Original Article

A better option for localization of multiple pulmonary nodules in the ipsilateral lung: electromagnetic navigation bronchoscopy-guided preoperative localization

Rui Wang[#], Yongjiang Chen[#], Chudong Wang, Zijian Li, Yunpeng Zhong, Yunjuan Liang, Shuben Li

Department of Thoracic Surgery and Oncology, the First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, Guangzhou, China

Contributions: (I) Conception and design: S Li, Y Liang; (II) Administrative support: Y Liang, S Li; (III) Provision of study materials or patients: Y Zhong; (IV) Collection and assembly of data: R Wang, Y Chen, Z Li, C Wang; (V) Data analysis and interpretation: R Wang, Y Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Shuben Li, MD, PhD; Yunjuan Liang, BN. Department of Thoracic Surgery and Oncology, the First Affiliated Hospital of Guangzhou Medical University, No. 28 Qiaozhong Middle Road, Guangzhou 510000, China. Email: 13500030280@163.com; 13538780068@139.com.

Background: Pulmonary nodules are the most common manifestation of lung cancer. The detection rate of multiple nodules has been increasing and it is essential to figure out a precise way for localization of the nodules. The purpose of this study is to evaluate the efficacy, accuracy and safety of electromagnetic navigation bronchoscopy (ENB)-guided dye marking for localizing multiple ipsilateral nodules compared with computed tomography (CT)-guided lung puncture.

Methods: We performed a retrospective cohort study of patients with multiple nodules in the ipsilateral lung who received preoperative localization [including ENB-guided dye marking (ENBDM) or CT-guided lung puncture] and video-assisted thoracoscopic surgery between September 2018 and April 2023. Data were statistically analyzed and visualized using SPSS v25.0 and Microsoft Excel 2019 software.

Results: A total of 203 patients were evaluated, among whom 99 underwent ENBDM to localize nodules preoperatively, and 104 were located by CT-guided lung puncture. In terms of localization time, ENB group compared with CT group consumed less time (8.00±4.66 *vs.* 22.00±8.82 min, P<0.001). In the ENB group, compared with the CT group, there was no radiation exposure. No related complications occurred in the ENB group, including pleural reaction [0 *vs.* 8 (7.7%), P=0.01], pneumothorax [0 *vs.* 36 (34.6%), P<0.001], and hemothorax [0 *vs.* 15 (14.4%), P<0.001]. However, no significant differences were observed in the success localization rate (97.4% *vs.* 94.9%, P=0.48) between the two groups.

Conclusions: For patients with multiple ipsilateral pulmonary nodules, ENBDM can achieve the similar localization accuracy as CT-guided lung puncture, with shorter localization time and no complications. ENBDM is a safe and effective preoperative localization method for multiple ipsilateral pulmonary nodules.

Keywords: Electromagnetic navigation bronchoscopy (ENB); pulmonary nodule; localization

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Introduction

Lung cancer is a prevalent form of cancer and a significant contributor to cancer-related mortality (1). Pulmonary nodules are the most common manifestation of lung cancer (2). The detection rate of nodules has significantly increased with the implementation of health screening using low-dose spiral computed tomography (LDCT), and it is not uncommon that small and multiple pulmonary nodules are frequently detected. Surgical removal of pulmonary nodules with potential malignancy may be considered as a more favorable treatment approach. During video-assisted thoracoscopic surgery (VATS), the localization of small peripheral non-solid nodules can be challenging (3). Failure to accurately localize pulmonary nodules may lead to excessive resection of normal lung parenchyma and even necessitate conversion to thoracotomy. Preoperative localization can ensure precise resection of the multiple nodules.

Traditionally localizing nodules is through palpation with the surgeon's finger, and this technique is often limited due to its time-consuming, experience-dependent nature, and high failure rates (4,5). Therefore, various preoperative localization techniques for marking target pulmonary nodules have been developed, which makes it possible to precisely remove nodules using VATS. Most preoperative localization procedures utilized in clinical practice are based on computed tomography (CT)-guided percutaneous lung puncture (CTPLP). These methods include dye marking (6,7), radiotracer labeling (8), hook wire or micro-coil placement (9-11), ethiodized oil injection (12,13), etc. In the case of multiple ipsilateral nodules, the above localization methods have flaws. For localization of multiple pulmonary nodules, patients are required to undergo excessive radiation exposures. Additionally, repeated percutaneous lung punctures inevitably lead to pain and complications in the process.

In recent years, electromagnetic navigation bronchoscopy (ENB)-guided dye marking (ENBDM) has been widely utilized and showed reliable outcomes with minimal invasion, high accuracy and few complications (14-18). For patients with solitary pulmonary nodules, comparing the two methods of CTPLP and ENBDM, the latter shows the advantages of painless, no radiation exposure, fewer complications, and shorter localization time (19-21). However, as of yet, no literature reports the utilization of ENBDM for preoperative localization of multiple ipsilateral lung nodules. The main purpose of this study was to evaluate the efficacy, accuracy and safety of ENBDM for localizing multiple ipsilateral lung nodules compared with CTPLP. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-901/rc).

Highlight box

Key findings

- Electromagnetic navigation bronchoscopy (ENB)-guided dye marking (ENBDM) is a safe and effective preoperative localization method for multiple ipsilateral pulmonary nodules, compared to computed tomography-guided percutaneous lung puncture (CTPLP).

What is known and what is new?

- CTPLP is the traditional localization method but carries risks such as radiation exposure, pneumothorax, hemothorax, and pleural reactions. ENB has been previously validated for localizing single pulmonary nodules, showing fewer complications and no radiation exposure.
- Compared to CTPLP, ENBDM is particularly beneficial when multiple nodules are located, as it significantly shortens localization time, avoids radiation exposure, and reduces complications.

What is the implication, and what should change now?

- ENBDM offers a safer and faster alternative to CTPLP for preoperative localization of multiple pulmonary nodules in the ipsilateral lung. ENBDM should be incorporated into routine clinical practice for preoperative localization of multiple pulmonary nodules, especially in patients with higher risks of complications or requiring multiple localizations. The safety profile and reduced procedural time of ENBDM may lead to lower overall healthcare costs. Prospective, multicenter studies with larger sample sizes should be conducted to validate these findings and address limitations like cost and accessibility.

Methods

Study design

This was a retrospective, single-center, cohort study comparing ENBDM versus the conventional CTPLP method for preoperative localization of multiple pulmonary nodules in the ipsilateral lung from September 2018 to April 2023 in the First Affiliated Hospital of Guangzhou Medical University. The study was designed to assess the efficacy and safety of the ipsilateral multiple pulmonary nodules localization using the ENBDM method before surgery. This study was approved by the Institutional Review Board at the First Affiliated Hospital of Guangzhou Medical University (No. 2020K-43), and individual consent for this retrospective analysis was waived. This study was

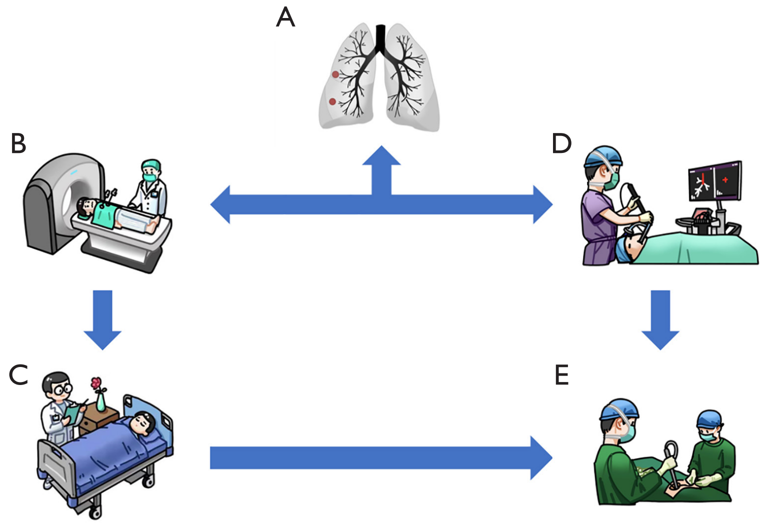

Figure 1 The brief operation process of two group with multiple nodules in the ipsilateral lung. (A) The pulmonary nodules were revealed from chest CT scan; (B) the patient underwent CT-guided percutaneous lung puncture in the CT room to locate the nodule; (C) when localization for nodules in the CT room was finished, the patient was sent back to the inpatient ward to wait and then sent to the operating room for nodule resection; (D) the patient underwent ENB-guided dye marking in the integrated operating room to localize nodules; (E) the patient underwent VATS in the operating room to resect the nodules. CT, computed tomography; ENB, electromagnetic navigation bronchoscopy; VATS, video-assisted thoracoscopic surgery.

conducted in accordance with the Declaration of Helsinki (as revised in 2013) (22).

Patient selection

Patients were included based on the following criteria: (I) the age ranged from 18 to 80 years old; (II) chest CT scan confirmed multiple pulmonary nodules (number ≥2, not limited to the same lung lobe or segment) in the ipsilateral lung; (III) preoperative chest CT revealed that the lesions were challenging to localize or identify with observation or palpation during surgery; (IV) the localization of nodules was performed by ENBDM or CTPLP before surgery; (V) VATS was performed to resect the nodules after localization; (VI) cardiopulmonary function can tolerate surgery; (VIII) no surgical contraindications. Exclusion criteria included: (I) patients had poor cardiopulmonary function and could not tolerate bronchoscopy, CT-guided puncture and VATS; (II) preoperative evaluation revealed regional invasion or distant metastasis.

Localization procedure

The brief operation process of ENBDM and CTPLP are shown in *Figure 1*. Patients were divided into two groups (ENBDM and CTPLP groups). An experienced surgeon and his team performed preoperative localization and subsequent resection by VATS in both groups. More importantly, considering the safety, patients included in both groups were only targeted in the ipsilateral lung during localization and resection.

CTPLP

In the CTPLP group, the entire process of localization was carried out in the CT room. Before localization, a low-dose chest CT (Definition AS+128, Siemens, Munich, Germany; or Revolution 256, GE, Pittsburgh, USA) scan was routinely performed to determine the nodule location, size, and relationship with surrounding anatomical structures. We used metal markers on the body surface to determine the puncture location. The patients were administered with 5 mL of 2% lidocaine to achieve local anesthesia. Fine-needle puncture (Coaxial Needle C2016A, BARD, New Jersey, USA) was then performed under CT guidance and adjusted after multiple CT scans to confirm that the needle tip was located in the target region. Finally, 0.3 mL indocyanine green (ICG; 0.6 mg/mL; Dandong Yichuang Pharmaceutical Co., Ltd., Liaoning, China) was injected into the target region, and a CT scan was performed to observe whether the positioning was satisfactory and whether there were complications such as pneumothorax and bleeding. Patient remained awake overall process and received multiple CT radiation exposures until all the target nodules were localized, then was sent back to the inpatient ward to await surgical notification. Finally, the patients were sent to the operating room (OR) to receive the resection of nodules.

ENBDM

As for the ENB-guided dye marking group, the entire procedure, including preoperative navigation track planning, registration, and localization, and resection of nodules, was performed in an integrated OR. The patient underwent spontaneous respiratory anesthesia with a laryngeal mask on a special electromagnetic navigation table followed by localization of pulmonary nodules. The nodules were localized using planning software and the computer console of the LungCare navigation system (Suzhou LungCare Medical Technology Co., Ltd., Jiangsu, China). The planning software helps us plan a route to the target region. Under bronchoscopy dedicated to visual electromagnetic navigation, each target nodule was localized with an electromagnetic guide and a computer console by using a positionable electromagnetic guide and an extended working catheter. After the nodule was localized, the electromagnetic guide was removed and the extended working catheter was left in place. A mixture of 0.3 mL ICG and 2 mL air was infused into the target region with the aid of a visual bronchoscope through an extended working catheter. After removing the bronchoscope and the extended working catheter, the patient's respiratory secretions were cleaned, and then followed by nodules resection under VATS in the OR.

Statistical analysis

Clinical parameters were extracted from the medical record system. CT results were recorded from the imaging system, including lesion size and location. Pathology-related results were extracted from the pathology reporting system. Localization details were extracted from the center's prospectively maintained thoracic surgery database. Analysis of comparisons were conducted using SPSS 26.0 (IBM Corp, Armonk, NY, USA) software in a Chi-squared test for categorical variables and a Mann-Whitney *U* test for continuous variables, respectively. Microsoft Excel 2019 software (Microsoft, Redmond, WA, USA) was used to visualize the radar map. Microsoft Excel 2019 software was also used to visualize localization times for different numbers of nodules. A P value less than 0.05 was considered statistically significant.

Results

Basic characteristics of patients

The basic characteristics of the patients are presented in *Table 1*. Totally, 203 patients undergoing preoperative nodules localization were reviewed (ENBDM: n=99, CTPLP: n=104). Patients included in the ENBDM group did not differ significantly from CTPLP group with respect to age (P=0.21), gender (P=0.16), distance from pleura (P=0.33), number of localized nodules (P=0.09), number of resected nodules (P=0.16), lobe location (P=0.09) and surgical approach (P=0.10). A total of 272 nodules were localized in the ENBDM group, and 258 were actually resected. As for CTPLP group, a total of 306 nodules were localized, while 298 were also actually removed. When it came to the size of nodules, we found that most nodules were ≤10 mm in diameter in CTPLP and EMBDM groups [268 (87.6%) *vs.* 251 (92.3%)]. There were no statistical differences between two groups in terms of surgical methods (P=0.10). Wedge resection was the most important surgical method in both groups, accounting for 84.9% and 79.7%, respectively.

Localization characteristics and nodule pathological diagnosis

The localization characteristics, pathological diagnosis and complications are shown in *Table 2* and *Table 3*. Compared with CTPLP group, ENBDM group showed its unique advantages, including no radiation exposure, shorter localization time, and no complications (*Figure 2*). However, a short registration time was required [0.65 min (IQR, 0.59 min)]. Patients in the CTPLP group, however, had more radiation exposure [6 (IQR, 2)] and more complications, such as pneumothorax in 36 cases (34.6%), hemothorax in 15 cases (14.4%) and pleural reaction in 8 cases (7.7%).

In terms of localization time, ENBDM group compared with CTPLP group consumed less time (8.00±4.66 *vs.* 22.00±8.82 min, P<0.001). When locating 2 nodules, the localization time of ENBDM group was 6.27±4.07 min while that of CTPLP group was 16.69±6.28 min, which was

Table 1 Patient characteristics

Patient characteristic	CT-guided group (n=104)	ENB-guided group (n=99)	P value
Age, years	53.65±11.69	51.52±12.28	0.21
Sex			0.16
Male	17 (16.3)	24 (24.2)	
Female	87 (83.7)	75 (75.8)	
Distance from pleura, mm	2.00 [5.00]	2.00 [5.00]	0.33
Number of localized nodules	306	272	0.09
Number of resected nodules	298	258	0.16
Lobe location			0.09
Right upper	95 (31.0)	96 (35.3)	
Right middle	32 (10.5)	19 (7.0)	
Right lower	72 (23.5)	82 (30.1)	
Left upper	62 (20.3)	47 (17.3)	
Left lower	45 (14.7)	28 (10.3)	
Nodule diameter, mm			–
≤10	268 (87.6)	251 (92.3)	
10< diameter ≤20	32 (10.5)	20 (7.4)	
20< diameter ≤30	5 (1.6)	1 (0.3)	
30< diameter ≤40	1 (0.3)	0	
Surgical approach			0.10
Wedge resection	244 (79.7)	231 (84.9)	
Segmentectomy	62 (20.3)	41 (15.1)	

Data are presented as mean ± SD, median [IQR], or n (%). CT, computed tomography; ENB, electromagnetic navigation bronchoscopy; IQR, interquartile range; SD, standard deviation.

also statistically different (P<0.001). This difference was also manifested when locating 3 nodules, or 4 or more nodules (*Figure 3*). The localization success rate of ENBDM group was 258/272 (94.9%), while that of CTPLP group was 298/306 (97.4%), with no statistical difference (P=0.48).

There were no statistical differences between two groups in terms of postoperative pathology (P=0.86). The resection rate of malignant nodules (refers to minimally invasive adenocarcinoma and invasive adenocarcinoma) in the ENBDM group was 47.7%, while that in the CTPLP group was 52.2%.

Discussion

Resection of pulmonary nodules through VATS is a minimally invasive, effective and safe surgical procedure, which is also the common choice of thoracic surgeons (23). However, small peripheral non-solid nodules are difficult to be found by palpation or direct vision during the VATS. Thus, accurate nodule localization is crucial for thoracic surgeons, which can shorten the length of operation to some extent (24). At present, the preoperative localization method of nodules is mainly CTPLP. Compared with CTPLP, ENBDM is performed under intravenous anesthesia, which can significantly reduce patients' psychological stress and pain. The localization and surgical resection of nodules are performed in the integrated OR, which avoids the patient's transportation from the CT scan room to OR and simplifies the entire treatment process.

Preoperative localization of multiple ipsilateral

Table 2 Localization details and nodule pathological diagnosis between the two group

Parameter	CT-guided group	ENB-guided group	P value
Successful localization rate	97.3 (298/306)	94.9 (258/272)	0.48
Number of radiation exposures	6 [2]	0	–
Registration time (min)	0	0.65 [0.59]	–
Localization time (min)	22.00±8.82	8.00±4.66	<0.001
Localized nodules =2	16.69±6.28	6.27±4.07	
Localized nodules =3	23.38±6.32	9.30±4.91	
Localized nodules =4	25.06±6.28	10.39±2.81	
Localized nodules >4	33.30±8.98	13.96±3.18	
Pathological diagnosis			0.86
AAH	53 (17.8)	49 (19.0)	
AIS	53 (17.8)	49 (19.0)	
MIA	114 (38.4)	95 (36.8)	
IAC	41 (13.8)	28 (10.9)	
Other malignant	7 (2.4)	6 (2.3)	
Benign	29 (9.8)	31 (12.0)	

Data are presented as % (n/N)[†], median [IQR], mean ± SD, or n (%). [†], % means the rate of successful localization of nodules; n means the number of successfully located nodules; N means total number of nodules in each group. AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; CT, computed tomography; ENB, electromagnetic navigation bronchoscopy; IAC, invasive adenocarcinoma; IQR, interquartile range; MIA, minimally invasive adenocarcinoma; SD, standard deviation.

Table 3 Complications in the two groups

Parameter	CT-guided group	ENB-guided group	P value
Pneumothorax	36 (34.6)	0	<0.001
Hemothorax	15 (14.4)	0	<0.001
Pleural reaction	8 (7.7)	0	0.01

Data are presented as n (%). CT, computed tomography; ENB, electromagnetic navigation bronchoscopy.

pulmonary nodules is more challenging and critical in early-stage thoracic disease. The safety of ENB has been confirmed in some previous studies and was also observed in our study. Towe *et al.* reported a low risk of pneumothorax with ENB (25). Lee *et al.* reported that the prevalence of pneumothorax with ENB-guided biopsy was lower than that with CT-guided needle biopsy for peripheral lung lesions (26). Previous and our studies confirmed that ENB-guided dye marking can be safely used for the localization of small pulmonary nodules (27,28). Sequential ENB-guided nodule localization and VATS can accurately diagnose and treat small pulmonary nodules with minimal invasiveness and risk (29). According to previous studies, CTPLP may cause more localization -related complications compared with ENBDM. Chen *et al.* reported that the incidence of pneumothorax was 32.3% and 33.3% in the simultaneous and sequential groups with preoperative CT-guided localization of multiple pulmonary nodules, while the incidence of pulmonary hemorrhage was 6.3% and 3.0% (30). Xu *et al.* reported that the incidence of localization-related complications in localization of multiple ipsilateral pulmonary nodules with CTPLP were 18.9% and 56.8% respectively (31). Wang *et al.* reported that no localization-related complications occurred when ENBDM

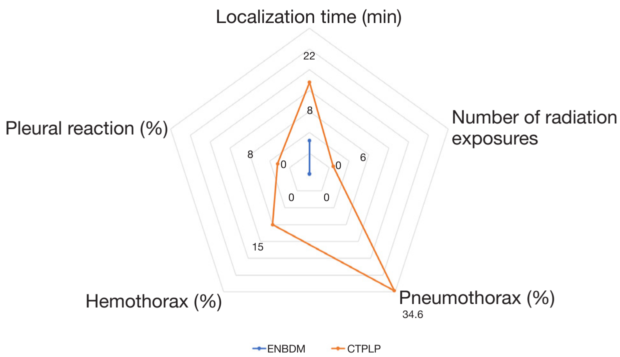

Figure 2 The radar map shows the comparison of positioning-related indicators between the ENBDM group and the CTPLP group, including localization time, radiation exposure times, pneumothorax rate, hemothorax rate and pleural reaction rate. CTPLP, computed tomography-guided percutaneous lung puncture; ENBDM, electromagnetic navigation bronchoscopy-guided dye marking.

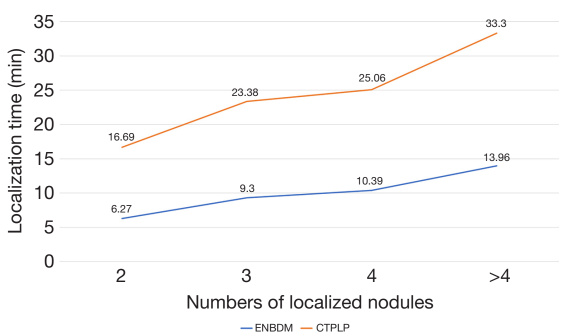

Figure 3 Comparison of the average localization time required for different numbers of nodules in the ENBDM group and the CTPLP group. CTPLP, computed tomography-guided percutaneous lung puncture; ENBDM, electromagnetic navigation bronchoscopy-guided dye marking.

was used to locate pulmonary nodules before surgery (32). Tian *et al.* reported that ENB localization resulted in fewer complications (0/52) compared with CT-guided localization (14/105) (20). In our previous study, no complication was reported in the ENBDM (28). Compared with CTPLP, no complications occurred in ENBDM, including pleural reaction [0 *vs.* 8 (7.7%), P=0.01], pneumothorax [0 *vs.* 36 (34.6%), P<0.001], and hemothorax [0 *vs.* 15 (14.4%), P<0.001] in our study, such results are consistent with our previous and other studies. Preoperative utilization of CTPLP to localize pulmonary nodules resulted in more complications, while fewer complications occurred by ENBDM. Our study shows that preoperative application of ENBDM to locate multiple ipsilateral pulmonary nodules is safer.

In our study, ENBDM had no radiation exposure [0 *vs.* 6 (IQR, 2)]. ENBDM is performed through a natural orifice, which avoids radiation exposure and significantly reduces puncture-related complications (19). In addition, 9 patients (9/81, 11.1%) of pneumothorax was detected by CT after the first localization, 35 new cases (35/81, 43.2%) after the second, and another 2 new cases (2/7, 28.6%) after the third (31). The number of localized nodules increases, resulting in a higher complication rate due to puncture in CTPLP. Based on our research, ENBDM demonstrates superior efficacy over CTPLP in the localization of ipsilateral multiple pulmonary nodules. However, as of the current literature, studies involving a substantial case series have not been reported.

Compared with CTPLP, ENBDM had shorter localization time (8.00±4.66 *vs.* 22.00±8.82 min, P<0.001) in our study. Another finding of this study is that as the number of localized nodules increases, the localization time of the ENBDM group is significantly lower than that of the CTPLP group (*Figure 3*). This is another benefit of ENBDM for ipsilateral multiple pulmonary nodules, which helps to shorten the overall operation time.

In addition, we have previously attempted staining with methylene blue (MB) in some cases and used small doses of MB to achieve precise localization (33). Some nodules are distant from the pleura and the poor penetration of MB makes these nodules difficult to visualize (34). As a near-infrared fluorescent dye, ICG has a higher penetration rate into tissues and is easy to identify. When locating multiple nodules in the same lobe, multiple injections of MB tend to diffuse and cause large-area staining that is difficult to observe. In addition, it is difficult for pathologists to identify lesions in MB-stained areas, while fluorescent dyes in their natural state do not cause trouble to pathologists. Therefore, we prefer ICG for preoperative nodule localization.

Our study showed that the success rate of locating ipsilateral multiple pulmonary nodules was 258/272 (94.9%) in the ENBDM group, and 298/306 (97.4%) in the CTPLP group, and the difference was not statistically significant (P=0.48), which confirmed that ENBDM and CTPLP were equally accurate for localizing ipsilateral multiple pulmonary nodules. For those nodules that failed to be successfully located, we expanded the scope of resection based on preoperative imaging examinations and three-dimensional reconstructed images, and finally successfully removed the lesions. We believe that the main reason for failure was that these nodules were located in the inner 1/3 of the lung. In the ENBDM group, the causes of localization failure also included congenital bronchial variation defects, occluded peripheral bronchial branches, and excessive bronchoscope diameter. We suggest that preoperative three-dimensional reconstruction is a better choice instead of invasive localization methods such as ENBDM and CTPLP for nodules located in the inner 1/3 of the lung.

Study limitations

This study was limited by the retrospective nature of data collection and selection bias. ENBDM also has some limitations. ENBDM has a higher cost than CTPLP. When the airway is abnormal or the nodule is located in the inner 1/3 of the lung, localization by ENBDM may fail. ENBDM requires experienced and skilled surgeons. The accuracy of positioning and operation duration will directly affect the nodule resection surgery. Therefore, operators need systematic training and continuous practice to accumulate experience. Encouragingly, our prior study has demonstrated that this technique can be rapidly mastered, exhibiting enhanced success and precision rates, alongside reduced duration of surgical procedures (35).

Conclusions

We proposed for the first time that for patients with multiple pulmonary nodules in the ipsilateral lung, ENBDM can achieve the similar localization accuracy as CTPLP, with shorter localization time, no radiation exposure, and fewer complications. ENBDM is an accurate, effective and safe preoperative localization method for ipsilateral multiple pulmonary nodules.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-901/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-901/dss

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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 the First Affiliated Hospital of Guangzhou Medical University (No. 2020K-43) and individual consent for this retrospective analysis was waived.

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