [4]. However, pleural adhesion or anthracotic pigmentation would increase the failure rate because the puncture hole or hematoma of the visceral pleura cannot be identified easily. Intraoperative modalities require additional specialized or expensive equipment such as ultrasound, fluoroscopy, or a Gamma ray detector, which can be time consuming and carries the risk of radiation exposure [13,20–22]. Moreover, the detection rate of ultrasound can be influenced by emphysematous lung or deeper nodules. Injection of various liquid materials, such as MBD, indigo carmine and barium, is also a simple way to perform the localization and has a good success rate [7–12]. However, the diffusion effect of MBD and indigo carmine and anthracotic pigmentation can hamper the correct nodular identification [10,11]. Furthermore, barium injections can induce acute inflammatory reactions, which might interfere with pathologic interpretation [12]. Percutaneous hook-wire placement is the oldest and most commonly used technique. The high risk of wire dislodgement and severe chest wall pain limit the use of the procedure [3]. Moreover, marked air embolism has also been reported [23]. The placement of microcoils is a relatively useful method but also presents the risk of radiation exposure, coil migration and air embolism [5,6]. Because of availability, we shifted to PBD injection to localize nodules at our institute. Compared with other techniques, CT-guided localization with PBD injection has several features and advantages. (a) This procedure is a simple protocol and requires a relatively short procedure time. (b) The staining condition is not influenced by pleural anthracotic pigments or pleural adhesions. (c) Despite the different properties of all dyes, the diffusion effect of PBD is less obvious than others, according to our results. One reason might be related to the lower dose we injected, which corresponded to different nodular depths. This feature may avoid over-resection of normal lung parenchyma. (d) This procedure may allow for more flexibility in the surgical schedule because its staining effect seems to be strong and allow for a longer time interval (> 15 h) between localization and surgery. (e) Surgeons and patients can avoid additional intraoperative radiation exposure. (f) This procedure is associated with only minor complications. Based on these advantages, we expect that this technique could be used by more institutes in the future.

This study does have some limitations. First, it has a retrospective design and was conducted at a single institution with a relatively small sample size. To validate the current results, a larger, multi-institutional prospective study is warranted. Second, distinguishing focal parenchymal hemorrhage and dye staining on CT images is sometimes difficult because both conditions have a similar ground-glass opacity. In general, focal parenchymal hemorrhage may frequently occur in deep localization and ground-glass opacities usually spread to adjacent areas more rapidly and obviously because of injured vasculature. However, according to this study, this condition did not seem to interfere with the correct localization. Therefore, standardizing PBD injections may be beneficial for adequate localization and to manage the concern regarding the staining outcome on CT images. Third, we used PBD rather than methylene blue to perform preoperative nodular localization. Whether the criteria of this study can be applied to methylene blue injection or if the same results can be achieved is unknown. A further study that compares both dye localizations should be designed in the future.

5. Conclusions

The results of this study showed that injection of a lower dose of PBD under CT guidance based on the distance between the nodule and the visceral pleura could achieve a high success rate with respect to nodular localization. This technique is a simple, safe and efficient method that enables surgeons to resect peripheral and deep impalpable nodules via a VATS procedure even if a long interval between localization and the operation is required.

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Declaration of Competing Interest

None.

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