Original Article

Preoperative localization of pulmonary nodules by electromagnetic navigation bronchoscopy combined with methylene blue injection

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Background: Electromagnetic navigation bronchoscopy (ENB) can help to accurately locate pulmonary nodules using a minimally invasive approach. This study sought to evaluate the clinical efficacy and safety of dye marking localization under the guidance of ENB followed by surgery.

Methods: A retrospective analysis was performed of 61 patients who underwent ENB localization using methylene blue dye marking before surgery at Shanghai General Hospital from October 2021 to February 2022. The clinical efficacy and safety of ENB localization and the related factors affecting the navigation time of ENB location were analyzed.

Results: ENB was performed on 170 pulmonary nodules in 61 patients with a median age of 60 [interquartile range (IQR), 18] years. The majority of patients (70.69%) had more than two pulmonary nodules. The median maximum nodule diameter was 10 (IQR, 8) mm, and 48.21% of the nodules were mixed ground-glass nodules. Median time for ENB navigation was 10.5 (IQR, 6) min. The navigation success rate was 92.96%, and the ENB location success rate was 95.89%. The rate of complications related to ENB localization was 1.64% (there was only one case of pulmonary hemorrhage). The multivariate analysis showed that the factors related to the navigation time included the node location (P=0.001) and location mode (P=0.04).

Conclusions: ENB-guided methylene blue injection is an effective and safe tool for localizing and marking pulmonary nodules, and can be used to assist the diagnosis and treatment of early lung cancer. The node location and location mode had significant effects on navigation time.

Keywords: Electromagnetic navigation bronchoscopy (ENB); methylene blue; lung nodule; localization

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Introduction

Based on GLOBOCAN 2022 estimates, lung cancer was the most frequently diagnosed cancer and the leading cause of cancer-related death globally (1). The early diagnosis of lung cancer contributes to improving patient prognosis and survival (2). Based on a large-scale real-world Chinese sample of 26,226 cases, the 5-year survival rates of stages I, II, III, and IV lung cancer were 84.20%, 56.41%, 34.39%, and 18.41%, respectively (3). Therefore, early detection and treatment of lung cancer are crucial to survival (4). Pure ground-glass nodules and sub-solid nodules are difficult to detect during surgery. Due to the deviation in terms of location of lesions before and after the collapse of the lungs, preoperative CT scan images was difficult to locate the pulmonary nodules accurately (5).

Electromagnetic navigation bronchoscopy (ENB) is a transbronchial location tool that can assist in the minimally invasive resection of peripheral pulmonary nodules, and is recommended for use in the biopsy of peripheral pulmonary nodule lesions for definitive diagnosis (5,6). It combines three-dimensional (3D) reconstruction technology and magnetic navigation with bronchoscopy to reach deep into grade 12 to 14 bronchi and realize the real-time navigation and accurate localization of lung lesions (7). ENB has gained increasing popularity, as it has advanced the preoperative marking of small pulmonary nodules, is highly effective, and is low risk (8,9). The prospective, multicenter NAVIGATE study (10) showed that ENB-aided diagnosis can be obtained concomitantly in approximately 75% of patients undergoing ENB-guided biopsy and has a low procedural complication rate.

Highlight box

Key findings

- Electromagnetic navigation bronchoscopy (ENB)-guided methylene blue marking is an effective method of localizing pulmonary nodules.
- Only one complication was observed in our study cohort of 61 patients (1.64%), which was a patient who sustained pulmonary hemorrhage during ENB bronchoscopy.
- The univariate and multivariate logistic regression analyses showed that the node location and location mode had significant effects on the navigation time.

What is known, and what is new?

- The ENB-guided location of pulmonary nodules has been shown to be an effective, safe, and minimally invasive technology. However, the factors affecting the navigation time in pulmonary nodule localization using ENB-guided methylene blue injection remain unclear.
- This study evaluated the clinical efficacy and safety of methylene blue marking localization under the guidance of ENB, and further investigated the factors affecting navigation time.

What is the implication, and what should change now?

- Methylene blue injection guided by ENB is a promising option for the preoperative localization of pulmonary nodules. Greater experience at setting the target and selecting the location mode is necessary to enhance the accuracy of ENB-guided dye localization and to standardize the procedure. The shorter navigation time will be achieved at the later phase of the learning process of ENB localization.

In this study, we sought to evaluate the clinical efficiency and safety of using ENB combined with methylene blue marking for the preoperative localization of pulmonary nodules, and to further investigate the factors affecting navigation time. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1358/rc).

Methods

Patients

From October 2021 to February 2022, patients who had been diagnosed with pulmonary nodules, and underwent ENB-guided preoperative localization followed by surgery, were enrolled for the study. The inclusion criteria were: (I) small pulmonary lesions (diameter ≤8 mm) were presumed to be undetectable and unpalpable based on the surgeon's experience and the presence of two or more pulmonary nodules; (II) pulmonary lesions (diameter >8 mm) located >10 mm deep from the pleural surface. Patients allergic to methylene blue were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Shanghai General Hospital (No. 2021KY175). Informed consent was obtained from all the participants.

ENB location and surgery

All the ENB procedures used the superDimension™ navigation system (version 7.0) in accordance with the manufacturer's instructions (and as described previously) (11,12). General anesthesia with intubation in a supine position was performed first before surgery. A chest computed tomography scan was performed to generate a 3D channel before the ENB operation. Based on the already established route to access the pulmonary, every nodule was successfully located with the help of a navigation console system, locatable electromagnetic catheter, and extended injection catheter. And then, the electromagnetic guide catheter was removed, and the extended injection catheter was left (11-13). 0.2–0.8 mL of methylene blue and the appropriate amount of air was then injected. The operating process is shown in *Figure 1*. The pulmonary nodules were resected according to the staining markers. All patients were scheduled to undergo VATS surgical procedures including wedge resection, segmentectomy, and lobectomy after localization.

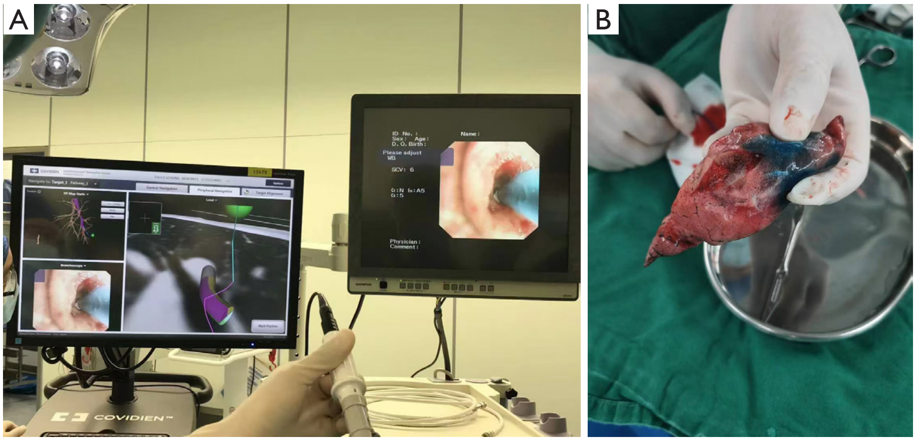

Figure 1 Preoperative pulmonary nodule localization under the guidance of ENB. (A) ENB localization system; (B) methylene blue marking of pulmonary nodules. ENB, electromagnetic navigation bronchoscopy.

Table 1 Patient characteristics

Parameters	Patient data (n=61)
Age (years)	60 [18]
≥60	33 (54.10)
<60	28 (45.90)
Gender	
Male	25 (40.98)
Female	36 (59.02)
Active smoking	21 (34.40)
Male	18 (72.0)
Female	3 (8.33)
Body mass index (kg/m^2)	24 [3.6]
Pulmonary function	
FEV1 (L)	2.34 [0.89]
FVC (L)	2.88 [1.28]
Missing	16
Nodules per patient	
1	17 (29.31)
≥2	41 (70.69)
Missing	3
Emphysema	9 (14.75)
Pulmonary bulla	2 (3.28)

Data are presented as median [interquartile range], n (%) or n. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.

Statistical analysis

The data are expressed as the total number with the percentage for the categorical variables, and as the median [interquartile range (IQR)] for the continuous variables. After the single-factor analysis, the relevant factors affecting the navigation time were screened, and a multi-factor analysis was conducted. Data analysis was performed using SAS 9.4 version. All P values <0.05 were considered statistically significant.

Results

Characteristics of the patients

In total, 61 patients were included in the study from October 2021 to February 2022. The median age of the patients was 60 (IQR, 18) years, and 36 (59.02%) were women. The median body mass index of the patients was 24 (IQR, 3.6) kg/m^2. Of the 61 patients, the majority of patients (70.69%) had two or more nodules. Nine patients had emphysema, and two patients had pulmonary bulla (*Table 1*).

Characteristics of pulmonary nodules

ENB localization was performed on 170 nodules in 61 patients. The characteristics of the pulmonary nodules are summarized in *Table 2*. The pulmonary nodules were most commonly located in the right upper lobe (38.92%), followed by the left lower lobe (19.76%), left upper lobe

Table 2 Characteristics of pulmonary nodules

Parameters	Nodule data (n=170)
Nodule size (mm)	58 [3]
<5	58 (34.12)
5–8	45 (26.47)
>8	67 (39.41)
Maximum diameter (mm)	10 [8]
Unilateral/bilateral lung nodules	
Unilateral	25 (43.10)
Bilateral	33 (56.90)
Missing	3
Location of lung nodules	
Right upper lobe	65 (38.92)
Right middle lobe	11 (6.59)
Right lower lobe	25 (14.97)
Left upper lobe	30 (17.96)
Left middle lobe	3 (1.80)
Left lower lobe	33 (19.76)
Missing	3
Characteristics	
Mixed ground-glass nodule	27 (48.21)
Pure ground-glass nodule	14 (25.00)
Solid nodule	10 (17.86)
Other	5 (8.93)
Missing	5

Data are presented as median [interquartile range], n (%) or n.

(17.96%), right lower lobe (14.97%), right middle lobe (6.59%), and left middle lobe (1.80%). A large proportion of nodules were pure ground-glass opacity nodules (14, 25.00%) and mixed ground-glass opacity nodules (27, 48.21%).

Localization and operative results

Patients were injected with 0.5 (IQR, 0.1) mL of methylene blue dye. The median ENB navigation time was 10.5 (IQR, 6) min. The median distance from the target nodule was 0.9 (IQR, 0.6) cm. Pulmonary hemorrhage occurred in one patient (1.64%), and no other complication directly related to ENB-guided localization was observed in this study. Postoperative pathology was performed on each resected nodule. The pathological results are shown in *Table 3*. There were 27 cases of minimally invasive adenocarcinoma, 16 cases of invasive adenocarcinoma, and 14 cases of benign lesion.

Table 3 Location and surgery results

Parameters	Value
Navigation time (min)	10.5 [6]
Dose of methylene blue (mL)	0.5 [0.1]
Location mode	
Perinodular	43 (70.49)
Pleura	16 (26.23)
Midnodular	2 (3.28)
Distance from the target nodule (cm)	0.9 [0.6]
Operation mode	
Segmentectomy	11 (18.03)
Lobectomy	10 (16.39)
Wedge resection	40 (65.57)
Surgery time (min)	140 [55]
Complications	
Hemorrhage	1 (1.64)
Pneumothorax	0
Pathological diagnosis	
MIA	27 (44.26)
IA	16 (26.23)
Benign	14 (22.95)
Highly differentiated adenocarcinoma	1 (1.64)
Bronchial adenocarcinoma	1 (1.64)
Poorly differentiated squamous cell carcinoma	1 (1.64)
Small cell neuroendocrine carcinoma	1 (1.64)
Adenocarcinoma	2 (3.28)
Squamous carcinoma	1 (1.64)
Navigation success	66 (92.96)
Location success	70 (95.89)

Data are presented as median [interquartile range] or n (%). MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma.

Table 4 Univariate analysis of navigation time

Parameters	Navigation time, min	R	P value
Age (years)	59.23 (14.16)	−0.19	0.15
Sex			0.96
Male	12.6 (6.09)		
Female	12.7 (10.18)		
Dose of methylene blue (mL)			0.09
<0.3	15.6 (8.67)		
0.3–0.5	11.34 (5.37)		
>0.5	15.22 (8.24)		
Nodule location			<0.001
Upper lobe	10.4 (4.0)		
Middle lobe	9.67 (1.53)		
Lower lobe	11.9 (5.68)		
Other	21.67 (8.49)		
Nodule size (mm)			0.26
<5	–		
5–8	14.73 (6.07)		
>8	12.18 (6.86)		
Distance from pleura (mm)	2.57 (4.15)	−0.07	0.65
Location mode			0.04
Perinodular	11.4 (6.23)		
Pleura	16.5 (6.98)		
Midnodular	12.0 (2.83)		
Surgery experience			0.02
Year 2021	16.0 (6.6)		
Year 2022	11.49 (6.3)		
Breath			0.29
End-exhalation	14.29 (7.58)		
End-expiratory	12.14 (6.31)		

Data are presented as mean (standard deviation).

Relevant factors influencing the navigation time

The factors affecting the navigation time based on the univariate analysis are shown in *Table 4*. Age, sex, methylene blue dose, node location, node size, distance from pleura, location mode, surgical experience, and breath were included in the univariate analysis. The results showed that the node location, location mode, and surgical experience affected the navigation time. The multivariate logistic regression analysis of the above-mentioned variables showed that the node location (P=0.001) and location mode (P=0.04) significantly affected the navigation time (*Table 5*).

Table 5 Multivariate analysis factors affecting navigation time

Parameters	Type III sums of squares	Mean square	F value	P value
Age	32.89	32.89	1.15	0.29
Sex	0.03	0.03	0.00	0.97
Dose of methylene blue	45.26	22.63	0.79	0.46
Nodule location	604.20	201.40	7.05	0.001
Nodule size	47.65	47.65	1.67	0.20
Location mode	206.47	103.23	3.61	0.04
Distance from pleura	9.17	9.17	0.32	0.57
Breath	25.60	25.60	0.90	0.35

Discussion

In this study, ENB guidance and methylene blue injection were performed on 170 nodules in 61 patients. Of the patients, 41 (70.69%) had more than two nodules. The median ENB navigation time was 10.5 (IQR, 6) min. The navigation success rate was 92.96%, and the ENB location success rate was 95.89%. During the study, only one case of pulmonary hemorrhage directly related to ENB-guided localization was observed in the participants. The results of this study showed that the ENB-guided methylene blue marking of pulmonary nodules can effectively and safely localize and mark pulmonary nodules. As previously reported, the application of methylene blue injection guided by ENB in the localization of pulmonary nodules is an accurate and safe method for successful minimally-invasive surgery of multiple pulmonary nodules (12,14).

ENB has a considerable learning curve, and the success rate of ENB localization and localization accuracy increase significantly as experience with ENB technology increases (13). In this study, the shorter navigation time was achieved at the later phase of the learning process of ENB localization. Type of injected dye and the dye dosage also play an important role in ENB-guided location of pulmonary nodules. Indocyanine green is a near infrared

Table 6 ENB-guided methylene blue studies in literature

First author (reference)	No. of patients	Dose of methylene blue (mL)	Mean navigation time (min)	Postoperative complications, n (%)
Wang LL (4)	25	0.2–1.0	12.6	2 (8.0)
Awais O (9)	29	0.5	9.7	0
Yao YS (13)	20	1.5	NA	0
Cheng X (17)	79	0.15	10	5 (2.7)

NA, not available; ENB, electromagnetic navigation bronchoscopy.

fluorescent dye. It is necessary to use a near-infrared fluorescence thoracoscope for observation (4). Methylene blue is water soluble and easy to spread, and a small amount of methylene blue may lead to staining failure or difficulties in distinguishing nodules, while the over-injection of methylene blue may also cause diffuse staining and result in localization failure (15,16). A clinical analysis at a single center (17) recommended that 0.3–0.5 mL of methylene blue be applied in ENB-guided preoperative staining. In lung nodule located more than 5 mm from the pleural surface, an additional injection of no more than 0.5 mL methylene blue was used to mark the pleural surface with a 97.2% success rate, and extravasation of methylene blue into the pleural surface occurred in only two cases (18). Previous ENB-guided methylene blue studies (*Table 6*) have reported that ENB-guided methylene blue staining localization method is an accurate and safe modality.

The location of pulmonary nodules and movement of the lung occurs with respiratory variation during bronchoscopy can affect ENB navigation (19,20). Hyun *et al.* reported that compared with targets in the middle or lower zones, the navigation time was longer in the upper zone, while the target distance remained relatively constant (19). Respiratory movement is another factor that influences navigation accuracy of ENB. Control of respiratory movements would enhance the accuracy of ENB navigation (20).

In this study, we conducted a univariate analysis to further investigate the factors affecting the navigation time, and found that the node location, location mode, and surgical experience affected the navigation time. The multivariate logistic regression analysis showed that the node location (P=0.001) and location mode (P=0.04) significantly affected the navigation time.

This study had a number of limitations. Notably, it used data from a single center. In the future, we will recruit more patients to further monitor the clinical effects and safety of ENB-guided methylene blue location and analyze any other relevant factors affecting the navigation time. Robotic-assisted bronchoscopy with advantage of an easier learning curve has recently emerged as an alternative to ENB for the evaluation of peripheral pulmonary lesions. The first known cluster randomized pragmatic trial in the interventional pulmonology field (RELIAN) will elucidate whether it has comparable diagnostic utility as ENB in the future (21).

Conclusions

ENB-guided preoperative methylene blue location has a high localization success rate and a low complication rate, which proves that it is a safe and effective method for the accurate identification and successful resection of small pulmonary nodules. Methylene blue injection guided by ENB is a promising option for the preoperative localization of pulmonary nodules. In addition, the node location and location mode had significant effects on the navigation time.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1358/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1358/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.

com/article/view/10.21037/jtd-24-1358/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Shanghai General Hospital (No. 2021KY175) and informed consent was obtained from all the participants.

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