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Preresection Stained Glue Injection to Localize Pulmonary Small Nodules and Ground-glass Opacities

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Objective: We sought to introduce a localization procedure (methylene blue-stained N-butyl cyanoacrylate and N-octyl cyanoacrylate glue) in localizing pulmonary small nodules and ground-glass opacities before thoracoscopic resection, and to evaluate its efficacy.

Methods: A total of 20 patients with pulmonary small nodules and/or ground-glass opacities, who underwent video-assisted thoracoscopic surgery from August 1, 2017 to March 1 2018, were included in the study.

Results: A total of 24 lesions in 20 patients underwent blue-stained glue localization. The success rate of localization was 100%, with a mean dose of 0.04 ± 0.01 mL blue dye and 1 mL glue used for each lesion. The average time for the whole localization procedure was 15.4 ± 6.3 minutes. All lesions were intraoperatively localized by visual inspection in combination with palpation. The complications related to the localization procedure included mild pneumothorax occurring in 9 patients and minor pulmonary hematoma in 4 patients. No pain or distress was reported.

Conclusions: Blue-stained glue injection is technically feasible and safe to localize pulmonary small nodules and ground-glass opacities before thoracoscopic resection.

Key Words: pulmonary nodule, ground-glass opacity, computed tomography, localization, video-assisted thoracoscopic surgery

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Varied methods have been created to localize small pulmonary nodules and ground-glass opacities (GGOs) for facilitating video-assisted thoracoscopic surgery (VATS).[1] Currently, computed tomography (CT)-guided localization techniques that are used most commonly in clinical practice include hook-wire placement,[2–5] microcoil and fiducial marker placement,[1,6–8] contrast medium injection,[9–11] and dye localization.[12,13] These localization techniques are very important for a successful VATS tumor excision due to the lesions' small size and nonpalpability.

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Although minimally invasive, these CT-guided techniques have different advantages and disadvantages. The hook-wire placement technique is often painful.[14] There is also the risk of hook-wire dislodgement during the time between placement and surgery.[1–5] The main concern about dye localization is the rapid diffusion of dye into the surrounding lung parenchyma, necessitating immediate surgery upon completion of localization.[1,13] Other common limitations implicated in the aforementioned techniques include the potential complications of pneumothorax, hemothorax, and focal intrapulmonary hemorrhage.

An ideal localization technique should have a high accuracy rate, a low complication rate, cause minimal patient discomfort, and be easily performed. In the present study, we sought to introduce a technique using a medium of methylene blue-stained glue, which combines the advantages of dye localization and contrast medium injection, theoretically with a lower complication rate and a high success rate. We aimed to evaluate the feasibility and efficacy of blue-stained glue injection in pre-VATS localization of pulmonary small nodules and GGOs.

METHODS

The study was retrospective, and the protocol was approved by the Institutional Review Board. Informed consent for preoperative localization was obtained from the patients or their immediate family members. Informed consent for collecting medical data from the patients was also obtained.

Study Subjects

The study included 20 patients, aged 52.7 ± 10.5 years, scheduled to undergo VATS in our hospital from August 1, 2017 to March 1, 2018. Before VATS, CT-guided blue-stained glue localization was conducted for all patients. The decision to use CT-guided blue-stained glue localization was made by the surgeons, dependent upon the lesion's size and the distance to the pleural surface. Inclusion criteria were a solid nodule or the solid portion of a part-solid GGO with a diameter ≤ 1 cm, or a complete GGO, if the distance to the visceral pleura was > 0.5 cm, but < 3 cm.[6,14]

Blue-stained Glue Localization

Preparation of Blue-stained Glue

The blue dye used in the study was methylene blue (2 mL: 20 mg, JumpCan Pharmaceutical, Jiangsu, China), and the glue (1 mLper ampoule, Fuaile Co. Ltd, Beijing, China) was a liquid consisting of N-butyl cyanoacrylate (NBCA) and N-octyl cyanoacrylate (NOCA), which is primarily used for vascular embolization. Empirically, we first collected 1 mL glue in a 1 mL syringe and then mixed it with 0.05 mL methylene blue. According to our limited experience, the glue would be

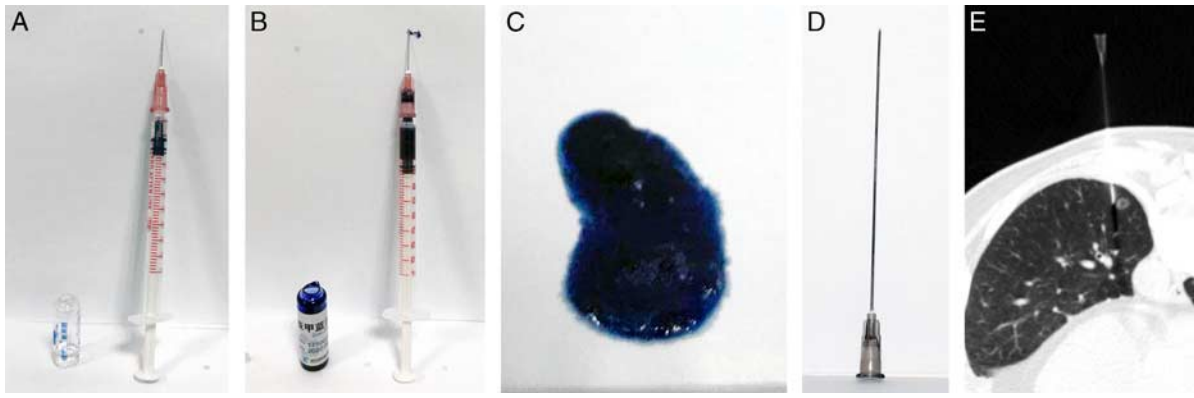

FIGURE 1. Illustration of preparing methylene blue–stained glue for CT-guided localization. A, Using a 1 mL syringe to collect 0.2 mL glue. B, The glue is then mixed with methylene blue in the syringe. C, The blue-stained glue. D, An 80 mm-long 21 G needle for puncture. E, The needle tip at the margin of the lesion primed for injection of blue-stained glue.

solidified in 30 seconds if mixed with the dye. Solidification would cause difficult injection. Hence, we only mixed the glue and the dye when the puncture was completed and the puncture needle got its position (Fig. 1).

CT-guided Localization

The patient positioning on the CT table (Somatom Definition Flash Siemens, Erlangen, Germany) was similar to that described in the literature.[2,6] The targeted lesion was confirmed by obtaining an axial CT scan with 2-mm collimation (Liu L, with 10 y experience in CT scan). The ideal access route was as direct and short as possible for puncture. No special items except one 80-mm-long 21 G needle were required for the puncture. After local anesthesia, the needle tip was advanced with CT guidance to within 0 to 2 cm of the target lesion (J.W., and L.-B.G., with 5 and 15 years of experience in lung puncture, respectively). The needle hub was then connected with the syringe containing the blue-stained glue. Following this, we gently injected 1 mL of blue-stained glue near the target lesion. To reduce the risk of puncture-induced pneumothorax and hemorrhage, we gently emptied the syringe while withdrawing the needle, gluing the needle track. CT scanning was conducted to inspect the position of the glue and to evaluate for pneumothorax or hemorrhage.

Thoracoscopic Surgery

The VATS was conducted by a surgeon (J.W.) with 10 years of experience in thoracoscopic surgery. In the present study, visual inspection was first carried out to find where the blue-stained bulge was. Thereafter, palpation was carried out on the blue-stained bulge to reconfirm the location of the glue. Following this, pulmonary wedge resection using endoscopic staplers was performed. Intraoperative consultation with pathology was conducted on the incised specimens. On the basis of findings on the frozen section, the surgery was ended for patients with benign lesions or noninvasive lung cancer.

Evaluations

Two authors undertook the review of patients' medical records and images. In all patients, they evaluated the following (and they are): lesion characteristics (size, location, the distance to the pleural surface, solid or GGO, and number); successful or unsuccessful localization with blue-stained glue; the average dose of methylene blue and glue used; the time for the localization procedure; the time patients waited before the VATS was performed; and the presence of complications.

RESULTS

Technical Success Rate

A total of 24 lesions in 20 patients (17 patients with a single lesion, 2 with 2 lesions, and 1 with 3 lesions) underwent CT-guided localization. Nineteen of 24 lesions (79.2%) were regarded as GGO on CT, 4 (16.7%) as solid nodules, and 1 (4.2%) as part-solid GGO. The average size of the lesions was 7.7 ± 1.9 mm. Furthermore, based on the type of lesions, the average size of GGOs, solid nodules, and part-solid GGO was 7.6 ± 1.8, 8.5 ± 1.9, and 10 mm, respectively. The characteristic of pulmonary nodules was listed in Table 1.

CT-guided placement of blue-stained glue was successful in all lesions, with a technical success rate of 100%. Only the first patient was required to prepare the glue again due to rapid solidification. A typical case is shown in Figure 2. The average time for the whole localization

TABLE 1. Characteristics of the 24 Pulmonary Nodules

Location	
Right upper lobe	8
Right middle lobe	3
Right lower lobe	6
Left upper lobe	5
Left lower lobe	2
CT findings	
Pure GGO	19
Semisolid	1
Solid	4
Size (mm)	7.7 ± 1.9 (5-10)
Distance from the pleura to superficial depth (mm)	7.5 ± 7.2 (3-27)
Postoperative diagnosis	
Adenocarcinoma in situ	6
Minimally invasive adenocarcinoma	10
Invasive adenocarcinoma	3
Atypical adenomatous hyperplasia	2
Benign nodule	3

Data are presented as n or mean ± SD (range).

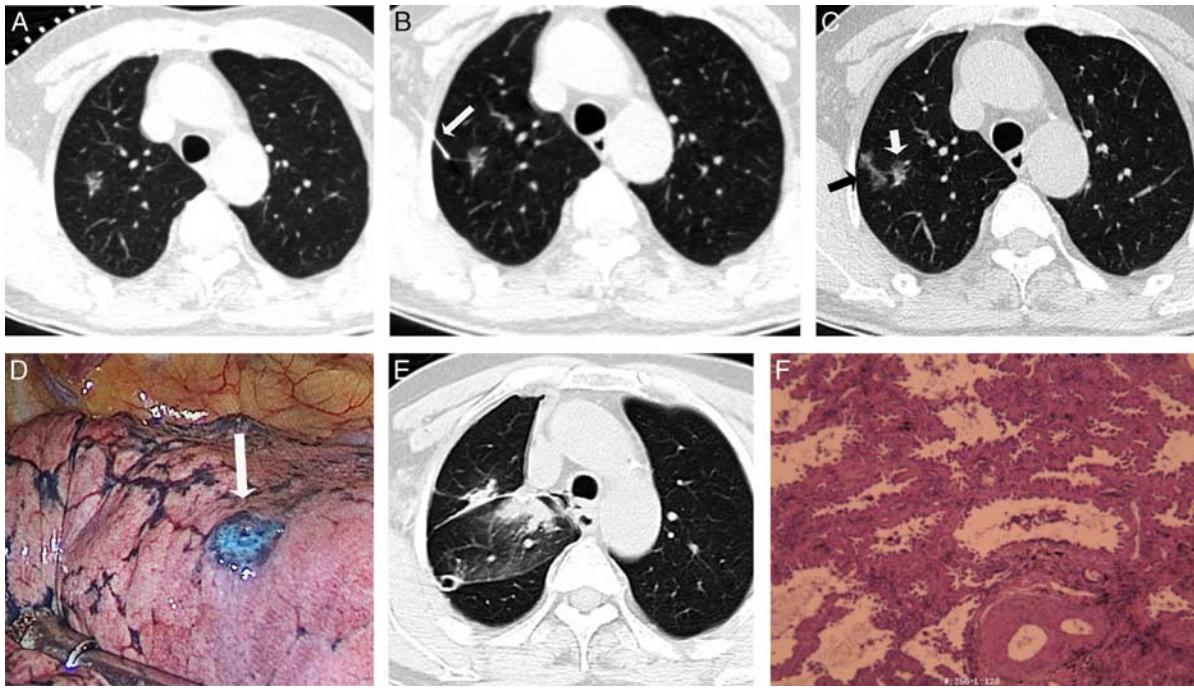

FIGURE 2. A typical case showing blue-stained glue localization. A, Prelocalization CT shows a GGO in the right upper lobe. B, The needle tip (white arrow) is positioned near the GGO. C, The injected glue (black arrow) is localized external to the GGO (white arrow). No puncture-related complications occurred. D, Visual inspection during the VATS reveals a blue-stained bulge on the pleural surface (white arrow). E, CT obtained 3 days after VATS shows successful resection of the GGO. F, Pathologic examination with hematoxylin and eosin staining reveals a minimally invasive adenocarcinoma.

procedure was 15.4 ± 6.3 minutes, dependent upon the lesion location and number. One milliliter of glue was used for each lesion, with 0.04 ± 0.01 mL methylene blue on average.

Complications

CT scan immediately after the procedure of localization unveiled no severe complications, except grade 1 pneumothorax occurring in nine patients (45%) and mild pulmonary hemorrhage in 4 patients (20%). They were all asymptomatic, requiring no further treatment. No spillage of dye into the pleural space was observed. During the waiting time, no patients reported discomfort.

Thoracoscopic Surgery

All patients underwent thoracoscopic surgery. The interval between postlocalization and the surgery was 182.8 ± 100.9 minutes. During the surgery, all lesions were localized through the blue-stained bulge beyond the visceral pleura by visual inspection in combination with palpation of the glue, resulting in a success rate of 100% for intraoperative localization. All lesions, including solid nodules and GGOs, were successfully resected. Postoperative pathologic examination revealed 6 cases of adenocarcinoma in situ, 10 cases of minimally invasive adenocarcinoma, 3 cases of invasive adenocarcinoma, 2 cases of atypical adenomatous hyperplasia, and 3 cases of benign nodules (2 were inflammatory granulomas, and 1 benign lymphadenosis).

DISCUSSION

We have reported our preliminary experience of CT-guided localization using methylene blue–stained glue before VATS for pulmonary small nodules and GGOs. This localization procedure can avoid the disadvantage of rapid diffusion of the dye and difficulty in visual inspection of the localization. This provides 2 advantages: the methylene blue dye can provide a blue-stained mark on the pleural surface, helping to find the lesion, and the solidified glue in the lung parenchyma is palpable. The intraoperative localization using visual inspection plus palpation can add convenience and accuracy to the subsequent VATS. Moreover, the glue can help to seal up the needle track, theoretically decreasing the rate of puncture-related complications, such as severe pneumothorax and pulmonary hemorrhage. The patients reported no discomfort during the waiting time. In our experience, localization using methylene blue–stained glue is technically simple and safe, with no special items (eg, coil or wire) required.

Although many methods have been invented for pulmonary nodule localization, the use of a hook wire is still the first choice and probably the most common method.[15] This method has a favorable success rate of localization ranging from 93.6% to 97.6% and a short procedure duration.[1,4,5] In addition, the method can provide surgeons with a visual mark directing the subsequent resection, with no need for intraoperative fluoroscopy and radiation exposure. However, hook wire placement is associated with patient discomfort and complications (eg, dislodgement and pneumothorax). The reported dislodgement rate is 2.4% to 6.9%, while the rate of minor pneumothorax and lung parenchyma hemorrhage can reach as high as 40% and 36%, respectively, some of which can be moderate to severe.[1,4,5] Although mild, the rate of pneumothorax and hemorrhage in the present study was 45% and 20%, respectively. The rate was comparable to that associated with the use of hook

wire. Another useful method for localization is with metallic microcoils. Compared with hook wire placement, the use of microcoils is associated with less discomfort, but no direct mark on the pleural surface results, necessitating intraoperative fluoroscopy, resulting in increased radiation exposure to the patient and operators. Microcoil placement may yield a failure rate of 3% to 10% for localization.[8,16,17] Some authors[6,18] invented a "trailing method" to deploy a microcoil, with the proximal part coiling beyond the parietal pleura and the distal part anchoring in the lung parenchyma. The trailing method can as well provide a direct visual mark for surgeons during the VATS.

The use of methylene blue dye to localize pulmonary nodules was first reported 20 years ago.[12] This localization procedure requires no special items for puncture and injection, can be easily performed in most medical centers, and has almost no anatomic limitation for puncture. However, the major disadvantage of rapid diffusion of the blue dye limits its clinical utility. Instead, some physicians inject an insoluble contrast medium, such as barium or lipiodol, within or around the lung nodule for localization, yielding a reported success rate of 100%.[9,10] The major disadvantage of such localization procedures is that they cannot provide a direct visual mark during the VATS, but require intraoperative fluoroscopy to guide the surgeons. Single-use of cyanoacrylate, a medical adhesive product, was also reported to localize a pulmonary nodule, with a favorable success rate.[14]

In the present study, we used 2 marking materials (blue dye and glue) to localize pulmonary small nodules and GGOs. To our knowledge, it is the first report with regard to the combined use of methylene blue dye and glue in the localization of pulmonary small nodules and GGOs. This procedure can be referred to as a "dual localization technique." Kang and colleagues also used dual localization with a hook wire and radiotracer/lipiodol for needlescopic resection of small lung nodules, with a success rate of 100%.[19,20] Additional use of radiotracer/lipiodol was to avoid failure from hook wire dislodgement. In our opinion, dual localization using different marking materials can be an alternative to single localization in some selected patients.

The complications of dual localization using blue dye and glue should be noted; however, these can be eliminated if good care is taken of the following: (1) The dose of glue. In our opinion, 1 mL of glue is enough for localizing one lesion. (2) The position of the needle tip. The tip should not be too close to the lesion. We recommend no injection of glue within the lesions. (3) The timing for preparing the mixture of blue dye and glue. Because of the rapid solidification of glue and blue dye, which may cause difficult injection, we suggest the preparation of the mixture just after the completion of needle puncture under CT guidance. According to our limited experience, we suggest that a waiting time before VATS ≤ 7 hours may be appropriate. In the study, we had a multidisciplinary team, including a CT scan technician, radiologic interventionalist, and thoracic surgeon, to achieve the goal. The average waiting time in the study was 182.8 ± 100.9 minutes. Localizing pulmonary nodules and VATS was arranged at the same day. Once the targeted pulmonary nodule was localized in the CT room, the patient was then transferred to the operation room, awaiting the surgeon for performing VATS.

The limitations of the present study should be noted. First, the sample was very small. We did not perform a comparative study on dual localization using blue dye and glue versus single localization using coils, hook wires, or other methods. Therefore, the results from the present study might be limited if extended to other clinical practices. Second, although it was an easily performed procedure, the technical details of dual localization using blue dye and glue should be further verified, such as the optimal dose of dye and glue, the timing for preparation of blue dye and glue, and the waiting time before VATS. Finally, although it was a relatively safe procedure, dual localization using blue dye and glue was associated with some mild complications. Therefore, taking good care of each step is very important to reduce the rate of procedure-related complications.

In conclusion, blue-stained glue localization for pulmonary small nodules and GGO is technically feasible and safe. It is an easily performed procedure with no requirement for special instruments. We suggest that blue-stained glue localization can be in the range of choices for some selected patients.

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