Application of Electromagnetic Navigation Bronchoscopy in the early diagnosis and treatment of lung cancer: a narrative review

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Abstract: The diagnosis of lung cancer has long been a problem facing clinicians worldwide, and the emergence of electromagnetic navigation bronchoscopy (ENB) has played a critical role in the early diagnosis of lung cancer. Compared with other types of biopsy techniques (e.g., transthoracic needle biopsy, bronchoscopy, thoracoscopic biopsy, and thoracotomy), ENB guarantees high diagnostic accuracy and safety. In recent years, with the continuous development of ENB technology, the scope of its epitaxy has also expanded. This technology is no longer a simple auxiliary diagnosis test but an innovative technology that simultaneously assists in surgical treatment, opening new avenues of research for the treatment of early-stage lung cancer. However, ENB, as a human-mediated operating system, has some limitations and uncertainties in its actual clinical application and promotion, which need to be addressed as we continue to develop ENB technology. In response to the bottleneck in developing ENB technology in current clinical diagnosis and treatment, relevant scientific research and development personnel and clinicians have also performed continuing exploration and improvement of methods. However, to completely overcome the limitations of ENB, more technological innovations are needed. In this review, we describe the current major clinical application directions, application advantages, and limitations of ENB.

Keywords: Electromagnetic navigation bronchoscopy (ENB); biopsy; video-assisted thoracoscopic surgery (VATS); radiofrequency ablation (RFA); limitations

Introduction

Lung cancer is a leading cause of cancer-related death in China and worldwide (1). Most of the diagnoses of lung cancer occur at advanced stages with a poor prognosis and a 5-year overall survival rate of 17%. Moreover, patients with an early diagnosis have a 5-year survival rate of 70%.

These numbers indicate that the early diagnosis of lung cancer is essential for improving the prognosis and survival rate of patients. Patients with early-stage lung cancer usually present with no clear signs or symptoms but solitary pulmonary nodules (SPNs) on chest radiograms. With the increase in public health literacy and advances in chest

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imaging technology, the prevalence of pulmonary nodules has increased in recent years. Notably, the false-positive rate (FPR) of low-dose spiral CT can be as high as 96.4% (2). That is to say, 96.4% of the positive screening results in the low-dose CT group were false-positive results. Therefore, precisely diagnosing lung cancer in its early stage has become one of the most urgent tasks facing oncologists (3).

The common invasive diagnostic tests for SPNs include transthoracic needle biopsy, bronchoscopy, thoracoscopic biopsy, and thoracotomy, in which the sensitivity of transthoracic needle biopsy to peripheral malignant nodules can reach 81–97% (4-6). However, such complications as pneumothorax and bleeding are common in this type of invasive diagnostic test (7). A population-based study of more than 15,000 patients showed a 15% incidence of pneumothorax (40% of patients required chest tube placement) (8). Conventional bronchoscopy is an essential tool for diagnosing lung lesions with a low chance of complications (<1%), but its sensitivity toward peripheral nodules is merely 18–62% (9,10). Although the chest surgical method has high diagnostic accuracy, it has a strong effect on the patient's health status, and wedge-shaped resection or segmental resection of the lung lobe must be performed where the lung nodules are located, usually leading to an adverse effect on the prognosis of the patient. When the pathological result is a benign lesion, contradictions and disagreements between doctors and patients may ensue; thus, pre-surgery assessment of the nodules is vital.

With the evolution of bronchoscopy, its higher safety and yield are receiving increasing attention. Electromagnetic navigation bronchoscopy (ENB) has been used in the diagnosis of clinical SPNs since 2000, and it has been widely used in clinical practice because of the abovementioned characteristics. ENB combines virtual bronchoscopy and electromagnetic localization technology to obtain pathological examination of diseased tissue by transbronchial lung biopsy (TBLB) or transbronchial needle aspiration (TBNA) in real time and accurately through biopsy channels. At the same time, ENB can be used as a surgical auxiliary treatment by positioning the peripheral SPNs or mediastinal and hilar lymph nodes of the lung that cannot be reached by conventional bronchoscopy. In recent years, a new generation of assisted navigation technology represented by the SPiN Thoracic Navigation System has also gradually emerged. Prior to the CT scan, stickers equipped with electromagnetic sensors were placed on the patient's chest and kept in place during the procedure to help guide navigation and track the patient's breathing (*Figure 1A,B*). Next, a highly accurate 3D map of the lungs that can quickly calculate the shortest path from the lesion and accurately guide the positioning path was synthesized according to the inspiration/expiration CT scanning protocol, providing more strategies for the diagnosis and treatment of peripheral lung lesions.

ENB exhibits a combination of superior diagnostic efficacy, safety, and short positioning time (11-13) and is widely employed in major clinics for the early diagnosis and treatment of lung cancer. However, this technology is subject to a number of limitations and uncertainties in the application process. The following is a summary of the advantages and disadvantages of this technology.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-3020).

Methods

We systematically reviewed 63 research articles and review articles concerning ENB that were published between 1991 to 2021 and combined the system composition, operation methods, and practical applications of ENB in clinical practice. Finally, the bottlenecks and difficulties faced by ENB in the development and promotion process were analyzed based on the actual situation of the diagnosis and treatment of ENB in the current application.

Medical application and safety

The ENB operating system includes the main body of the tracheal mirror magnetic navigation system, electromagnetic board, navigation positioning catheter, tracheal mirror working channel extension catheter and navigation positioning sensor (*Figure 1C,D*). To operate ENB, the prior chest thin layer CT image is used for 3D reconstruction to establish a navigation route, and the guiding catheter is subsequently carried in the bronchoscopy to reach the lesion. Because the guiding catheter tip carries the electromagnetic positioning sensor, the lesion location can be reproduced in real time onto the pre-generated lung 3D roadmap. The patient lies on the magnetic plate such that the whole chest is in a weak magnetic field, and a special curved catheter with a microsensor inserted into the head end extends into the bronchial cavity. Finally, the catheter can be accurately delivered to the site where the lesion is located for a needle biopsy (*Figures 2,3*).
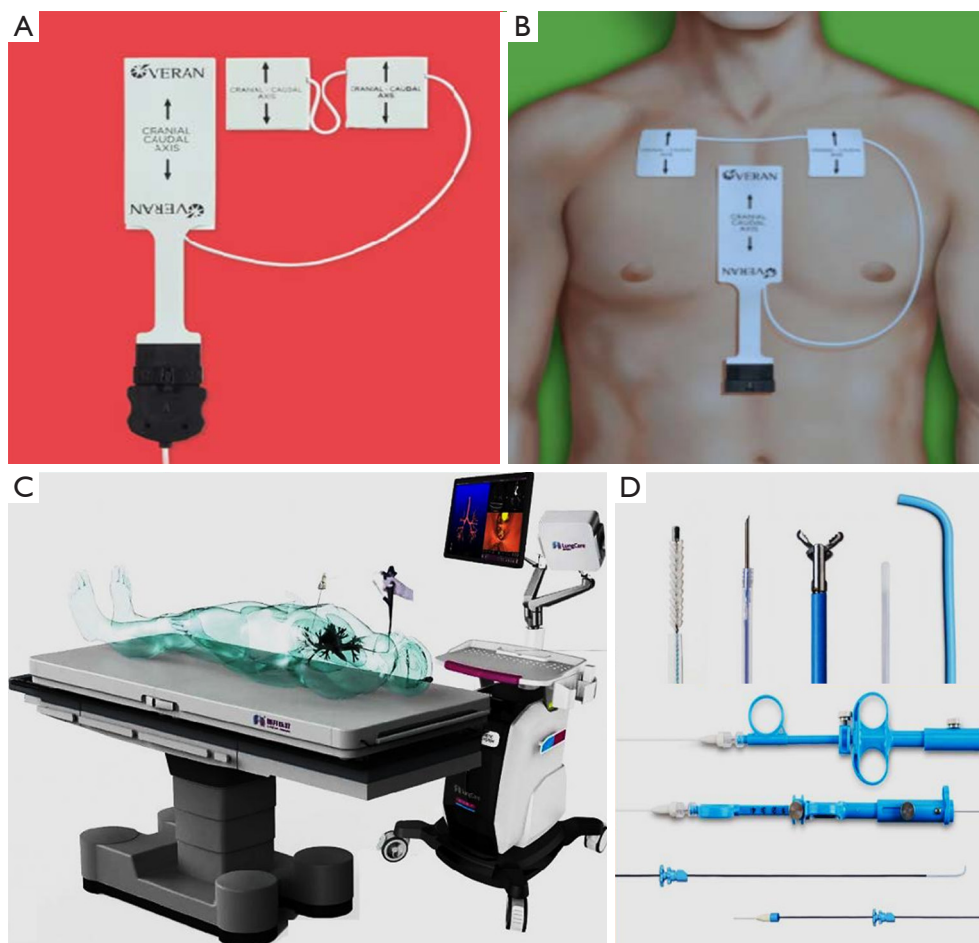
Figure 1 Compositions of ENB operating system. (A) Stickers. (B) Paste method. (C) Tracheal mirror magnetic navigation system, electromagnetic board, navigation positioning catheter, tracheal mirror working channel extension catheter and navigation positioning sensor. (D) Commonly used biopsy devices, including biopsy forceps, biopsy brushes, puncture needles, etc.

Pulmonary nodule biopsy

Since Solomon *et al.* (14) first reported the use of ENB in 1998, ENB has been widely used in clinical diagnosis and research. A meta-analysis on the accuracy and safety of ENB in the diagnosis of intrapulmonary nodules in 2014 (10) showed that the sensitivity of ENB for the diagnosis of lung cancer was 71.1%, the negative predictive value was 52.1%, and the incidence of pneumothorax was 3.1%, 1.6% of which required closed thoracic drainage. Another study in 2016 indicated an overall diagnostic yield of ENB of approximately 60% (15). A prospective multicenter study in 2017 (16) showed that ENB successfully guided 910 subjects (94.4%) and 1,036 lesions (91.8%) for biopsy, during which the rates of pneumothorax, bronchopulmonary hemorrhage, and respiratory failure were 4.9% (grade 2 or higher: 1.0%),

2.3% (grade 2 or higher: 2.3%), and 0.6%, respectively. Another large, multicenter cohort study (17) showed that approximately three-quarters of patients with evaluable lung lesions could be safely diagnosed in all medical institutions and in all challenging areas of the lung. The above findings provide a comprehensive indication that the use of ENB in lung nodule biopsy is safe and effective. Additionally, nodules located in the upper lobe or middle lobe of the right lung, nodules with a long diameter greater than 20 mm, small registration errors, bronchial aeration signs at the lesion site, and lymph node sampling were associated with an increased rate of ENB diagnosis. Additionally, a study has shown that the combined use of the radial scans of the endobronchial ultrasound probe (RP-EBUS) can increase the diagnostic yield of ENB for lung nodules to
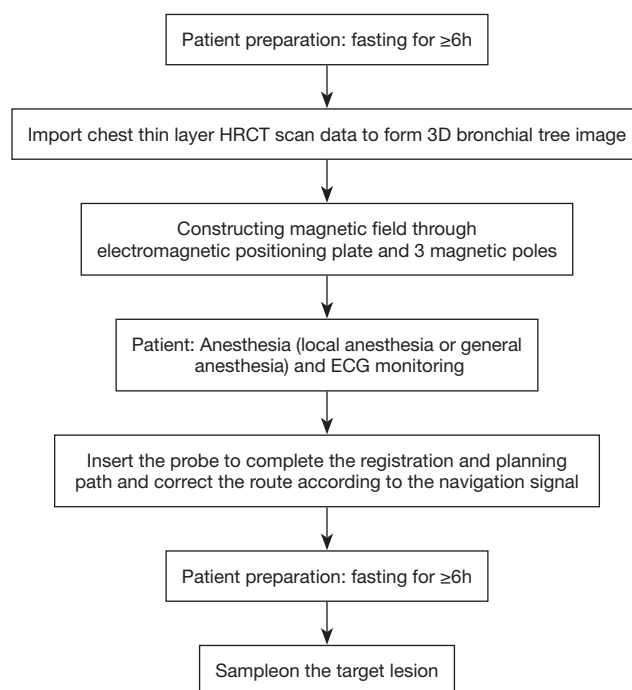
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Figure 2 Operation flow of ENB for SPN. HRCT, High-resolution computed tomography; ECG, Electrocardiogram; ENB, electromagnetic navigation bronchoscopy; SPN, solitary pulmonary nodules.

87.5% (18).

To further improve the diagnostic efficacy of ENB, Pritchett *et al*. (19) performed a biopsy of a pulmonary nodule with a median lesion size of 16.0 mm (range 7–55 mm) using cone beam CT-enhanced fluoroscopy combined with ENB. With a safety margin of 4%, the diagnostic accuracy rate obtained by these researchers reached 93.5%. However, patients using this technique received an average radiation dose of 2.0 mSv each time. Therefore, reducing the radiation dose is very beneficial to patients and doctors. Because the lung tissue has an air-filled alveolar structure, the natural contrast of the lung tissue structure is higher than that of air. Therefore, to a certain extent, reducing the tube current and tube voltage has no pronounced effect on the display and positioning of lung tissue lesions. Additionally, effectively reducing the repeated guidance and positioning of CT is an auxiliary improvement measure to reduce the radiation dose. These measures have effectively reduced the radiation dose and considerably reduced the loss of the tube and detector (20,21).

He *et al*. (22) showed that the diagnostic yield of ENB guidance cryobiopsy (ENBCB) for lung nodules less than 3.0 cm was 89.2%. Unfortunately, because of the use of cryosurgery, the complication rate of mild to moderate

bleeding was 40.5%. To reduce the occurrence of this complication, the clinic has also made further improvements and provided guidance. First, the freezing time of the probe site must be strictly controlled. Second, cryosurgery should be performed on the lung periphery where the blood vessel density is low. When performing operations on the area close to the hilar where the blood vessel density is high, norepinephrine can be injected into the airway in advance to contract the blood vessels properly. Finally, the balloon can be preinstalled before surgery to prepare for closure. Abundant clinical experience and skilled operation are also important factors in reducing bleeding complications.

Lymph node biopsy

Accurately determining the stage of early lung cancer is of great significance for treatment options and prognosis. In recent years, with insight into ENB, its diagnostic value and safety for lymph node metastasis and lung cancer staging have also been affirmed. Gildea *et al*. (23) performed ENB biopsy on enlarged lymph nodes (28.1±12.8 mm) in 60 patients for the first time in 2006 and obtained an overall success rate of 100%. A recent study compared the diagnostic value of ENB versus C-TBNA-guided TBNA
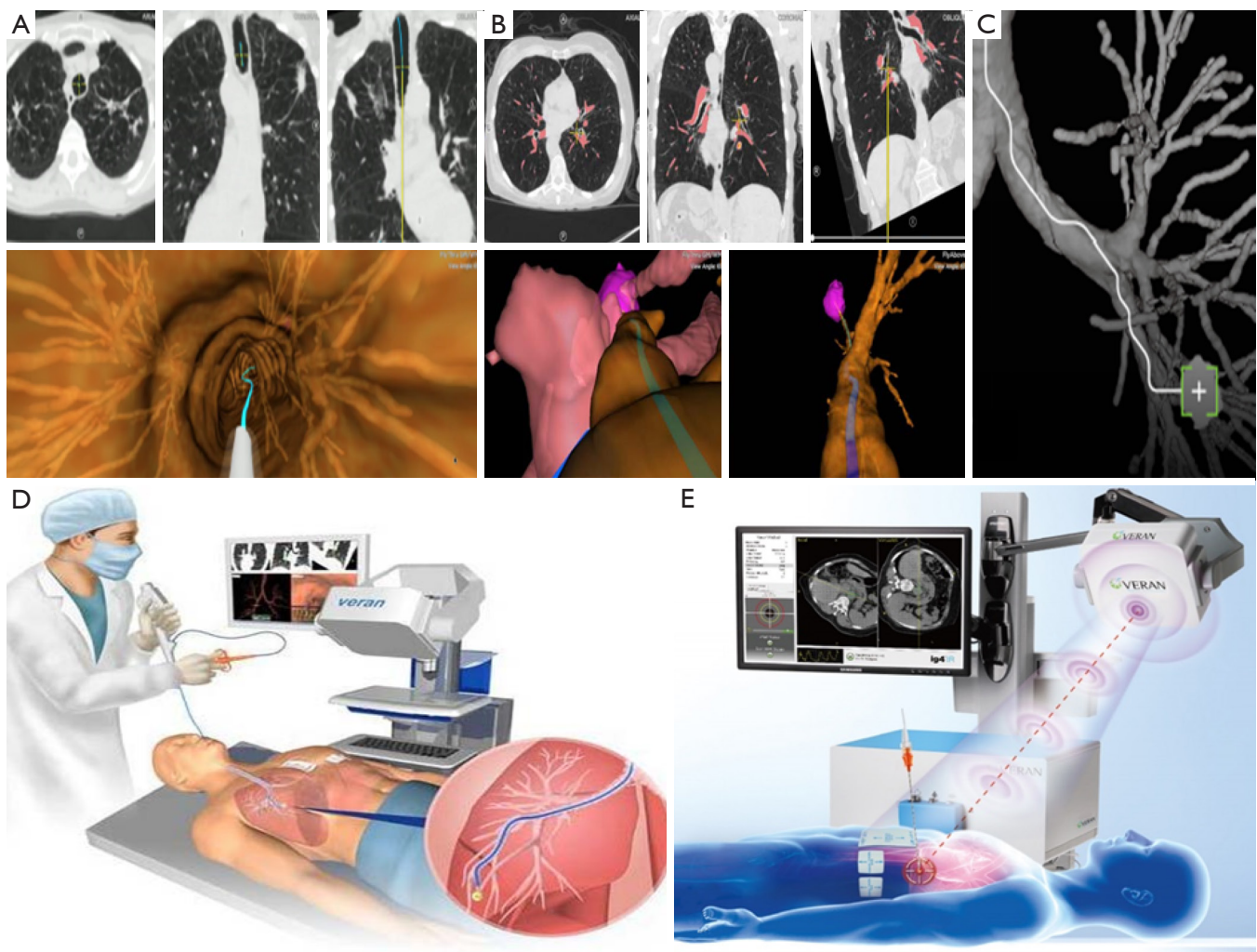
Figure 3 Implementation path of ENB technology. (A) Data collection. (B) Data processing. (C) Preoperative planning and shortest path calculation. (D) Real-time navigation. (E) Location and biopsy of lesions.

in mediastinal and hilar lymphadenopathy. The results showed that the diagnostic yield of ENB-TBNA was 72.8% compared with only 42.4% for C-TBNA (24) according to pathological confirmation. ENB combined with rapid on-site evaluation (ROSE) had a success rate of 82.1% for lymph node biopsies less than 15 mm and 89.4% for lymph node biopsies larger than 15 mm (25).

Moreover, ENB-TBNA also has a greater advantages than EBUS-TBNA. EBUS-TBNA has relatively strict requirements on the location and growth characteristics of lymph nodes. When enlarged lymph nodes are located close to the hilar and grow outside the trachea, EBUS-TBNA can achieve a higher biopsy success rate. However, once there is a tissue partition between the enlarged lymph node and

airway, the ultrasound probe cannot detect the lesion well, resulting in a greatly reduced biopsy success rate. ENB-TBNA is less affected by the above factors. For swollen lymph nodes that are not adjacent to the hilar, biopsy can still be performed under the conditions of no adherent growth and increased tissue separation from the airway.

In summary, ENB-guided lymph node biopsy not only has a higher diagnostic and sampling rate but also has less restriction and higher safety, during which the complication rate is only 1.2–3.5% (23,26).

Preoperative positioning of pulmonary nodules

In the early surgical treatment of lung cancer, thoracic

surgeons use more video-assisted thoracoscopic surgery (VATS) because of the advantages of smaller trauma, faster postoperative recovery, and safer surgical procedures than open lobectomy (2,27). However, this minimally invasive procedure is often difficult to identify for pulmonary nodules less than 1 cm during surgery (28,29). Once VATS fails to accurately identify and locate the nodule, it may be temporarily changed to thoracotomy with a risk of surgical resection failure (30). Studies have shown that VATS can result in up to a 46% conversion rate for thoracotomy in the event of failure to accurately identify lesions (28).

Clinical methods for the localization of small lesions include hookwire localization, coil localization, staining labeling localization and fiducial labeling localization (31-35), in which methylene blue *in situ* staining does not affect the pathological evaluation of excised specimens (36). Thus, it is more common to use methylene blue to stain the nodules, particularly after positioning under ENB guidance. Methylene blue can mark lung nodules more effectively. Marino *et al*. (37) recently conducted a large-scale clinical study of methylene blue staining of pulmonary nodules under ENB navigation. These researchers showed a 97.2% success rate and a 100% VATS nodule resection rate for a lung nodule with a median size of 8 mm (range, 4–17 mm). Additionally, no adverse events occur during the marking process under navigation. These results indicate a safer and more effective technique of assisting VATS in removing small pulmonary nodules. The report by Sun *et al*. (38) described a new method for locating pulmonary nodules with ENB-guided injection of methylene blue combined with percutaneous hookwire localization for patients with positive bronchial signs that was also proven to be safe and effective.

Radiofrequency ablation of lung cancer

For patients with early-stage non-small-cell lung cancer and partial lung metastases, surgical resection is the preferred treatment (39-41); however, not all patients have physical conditions that meet surgical requirements because of the presence of comorbidities or other contraindications. Therefore, for patients who cannot tolerate surgery, stereotactic radiotherapy or radiofrequency ablation (RFA) is recommended (42,43). Stereotactic radiotherapy is a noninvasive treatment, but its efficacy is restricted because of multiple factors, such as respiratory movements, treatment times, cost and complications of radiation pneumonitis. RFA is a promising alternative therapy with

overall survival data showing similar therapeutic effects to subarachnoidectomy and radiation therapy (44-46). However, percutaneous puncture in RFA often causes complications, such as pneumothorax, hemothorax, bronchopleural fistula and pleural effusion, exhibiting an incidence of 15.2–55.6% (44,47-49). Additionally, percutaneous puncture has difficulty reaching some specific anatomical sites and may cause tumor pleural metastasis or direct spread. However, RFA under bronchoscopy can effectively reduce these serious complications (50). Koizumi *et al*. (51) demonstrated for the first time that bronchoscopy-guided RFA is a safer and more effective method. Compared with ordinary electronic bronchoscopy, ENB not only can achieve navigation for peripheral lung lesions accurately but can also be used to place therapeutic tools and ablation catheters (52,53). A recent study showed that RFA under ENB navigation is a potentially effective treatment for patients with early-stage lung cancer or lung metastasis. However, limited by the navigation characteristics and heating radius, ENB-guided RFA is only suitable for lesions with a bronchial sign of less than 30 mm on chest thin-slice CT (54).

Discussion

The emergence of ENB has considerably improved the diagnostic efficiency of early lung cancer. However, compared with the results of 2007–2018 (9,15,18,19,25,38,55-58), the diagnostic efficiency of ENB alone has not improved significantly in the past 10 years (*Table 1*). The bottleneck restricting the further improvement of ENB diagnostic efficiency is largely the uncertainty associated with biopsy. Specifically, the objective factors of the patient's lung lesions (e.g., whether there is tracheal access in the lesion, whether the ENB probe can reach the lesion site, whether the lesion is positioned accurately, and the choice of biopsy method) and the subjective factors of ENB operators (e.g., experience, proficiency, correctness of clinical decision-making) collectively lead to uncertainty. In the case of ENB combined with other discriminant techniques for the diagnosis of early-stage lung cancer, the safety and effectiveness of the operation cannot be ensured at the same time, except for EBUS and ROSE (18,19,22,25), fully demonstrating the limitations of ENB in the diagnosis of early-stage lung cancer.

First, the location of the SPN has the most important effect on the efficacy rate of ENB. Clinical studies have

Table 1 Diagnostic yield of ENB for SPN

Study	Number of patients/lesions	Mean diameter mm	Navigate and assistant techniques	Diagnostic yield %
Makris, 2007 (55)	40/40	23.5	ENB	62.5
Eberhardt, 2007 (18)	39/39	28.0	ENB	59.0
Bertoletti, 2009 (56)	54/54	31.2	ENB	61.1
Al-Jaghbeer, 2016 (15)	92/98	26.0	ENB	60.0
Eberhardt, 2007 (18)	40/40	24.0	ENB+RP-EBUS	87.5
Lamprecht, 2009 (57)	13/13	30.0	ENB+ROSE	76.9
Lamprecht, 2012 (58)	112/112	27.1	ENB+ROSE	83.9
Karnak, 2013 (25)	54/103	16.5	ENB+ROSE	83.3
Pritchett, 2018 (19)	75/93	16.0	ENB+CBCT	93.5
He, 2019 (22)	37/37	21.0	ENBCB	89.2

ENB, Electromagnetic navigational bronchoscopy; RP-EBUS, Radial probe-endobronchial ultrasound; ROSE, Rapid on-site evaluation; CBCT, Cone-beam computed tomography; ENBCB, Electromagnetic navigation bronchoscopy guidance cryobiopsy.

shown that lesions in the upper and middle lobes of the right lung have higher diagnostic efficiency than other lung lobes using ENB (58). Being affected by the pulsation of the heart and great blood vessels, the left lung has greater mobility than the right lung. At the same time, being affected by respiratory movement, the lower lobe of the lung has greater mobility than the upper lobe (59). These differences can cause ENB navigation and positioning errors, which affect the diagnostic yield. Of course, research on ENB has also made further improvements to reduce errors in clinical applications. On the one hand, the CT data near the examination date (the same day or day before) are used to reconstruct the lung images accurately. On the other hand, a respiratory gating system is introduced based on ENB to restore the patient's accurate image data through respiratory compensation. However, it remains difficult to completely overcome the positioning errors caused by cardiovascular pulsation and respiratory motion. Additionally, studies have shown that the inner two-thirds of the lung using ENB biopsy is twice as large as the peripheral third diagnosis, and the yields in the central, intermediate, and peripheral lesions are 82%, 61%, and 53%, respectively (P=0.05) (9). In addition to the lesions near the periphery of the lung being more affected by respiratory movement, the ability to accurately detect, locate and biopsy the lesions is also an important reason for this phenomenon. In particular, ENB's endoscopic probe cannot reach the airway after level 12 because of its outer diameter and supporting force. Thus, ENB also focuses on developing transparenchymal nodule access (ENB-TPNA) technology in terms of technical exploration. The principle is to make an "artificial tunnel" leading to the lesion in the adjacent airway of the lesion that has no tracheal access or where the probe cannot reach and subsequently biopsy the lesion through this passage. However, the technology is still in the stage of continuous exploration and has not been popularized to date. Second, the size of the SPN is also a major factor affecting the efficacy of ENB. Compared with lesions larger than 20 mm, the diagnostic yield of peripheral lesions less than 20 mm is lower (60) and has become a consensus in the use of ENB. If ENB positioning technology is combined with percutaneous lung biopsy technology, it can effectively improve the diagnostic performance of lesions with a peripheral diameter of less than 20 mm. Currently, the 4D electromagnetic navigation system developed by related companies is working on this exploration. Third, the location of tumor cells within the SPN directly affects the positive rate of biopsy. Usually, the biopsy tool is located at the geometric center of the lesion. If most of the tumor cells in the lesion are located on the surface or periphery of the lesion, it will affect the accuracy of biopsy. Fourth, the choice of biopsy method, such as bronchoscope needle brushing, bronchial needle aspiration, or bronchial forceps biopsy, can also affect the performance and accuracy of ENB (61,62).

The clinical practice of ENB and its extensive utilization present several uncertainties that require further consideration. The first is that the diagnostic efficiency of

the actual clinical application of ENB technology is uneven at each medical center because of discrepancies in skills among ENB inspectors and medical instruments, such as the thin-slice CT scanning technology of the chest. These differences can be decisive in the promotion and extension of ENB. Second, compared with other endoscopy and navigation techniques, ENB has not significantly improved the diagnostic performance of lesions close to the hilar, such as biopsy of hilar enlarged lymph nodes, lesions in the large airways, and other easier-to-reach lesions. It is possible to use ordinary endoscopy techniques to achieve high-efficiency diagnostic capabilities. The choice of ENB biopsy strategy at this time will probably increase the burden on patients and the workload of doctors. Therefore, the use of ENB should be considered based on actual conditions. Finally, the choice of local anesthesia and general anesthesia has no significant effect on the diagnostic yield of ENB (63). For the clinical operation of ENB within the specific purposes, physicians must further investigate the selection of anesthesia method to raise the diagnostic yield of lung cancer in the early stage, highlighting the patients' outcomes and their long-term benefits.

Conclusions

The extensive utilization of ENB has provided an alternative for doctors in the clinical diagnosis and treatment of lung cancer. Because of its higher safety and efficacy, ENB shows unique advantages in the diagnosis and treatment of early-stage lung cancer. It also compensates for blind spots in peripheral lung lesions and minimizes unnecessary complications compared with surgery and standard biopsy. Consistent with advances in recent years, the diagnostic efficiency of ENB has escalated with the combination of various navigation and biopsy techniques, performing as an assistant diagnostic approach in determining lesion locations. Therefore, the promotion of ENB in clinical application helps to elucidate the precise diagnosis of lung cancer in the early stage, and navigation-based treatment also illustrates its potential in performing a precise biopsy for diagnosis and even radical treatment. However, the limitations of this technique cannot be denied. Whether ENB can be used in first-line diagnostic examinations warrants further study.

Acknowledgments

Footnote

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