Electromagnetic navigational bronchoscopy-directed dye marking for locating pulmonary nodules

Long-long Wang [1], Bi-fang He,[2] Jing-hua Cui,[2] Xing-lin Gao,[2] Ping-ping Chen,[2] Wen-zhao Zhong,[3] Ri-qiang Liao,[3] Jing Li,[2] Jia-yuan Sun[4]

[1]Department of Pulmonary and Critical Care Medicine, Southern Medical University, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Provincial Geriatrics Institute, Guangzhou, China
[2]Department of Pulmonary and Critical Care Medicine, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Provincial Geriatrics Institute, Guangzhou, China
[3]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
[4]Department of Endoscopy, Shanghai Jiao Tong University, Shanghai Chest Hospital, Guangzhou, China

Correspondence to
Dr Jing Li, Department of Pulmonary and Critical Care Medicine, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Provincial Geriatrics Institute, Guangzhou 510080, China; dr.lijing@foxmail.com

Received 27 August 2019
Revised 18 December 2019
Accepted 20 December 2019

To cite: Wang L, He B, Cui J, *et al. Postgrad Med J* 2020;**96**:674–679.

ABSTRACT
Background Small peripheral pulmonary nodules, which are usually deep-seated with no visual markers on the pleural surface, are often difficult to locate during surgery. At present, CT-guided percutaneous techniques are used to locate pulmonary nodules, but this method has many limitations. Thus, we aimed to evaluate the accuracy and feasibility of electromagnetic navigational bronchoscopy (ENB) with pleural dye to locate small peripheral pulmonary nodules before video-associated thoracic surgery (VATS).
Methods The ENB localisation procedure was performed under general anaesthesia in an operating room. Once the locatable guide wire, covered with a sheath, reached the ideal location, it was withdrawn and 0.2–1.0 mL of methylene blue/indocyanine green was injected through the guide sheath. Thereafter, 20–60 mL of air was instilled to disperse the dye to the pleura near the nodules. VATS was then performed immediately.
Results Study subjects included 25 patients with 28 nodules. The mean largest diameter of the pulmonary nodules was 11.8 mm (range, 6.0–24.0 mm), and the mean distance from the nearest pleural surface was 13.4 mm (range, 2.5–34.9 mm). After the ENB-guided localisation procedure was completed, the dye was visualised in 23 nodules (82.1%) using VATS. The average duration of the ENB-guided pleural dye marking procedure was 12.6 min (range, 4–30 min). The resection margins were negative in all malignant nodules. Complications unrelated to the ENB-guided localisation procedure occurred in two patients, including one case of haemorrhage and one case of slow intraoperative heart rate.
Conclusion ENB can be used to safely and accurately locate small peripheral pulmonary nodules and guide surgical resection.
Trial registration number ChiCTR1900021963.

INTRODUCTION
With the popularisation of low-dose CT scan, the detection rate of solitary pulmonary nodules has improved to 8%–51%, where the probability of malignant tumours is 3.8%–13%.[1] The overall 5-year survival rate of patients with lung cancer is as low as 15%, but can be as high as 80%,[2] post-surgery in the initial stages. Therefore, early detection and treatment of lung cancer are crucial to survival. Video-associated thoracic surgery (VATS) significantly aids in the diagnosis and treatment of small peripheral pulmonary nodules (PPNs). However, ground-glass opacities (GGOs), or subcentimetre nodules, which are usually deep-seated with no specific visual markers on the pleural surface, are often difficult to locate during surgery. Failure to locate PPNs during VATS may result in incomplete resection or switching to an open thoracotomy.

CT-guided percutaneous techniques are presently deployed to pinpoint pulmonary nodules, and include hookwire, microcoil, radiotracer, methylene blue or indocyanine green injections, and fiducial localisation.[3–8] However, such techniques often carry a high risk of haemothorax and pneumothorax,[9] and generally necessitate close cooperation between interventional radiologists and thoracic surgeons. Localisation procedures are often performed in the interventional radiology department, and patients need to be shifted to the operating room (OR) for surgery. Any unforeseen delays may cause displacement or even abscission of the solid localiser. Moreover, pleural dyes, such as indocyanine green and methylene blue, have a tendency to diffuse far beyond the site of injection, and such occurrences can induce localisation failure.

Electromagnetic navigational bronchoscopy (ENB) has emerged as a transbronchial location tool that can assist minimally invasive resection of PPNs. The procedure can be performed in the OR, thus circumventing potential localisation failures, which are typical with CT-guided percutaneous procedures.

We aimed to identify the value of ENB dye marking in small PPN localisations and present our initial experiences with this method.

METHODS
This prospective, single-centre study was conducted at the Guangdong Provincial People's Hospital from May 2018 to April 2019. The inclusion criteria were patients with small PPNs that were expected to be difficult to locate intraoperatively and the presence of multiple pulmonary nodules. All patients required lung resection (wedge resection, segmentectomy or lobectomy). The exclusion criteria were (1) allergies to dyes (methylene blue or indocyanine green), previous bronchial asthma or allergic constitution; (2) excessive obesity; or (3) chest CT that revealed large PPNs close to the pleura. The primary outcome was the pleural staining success rate and accuracy in locating PPNs. The secondary outcomes included procedure time and complications. The ENB procedure was considered successful if pleural staining was visible and the localisation accuracy was achieved. Each patient underwent a 1-month follow-up examination.

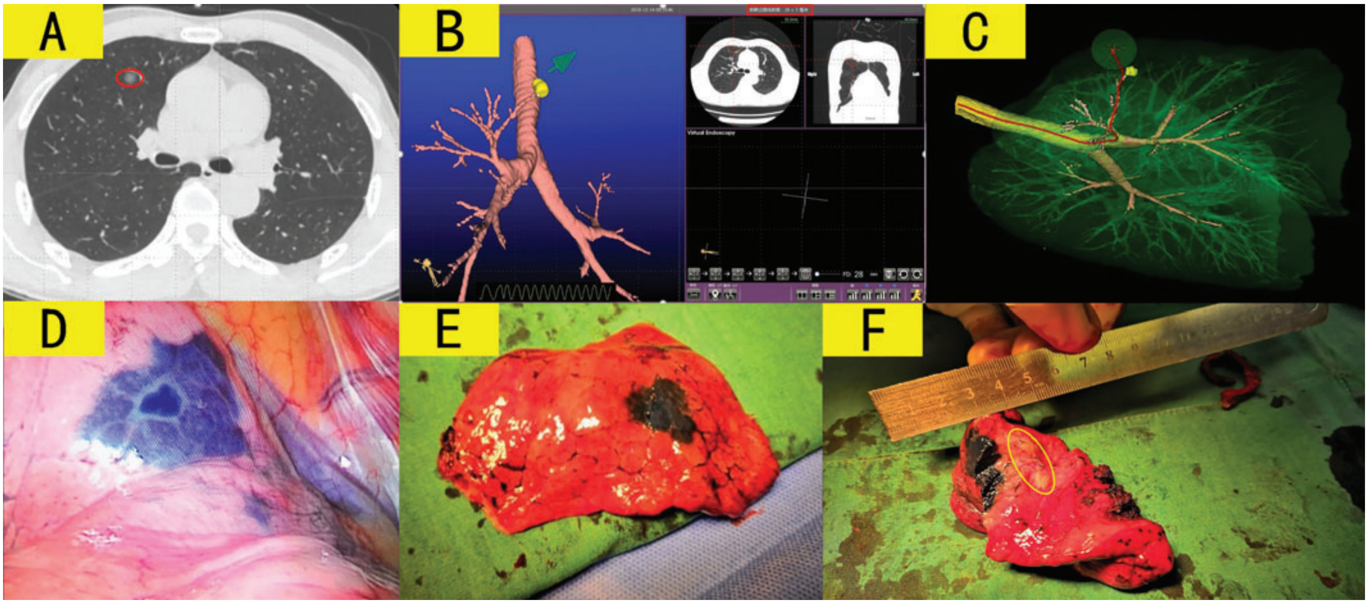

Figure 1 (A) CT image of a small pulmonary nodule (red circle). (B) Tip of the guide wire on the visceral pleural surface (green arrow), 28 mm (the red box shows the linear distance from the target [28 ± 5 mm], which was defined as the theoretical distance) from the centre of the nodule (yellow dot). (C) Location of the nodule (yellow dot) relative to pleural staining (red dot, dye was injected in the pleura), with the patient in left lateral decubitus position. The nodule and staining were 28 mm apart. (D) Pleural dye visualised on the surface during video-associated thoracic surgery. (E) Resected specimen stained with methylene blue dye. (F) The incised lesion (yellow circle) was approximately 20 mm away from the centre of the pleural staining (defined as the actual distance). The relative error was 8 mm. All images were from a single patient.

ENB dye marking and surgical procedure

A respiratory physician in the OR performed the ENB-guided pleural dye marking procedure, prior to VATS. The electromagnetic navigation system (Lungcare, Guangzhou, China) helped reconstruct the chest CT into a three-dimensional airway tree, generating an optimum pathway to the lesion. The patient lay on the examination bed after removing any metal objects from their body. The body position sensors were then attached to the patient's chest (three altogether; one attached to the manubrium sterni, and the other two attached to the eighth rib and the anterior axillary line intersection). General anaesthesia was subsequently administered to the patient through a single-lumen endotracheal tube, to perform the ENB-guided transbronchial dye marking procedure. First, the locatable guide wire was inserted into a flexible catheter, leaving the tip slightly exposed, and then fixed as an ensemble to prevent the guide wire from moving inside the catheter during the operation. Second, the ensemble was inserted into the working channel of the bronchoscope and advanced along the optimum pathway, as far as the bronchoscope could extend. The ensemble was then pushed further until it was set into the appropriate position (figure 1B). The guide wire was then withdrawn, leaving the catheter (extended working channel) in place. The flexible catheter was injected with 0.2–1.0 mL of dye (indocyanine green (10 mL: 25 mg) or methylene blue (2 mL: 20 mg)), and then rinsed with 20–60 mL of air to clear the remaining dye from the catheter. It is important that when resistance was sensed, the catheter was only slightly retracted, by 1–2 mm, before attempting to inject air, so as to prevent introducing an air embolism.

In general, if the nodule was less than 20 mm from the pleural surface, the dye was injected directly into the nodule. However, if the nodule was located more than 20 mm from the pleural surface, the dye injection was applied midway between the nodule and the nearest pleural surface (figure 1A). The doses of dye and air were also determined as per the distance between the position of the dye injected and the nearest pleural surface. We did not use endobronchial ultrasound or fluoroscopy at any time during the process to confirm the location of the nodules. After completing the dye marking process to locate the nodule, the single-lumen endotracheal tube was replaced with a double-lumen tube. With the patient in an appropriate lateral decubitus position, a minimally invasive resection of the PPN was initiated. During surgery, the pulmonary surface was inspected, and the pleural dye was visualised (figure 1D). Resection of the nodule was guided via the relative spatial relationship of the theoretical location of the pleural dye and the actual location of the nodule (figure 1C). The surgical specimen (figure 1E) was then dissected to locate the small pulmonary nodule, and the distance of the nodule from the centre point of the pleural staining was measured (figure 1F). Frozen-section analyses of the nodule and resection margin were then performed.

Statistical design and analysis

Information collected included patient demographics, nodule characteristics, intraoperative details and postoperative outcomes. Relevant descriptive statistics (proportions, range, median or mean, SD and 95% CI) were used to describe the research results. Paired sample t-tests were used to ascertain the accuracy of the ENB localisation procedure. Relevant statistical graphs were drawn using GraphPad Prism V.7.0. Statistical analyses were performed using SPSS V.23.0 statistical software for Windows. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Twenty-five patients (9 men, 16 women; mean age: 59 (42–76) years) with 28 pulmonary nodules combined underwent consecutive ENB-guided dye marking, to assist in nodule localisation

Table 1 Patient characteristics

Parameters	n (%) or mean±SD (range)
Total number of patients/nodules	25/28
Sex	
Male	9 (36.0)
Female	16 (64.0)
Age (years)	59±10 (42–76)
Body mass index	23.4±3.8 (16.2–33.3)
Smoking history	5 (20.0)
Smoking history, mean pack-years	30
Family history of malignancy	5 (20.0)

for VATS resection. Five patients (20.0%) were current or former smokers, with a mean pack-years of 30. Of the 25 patients, 5 (20.0%) had a family history of malignancy. The mean body mass index was 23.4 (16.2–33.3) (table 1).

Characteristics of pulmonary nodules

The majority of patients (22 of 25, 88.0%) had only one nodule, while three patients (3 of 25, 12.0%) had two nodules. Nine nodules were solid (32.1%), and 19 were mixed (17.9%) with pure GGOs (50.0%). The nodules were predominantly located in the upper lobe (57.1%). The mean largest diameter of the pulmonary nodules was 11.8 mm (range, 6.0–24.0 mm). The mean distance from the centre of the nodule to the nearest pleural surface was 13.4 mm (range, 2.5–34.9 mm), and an air bronchus sign was observed in nine nodules (32.1%) (table 2).

Intraoperative data

All 28 nodules were surgically removed, including 16 wedge resections (57.1%), 6 segmentectomies (21.4%) and 6 lobectomies (21.4%). The distance from the dye injection site to the centre of the nodule averaged 20.6 mm (range, 0–69.0 mm), while the distance from the injection site to the nearest pleural surface averaged 14.9 mm (range, 0–41.0 mm). The theoretical distance from the centre of the nodule to the expected pleural staining area (the pleura closest to the dye injection site) was measured using a navigation software and averaged 23.5 mm (range, 0–53.0 mm). We used indocyanine green injection in 4 nodules and methylene blue injection in 24 nodules. An average of 0.5 mL of dye and 32.5 mL of air were injected separately. Pleural staining was visible using thoracoscopy in 23 nodules (82.1%). The mean time for ENB localisation was 12.6 min (range, 4–30 min), and the average interval from the completion of dye injection to the discovery of pleural staining was 44.0 min (range, 25–67 min) (table 3).

Table 2 Characteristics of pulmonary nodules

Parameters	n (%) or mean±SD (range)
Total number of nodules	28
Patients with one nodule	22 (88.0)
Patients with two nodules	3 (12.0)
Nodule location	
Right upper lobe	9 (32.1)
Right middle lobe	2 (7.1)
Right lower lobe	7 (25.0)
Left upper lobe	7 (25.0)
Left lower lobe	3 (10.7)
Largest diameter (mm)	11.8±4.5 (6.0–24.0)
Depth from the pleura (mm)	13.4±8.4 (2.5–34.9)
Bronchus sign	9 (32.1)
Radiographic density	
Pure ground-glass opacity	14 (50.0)
Solid nodule	9 (32.1)
Mixed nodule	5 (17.9)

Table 3 Intraoperative data

Parameters	n (%) or mean±SD (range)
Distance from the nodule to dye injection site (mm)	20.6±15.5 (0–69.0)
Distance from the dye injection site to the pleura (mm)	14.9±10.9 (0–41.0)
Theoretical distance from the nodule to the central point of pleural staining based on CT (mm)	23.5±12.9 (0–53.0)
Marker used	
Methylene blue	24 (85.7)
Indocyanine green	4 (14.3)
Dose of the dye (mL)	0.5±0.2 (0.2–1.0)
Amount of air injected (mL)	32.5±10.1 (20–60)
Pleural staining visible	23 (82.1)
Duration	
ENB localisation time (min)	12.6±6.5 (4–30)
Time from completion of dye injection to the discovery of pleural staining (min)	44.0±12.5 (25–67)
Type of procedure	
Wedge resection	16 (57.1)
Segmentectomy	6 (21.4)
Lobectomy	6 (21.4)

ENB, electromagnetic navigational bronchoscopy.

Postoperative data

The average actual distance from the centre of the nodule to the central point of the pleural staining, based on the resected specimen, was 23.8 mm (range, 10.0–50.0 mm). The final pathological diagnosis was established in all of the nodules (24 adenocarcinomas, 2 granulomas, 1 hamartoma and 1 inflammation). The 21 nodules diagnosed as adenocarcinoma were sent for epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) fusion gene tests. The positive rates of EGFR and ALK mutations were 42.9% and 4.8%, respectively. All malignant nodules were completely resected, and resection margins were considered sufficient following gross and microscopic assessments. Two patients exhibited complications that were not directly related to the ENB localisation procedure (table 4).

Accuracy of ENB-guided dye marking

To determine the accuracy of ENB-guided localisation, we recorded the theoretical and actual distances from the centre of the nodule to the central point of pleural staining, and conducted a paired sample t-test (figure 2A). The average difference between the theoretical and actual distances was 1.9 mm (95% CI −1.2 mm to 4.9 mm), with an insignificant p value of 0.215. We further stratified the difference between the theoretical and actual distances and plotted the related statistical data (figure 2B). The results showed that the difference between the theoretical and actual distances of all dyed nodules ranged from −10.0 mm to 13.0 mm.

Table 4 Postoperative data

Parameters	n (%) or mean±SD (range)
Actual distance from the nodule to the central point of pleural staining based on resected specimen (mm)	23.8±10.6 (10.0–50.0)
Final diagnosis	
Adenocarcinoma	24 (85.7)
Granuloma	2 (7.1)
Hamartoma	1 (3.6)
Inflammation	1 (3.6)
Gene mutation detection	
EGFR	9 (42.9)
ALK	1 (4.8)
Complications	
Haemorrhage	1 (4.0)
Slow heart rate	1 (4.0)

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

DISCUSSION

In this prospective study, pleural staining was visible in most nodules. For the stained pleural nodules, we conducted paired sample t-tests on the theoretical and actual distances between the nodules and the pleural staining. We found that ENB-guided localisation was reliable and accurate for effectively guiding surgeons performing wedge resection of small PPNs. The average duration of the ENB localisation procedure was 12.6 min, which did not significantly prolong the operation time. No complications directly related to ENB-guided localisation procedures were observed. All nodules were completely resected, and resection margins were negative in all malignant nodules.

There are several potential advantages to applying ENB for the preoperative localisation of PPNs prior to minimally invasive resection. First, it can be safely and effectively implemented in the same OR, and VATS resection can be performed immediately following the localisation procedure. Therefore, multidisciplinary coordination (interventional radiology, surgeons, anaesthetists and other OR staff) may be avoided. Second, in this study, the average time from the completion of dye injection to the discovery of pleural staining was 44.0 min. Additionally, we did not observe any cases of localisation failure due to excessive dye diffusion. Bolton *et al*[10] revealed that the downtime for CT patients in their study was 189 min, and the longest delay was the wait between the completion of CT-guided nodule localisation and onset of surgery. The optimal mode is that surgical resection can be performed immediately following the localisation procedure. Nevertheless, CT-guided localisation is usually performed the day prior to surgery in our hospital. In addition, in our hospital, the thoracic surgeons tend to use CT-guided hookwire localisation for lung nodules. Such an extended time gap means that chest pain may occur during breathing since the distal end of hookwire was exposed out of skin, and also increases the possibility of pneumothorax or hookwire dislodgement. Conversely, pulmonary surgeons usually use the CT-guided injection of methylene blue for localisation. Similarly, the long delay resulted in that it was often difficult to locate the nodule using pleural staining during VATS resection because excessive diffusion and fading of methylene blue had occurred, particularly for substantially pigmented and anthracotic lung surfaces.[11] Third, there was no cause for concern over the risk of pneumothorax or haemorrhage associated with ENB-guided dye localisation because the surgery was performed immediately following localisation. However, with CT-guided localisation, patients had to wait for extended periods of time until the onset of surgery. If complications such as pneumothorax or haemorrhage occurred, it may seriously harm patients. A meta-analysis showed that the mean haemorrhage rates related to CT-guided hookwire and microcoil localisation were 16% and 6%, respectively. In contrast, the mean pneumothorax rates were as high as 35% and 16% for CT-guided hookwire and microcoil localisations, respectively, because the pleura was punctured.[12] Moreover, cases of air embolism were observed in CT-guided hookwire localisation studies,[13 14] and complications are more likely to occur in patients with multiple pulmonary nodules.[11]

We were sure the pathological assessment of resected specimens would be unaffected by the dye, as established in a previous study using methylene blue.[15] Additionally, we did not perform injections in situ during the majority of the procedures. Moreover, in this study, the stained nodules were also diagnosed via pathological evaluation.

Published studies revealed that the ENB localisation success rate was 79%–100%.[16–21] Awais and colleagues[20] performed ENB-guided localisation in 29 patients with a median lesion size of 10 mm. The median distance from the surface of the lung to the lesion was 13 mm, with a range of 3–44 mm. The mean navigation time was less than 10 min, and all nodules were successfully located and resected. Marino and colleagues[19] reported 72 nodules located through the ENB-guided localisation procedure. In their study, the median nodule size was 8 mm, with a median distance of 6 mm from the pleural surface. The

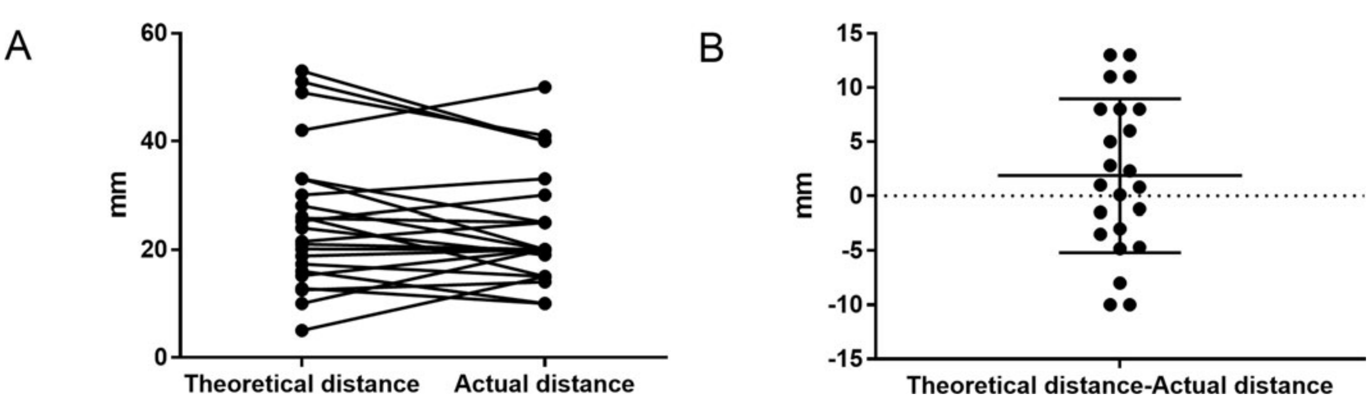

Figure 2 (A) Connection diagram between the theoretical and actual distances. (B) Scatter plot of the difference between the theoretical and actual distances. It can be seen from the figure that the relative error between the theoretical and actual distances of most dyed pulmonary nodules ranged from 0 mm to 10 mm. The maximum error did not exceed 15 mm.

localisation success rate was 97.2%. Neither study observed adverse events related to the ENB-guided localisation procedure.

Grogan and colleagues[22] reported lung nodule localisation by CT-guided percutaneous placement of technetium 99m in 84 patients. Among these patients, 77 nodules were successfully located and excised. In their study, the mean nodule size was 9.8 mm, with a mean distance of 11.7 mm from the pleural surface. However, complications occurred in 16% of patients, including pneumothoraces (eight patients), atrial arrhythmias (three patients) and prolonged air leak (one patient). The results indicated that ENB-guided and CT-guided localisations had the same high success rate, but that ENB-guided localisation may be associated with fewer complications. However, almost no study clearly defined the localisation accuracy of the ENB-guided localisation procedure. Thus, our study is the first to evaluate the accuracy of localisation via specific numerical values. The result of paired sample t-tests showed that there was no significant difference between the theoretical and actual distance from the centre of the nodule to the central point of pleural staining. We plotted such differences, showing a relative error between 0 mm and 13.0 mm, thus establishing the ENB localisation method as accurate and reliable, with an 82.1% success rate. In this study, only 32.1% of nodules had bronchus signs, with pleural staining visible in most. Additionally, the guide wire could directly reach the visceral pleura in five nodules. Thus, we can conclude that ENB localisation technology had no strict requirements for air bronchus sign.

It is very important to ensure pleural staining is visible, and this subject is worth exploring. In our study, staining was not observed in five nodules. Among these nodules, only 0.2 mL of dye was injected in three nodules; reflux occurred after the injection of 0.5 mL of methylene blue in one nodule; and in the remaining nodule, the site of dye injection was 41.0 mm from the pleura, with only 0.5 mL of methylene blue injected. Based on our experience, we believe that the following factors may lead to a higher success rate of pleural staining:

- ► Dose of the injected dye. When the locatable guide wire can reach the pleura directly, at least 0.3 mL of dye should be injected and the dosage should be correspondingly increased with increasing distances between the dye injection site and the visceral pleura. The maximum dose of dye in our study was 1.0 mL, with a distance of 31.0 mm between the injection site and the visceral pleura.
- ► Avoid dye reflux. We consider that dye reflux was related to huge resistance when we injected air, or when air was injected at a high speed. To avoid dye reflux, it is recommended that the flexible catheter be slightly adjusted until the resistance disappears, prior to injection. One can also attempt to push the dye to the distal end using the guide wire to avoid this problem; however, the efficacy of this approach needs to be further verified.
- ► Type of injected dye. This study used indocyanine green and methylene blue dyes. Since indocyanine green is a near-infrared fluorescent dye, it is necessary to use a near-infrared fluorescence thoracoscope to observe whether the pleura is stained.[23 24] For unknown reasons, the fluorescence thoracoscope was not available during surgery of one nodule where indocyanine green dye was used, and eventually pleural staining was not visible. Therefore, it is suggested that methylene blue dye be selected when a fluorescence thoracoscope is not available.

Complications occurred in two patients in this study. One of whom, with dyspnoea, had an increased heart rate and a decrease in haemoglobin, and was admitted to the intensive care unit for further treatment. We considered that this situation was related to the extended operation time and incomplete haemostasis during surgery. The other patient developed a slow heart rate, which was lowest during thoracic irrigation, at 30 beats per minute. Following atropine administration, the heart rate returned to normal. We deemed that this complication was not related to the ENB-guided localisation procedure, but rather surgical or anaesthetic stress. There were no other complications, such as allergies to the dyes. Remarkably, each patient underwent two intubations. Zias and colleagues[25] found that repeated intubation could cause mechanical damage to the mucosal tissue in the upper and middle segments of trachea, causing cell proliferation and granulation tissue formation, and thus leading to tracheal stenosis. Additionally, even if the endotracheal intubation time was very short or the intubation operation was smooth, nearly 97% of patients may develop laryngeal injury to varying degrees.[26] Therefore, this presents an urgent problem that must be resolved when performing ENB-guided localisation directly through the double-lumen endotracheal tube, instead of a single-lumen endotracheal tube.

The principal limitation of this study was the small sample size from a single centre. Therefore, studies with large sample sizes are required to identify the optimum dye dosage and injection sites, as well as the theoretical region of pleural staining.

CONCLUSION

ENB-guided dye marking is a safe and feasible technique to locate small pulmonary nodules.

Main messages

- ► Electromagnetic navigational bronchoscopy (ENB)-guided pleural dye marking was feasible to locate small peripheral pulmonary nodules.
- ► The ENB-guided pleural dye marking procedure was simple and did not significantly prolong the operation time.
- ► The ENB-guided localisation procedure was safe, with no complications directly related to the procedure being observed.

Current research questions

- ► What is the optimum dosage of the dye?
- ► How can the optimal dye injection position be determined?
- ► Is methylene blue or indocyanine green the most suitable dye?

Contributors All authors: study concept and design. Final approval of the manuscript: L-lW, JL: acquisition of data, and drafted and revised the manuscript. J-yS: technical guidance. B-fH, J-hC, X-lG, P-pC: performed the ENB-guided localisation procedure. W-zZ, R-qL: performed VATS.

Funding This work was supported by the National Key R&D Program of China (no 2017YFC0112700).

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval The protocol was approved by the local research ethics committee of the Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences). Informed consent to undergo ENB-guided pleural dye marking was obtained from all patients.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Data may be obtained by emailing 911698746@qq.com.

ORCID iD
Long-long Wang http://orcid.org/0000-0002-0840-3600

REFERENCES

1 Wahidi MM, Govert JA, Goudar RK, *et al*. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:94s–107.
2 Soubani AO. The evaluation and management of the solitary pulmonary nodule. *Postgrad Med J* 2008;84:459–66.
3 Klinkenberg TJ, Dinjens L, Wolf RFE, *et al*. Ct-Guided percutaneous hookwire localization increases the efficacy and safety of VATS for pulmonary nodules. *J Surg Oncol* 2017;115:898–904.
4 Finley RJ, Mayo JR, Grant K, *et al*. Preoperative computed tomography-guided microcoil localization of small peripheral pulmonary nodules: a prospective randomized controlled trial. *J Thorac Cardiovasc Surg* 2015;149:26–32.
5 Bellomi M, Veronesi G, Trifirò G, *et al*. Computed tomography-guided preoperative radiotracer localization of nonpalpable lung nodules. *Ann Thorac Surg* 2010;90:1759–64.
6 Findik G, Demiröz SM, Apaydın SMK, *et al*. Computed Tomography-Guided methylene blue labeling prior to thoracoscopic resection of small deeply placed pulmonary nodules. do we really need palpation? *Thorac Cardiovasc Surg* 2017;65:387–91.
7 Nagai K, Kuriyama K, Inoue A, *et al*. Computed tomography-guided preoperative localization of small lung nodules with indocyanine green. *Acta Radiol* 2018;59:830–5.
8 Sancheti MS, Lee R, Ahmed SU, *et al*. Percutaneous fiducial localization for thoracoscopic wedge resection of small pulmonary nodules. *Ann Thorac Surg* 2014;97:1914–9. discussion 1919.
9 Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ED: American College of chest physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e142S–65.
10 Bolton WD, Cochran T, Ben-Or S, *et al*. Electromagnetic navigational bronchoscopy reduces the time required for localization and resection of lung nodules. *Innovations* 2017;12:333–7.
11 Tseng Y-H, Lee Y-F, Hsieh M-S, *et al*. Preoperative computed tomography-guided dye injection to localize multiple lung nodules for video-assisted thoracoscopic surgery. *J Thorac Dis* 2016;8:S666–71.
12 Park CH, Han K, Hur J, *et al*. Comparative effectiveness and safety of preoperative lung localization for pulmonary nodules: a systematic review and meta-analysis. *Chest* 2017;151:316–28.
13 Ichinose J, Kohno T, Fujimori S, *et al*. Efficacy and complications of computed tomography-guided hook wire localization. *Ann Thorac Surg* 2013;96:1203–8.
14 Suzuki K, Shimohira M, Hashizume T, *et al*. Usefulness of CT-guided hookwire marking before video-assisted thoracoscopic surgery for small pulmonary lesions. *J Med Imaging Radiat Oncol* 2014;58:657–62.
15 Zhang Z, Liao Y, Ai B, *et al*. Methylene blue staining: a new technique for identifying intersegmental planes in anatomic segmentectomy. *Ann Thorac Surg* 2015;99:238–42.
16 Muñoz-Largacha JA, Ebright MI, Litle VR, *et al*. Electromagnetic navigational bronchoscopy with dye marking for identification of small peripheral lung nodules during minimally invasive surgical resection. *J Thorac Dis* 2017;9:802–8.
17 Luo K, Lin Y, Lin X, *et al*. Localization of peripheral pulmonary lesions to aid surgical resection: a novel approach for electromagnetic navigation bronchoscopic dye marking. *Eur J Cardiothorac Surg* 2017;52:516–21.
18 Abbas A, Kadakia S, Ambur V, *et al*. Intraoperative electromagnetic navigational bronchoscopic localization of small, deep, or subsolid pulmonary nodules. *J Thorac Cardiovasc Surg* 2017;153:1581–90.
19 Marino KA, Sullivan JL, Weksler B. Electromagnetic navigation bronchoscopy for identifying lung nodules for thoracoscopic resection. *Ann Thorac Surg* 2016;102:454–7.
20 Awais O, Reidy MR, Mehta K, *et al*. Electromagnetic navigation Bronchoscopy-Guided dye marking for thoracoscopic resection of pulmonary nodules. *Ann Thorac Surg* 2016;102:223–9.
21 Krimsky WS, Minnich DJ, Cattaneo SM, *et al*. Thoracoscopic detection of occult indeterminate pulmonary nodules using bronchoscopic pleural dye marking. *J Community Hosp Intern Med Perspect* 2014;4. doi:10.3402/jchimp.v4.23084. [Epub ahead of print: 17 02 2014].
22 Grogan EL, Jones DR, Kozower BD, *et al*. Identification of small lung nodules: technique of radiotracer-guided thoracoscopic biopsy. *Ann Thorac Surg* 2008;85:S772–7.
23 Ujiie H, Kato T, Hu H-P, *et al*. A novel minimally invasive near-infrared thoracoscopic localization technique of small pulmonary nodules: a phase I feasibility trial. *J Thorac Cardiovasc Surg* 2017;154:702–11.
24 Hachey KJ, Digesu CS, Armstrong KW, *et al*. A novel technique for tumor localization and targeted lymphatic mapping in early-stage lung cancer. *J Thorac Cardiovasc Surg* 2017;154:1110–8.
25 Zias N, Chroneou A, Tabba MK, *et al*. Post tracheostomy and post intubation tracheal stenosis: report of 31 cases and review of the literature. *BMC Pulm Med* 2008;8:18.
26 Benjamin B, Holinger LD. Laryngeal complications of endotracheal intubation. *Ann Otol Rhinol Laryngol* 2008;117:2–20.