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Electromagnetic Navigation Bronchoscopy Combined Endobronchial Ultrasound in the Diagnosis of Lung Nodules

Nan Wang, MD[a], Haitao Ma, PhD[b], Haitao Huang, PhD[b,*], Yu Feng, PhD[b]

Abstract

Electromagnetic navigational bronchoscopy (ENB) combined with a radial endobronchial ultrasound probe realizes a combination of magnetic navigation and ultrasound imaging, allowing for the accurate navigation of peripheral lung lesions in real time during surgery. ENB has been evaluated in many studies. However, a comparative report on the feasibility of ENB combined radial endobronchial ultrasound diagnosis in different density lung nodules was small, and few of these studies have reported long-term follow-up results to exclude false negative results. The aim of this study is to explore the applicability of ENB combined radial endobronchial ultrasound in the diagnosis of lung nodules with different densities.

Patients underwent biopsy in our medical center from 2016-09 to 2019-03 were divided into 2 groups: the solid nodule group and the subsolid pulmonary nodule group. We collected and analyzed the diagnostic accuracy, the diagnostic yield, the false negative rate and the incidence of complications between these 2 groups.

A total of 37 lesions in 25 patients were biopsied, 14 lesions were subsolid pulmonary nodules and 23 were solid nodules. The diagnostic accuracy (success rate to obtain meaningful pathology tissues) was 34/37 (91.8%). Lost to follow-up in 1 case and three cases were undiagnosed. After at least 12 months of follow-up, the total diagnostic yield (true positive rate+ true negative rate) was 27/36 (75%) ($P = .006$). The false negative rate was 9/19 (47.3%) ($P = .26$). Complications occurred in 1/36 (2.7%) lesions. For the subsolid pulmonary nodule group, the diagnostic accuracy was 13/14 (92.8%) and the diagnostic yield was 7/14 (50%). For the solid nodule group, the diagnostic accuracy was 21/23 (91.3%), and the diagnostic yield was 20/22 (90.9%).

Electromagnetic navigational bronchoscopy combined with radial endobronchial ultrasound in peripheral lung nodule biopsies is safe and effective, especially for solid nodules, but the diagnostic yield in subsolid nodule biopsies remains to be improved.

Abbreviations: CT = computed tomography, ENB = electromagnetic navigational bronchoscopy, EWC = extended working channel, FN = false negative, PTLB = percutaneous lung biopsy, R-EBUS = radial endobronchial ultrasound, SN = solid nodule, SSN = subsolid pulmonary nodule, TPNA = = transthoracic percutaneous fine needle aspiration.

Keywords: biopsy, early diagnosis, electromagnetic navigational bronchoscopy, pulmonary nodules, radial endobronchial ultrasound

1. Introduction

Currently, the incidence and mortality of lung cancer are still the highest among different types of cancer in the world. The incidence of lung adenocarcinoma, which occurs in the peripheral region of the lung, has exceeded that of lung squamous cell carcinoma, which occurs in the hilar region and ranks first in lung malignant tumors.[1,2] The conventional fiberoptic bronchoscope cannot reach the subsegmental bronchi or the lower bronchus because of the larger dimeter.[3] Meanwhile, percutaneous lung biopsy (PTLB) is accompanied by an increased risk of

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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pneumothorax between 19% to 25%, with 4% to 18% requiring chest tube drainage[4,5] and a false negative rate of approximately 49%. Furthermore, according to a recent meta-analysis, the diagnostic accuracy was only 60% when using PTLB to biopsy SSNs.[6] If the lesions are in a special position, such as the apex pulmonis, interlobar fissure, base of pulmonis or hilus pulmonis, the diagnostic rate of PTLB is further reduced. The application of these 2 conventional techniques is limited in actual clinical work. Therefore, diagnosing peripheral pulmonary nodules in the early stage, especially solitary pulmonary nodules (SPNs) found in regular medical examinations, is extremely important in the secondary prevention of lung cancer.[7]

Electromagnetic navigational bronchoscopy (ENB)[8,9] has been used in China for more than 5 years as an emerging technology. Compared with conventional biopsy techniques, the main advantages of this technology are as follows: using natural orifices that would significantly reduce complications such as pneumothorax and hemothorax associated with biopsy; an electromagnetic navigation system can be utilized in real-time and can reach the subsegmental bronchi or the lower bronchus, realizing high-precision and wide-ranging lesion biopsy. However, this technique also has certain limitations: if the lesion is located at the bottom of the lung with large respiratory motion, even the software compensates for the respiratory motion, and the accuracy of navigation can be reduced.[10–13] If the computed tomography (CT) image used in preoperative path planning has poor quality or if the navigation path calculated by the computer software exhibits deviation, accurate navigation cannot be performed. Therefore, using this technology alone has its limitations. On this basis, ENB technology has been improved.

ENB can be combined with radial endobronchial ultrasound (R-EBUS) such that the radial endobronchial ultrasound probe is placed in the ENB extended working channel (EWC) to perform real-time B-ultrasound examination of the tissue surrounding the lesion.[14–16] Even in the case of intraoperative navigational deviation or large respiratory motion, accurate biopsy can be performed according to the imaging manifestations of R-EBUS.

However, most studies only reported the impact of lesion diameter, lesion location, and imaging signs on the diagnostic yield, without further grouping lesions in terms of density. Now that the detection rate of ground glass lung nodules is relatively high, we believe that subgroup analysis of lesion density is more guiding significance for selecting suitable patients for ENB examination in the future. A comparative report on the feasibility of ENB combined R-EBUS diagnosis in different density lung nodules was small, and few of these studies have reported long-term follow-up results to exclude false negative results. The aim of our study is to explore the applicability of ENB combined with R-EBUS in the diagnosis of lung nodules with different densities. Thus, data from our medical center were collected. After completion of follow-up procedure, a retrospective study was conducted on the feasibility of ENB combined with R-EBUS biopsy of lung nodules and the factors that may affect the diagnostic yield. At the end of the article, we made a preliminary exploration on how to further improve this technology.

2. Patients and methods

2.1. Ethics approval

This study is being conducted in accordance with the Declaration of Helsinki and approved by the First Affiliated Hospital of Soochow University. Informed consent of all patients has been obtained. Ethical approval number: (2019) Hospital Ethics Committee of the First Affiliated Hospital of Soochow University No.044.

2.2. Pre-procedure assessments

All patients undergoing ENB between 2016-09 and 2019-03 at department of thoracic surgery of the First Affiliated Hospital of Soochow University, a 3A grade teaching hospital in southeast China. A total of 37 lesions in 25 patients were biopsied, and all patients completed a preoperative examination to exclude surgical contraindications. All lesions were examined by high-resolution computed tomography to confirm the presence of lesions before the surgery. According to the different densities of the imaging findings, the lesions were divided into 2 groups: the solid nodule (SN) group and the subsolid pulmonary nodule (SSN, including partial solid nodules and pure ground glass nodules).

The patient inclusion criteria included the following: age > 18 years old; cardiopulmonary function can tolerate ENB operation and general anesthesia; chest CT clearly resulted in the diagnosis of pulmonary nodules that required biopsy; peripheral lesions can hardly be reached by conventional bronchoscopy during preoperatively planning; and the patient had no anesthesia contraindications. The patient exclusion criteria were as follows: age < 18 years; cardiopulmonary function cannot tolerate ENB operation and/or general anesthesia; or the patient had coagulopathy or organ dysfunction.

2.3. Procedure

We used the superDimension^{TM} V.6 (Medtronic, Minneapolis, MN) navigation system for all ENB procedures. The ENB operating instrument includes a bronchoscope, EWC, a flexible and locatable guide tube combined with a sensor that can accept electromagnetic signals, biopsy tools and radial endobronchial ultrasound. All patients underwent preprocedure high-resolution computed tomography chest scans chest scans, and imaging data were exported in the DICOM format to a dedicated computer equipped with magnetic navigation path planning software inReach^{TM} to reconstruct virtual bronchial tree and plan the navigation paths. Then, 6 land markers were set on the virtual bronchial tree. The patient was placed in the horizontal recumbent position, and 3 electromagnetic emitters were placed separately at the sternal stalk and at the junction between the bilateral axillary midline and the eighth rib. Electromagnetic emitter and the tracking board create a magnetic field around the chest. The position was adjusted to ensure the patient's chest and 3 electromagnetic emitters were completely covered by the magnetic field during the ENB operation. All patients were under general anesthesia.

At the beginning of the biopsy, the positioning guide tube with the magnetic field sensor was passed through the EWC and sent to the 6 preoperatively planned landmarks so that the actual fiberoptic bronchoscopy image and the virtual bronchial tree image could be mutually matched. Then, after matching was complete, real-time navigation could be performed, and the radial endobronchial ultrasound was placed in the preplanned lesion position to detect abnormal echo (Fig. 1). The biopsy was performed using 3 methods: brush biopsy, biopsy forceps, and bronchoalveolar lavage. The ENB examination was performed

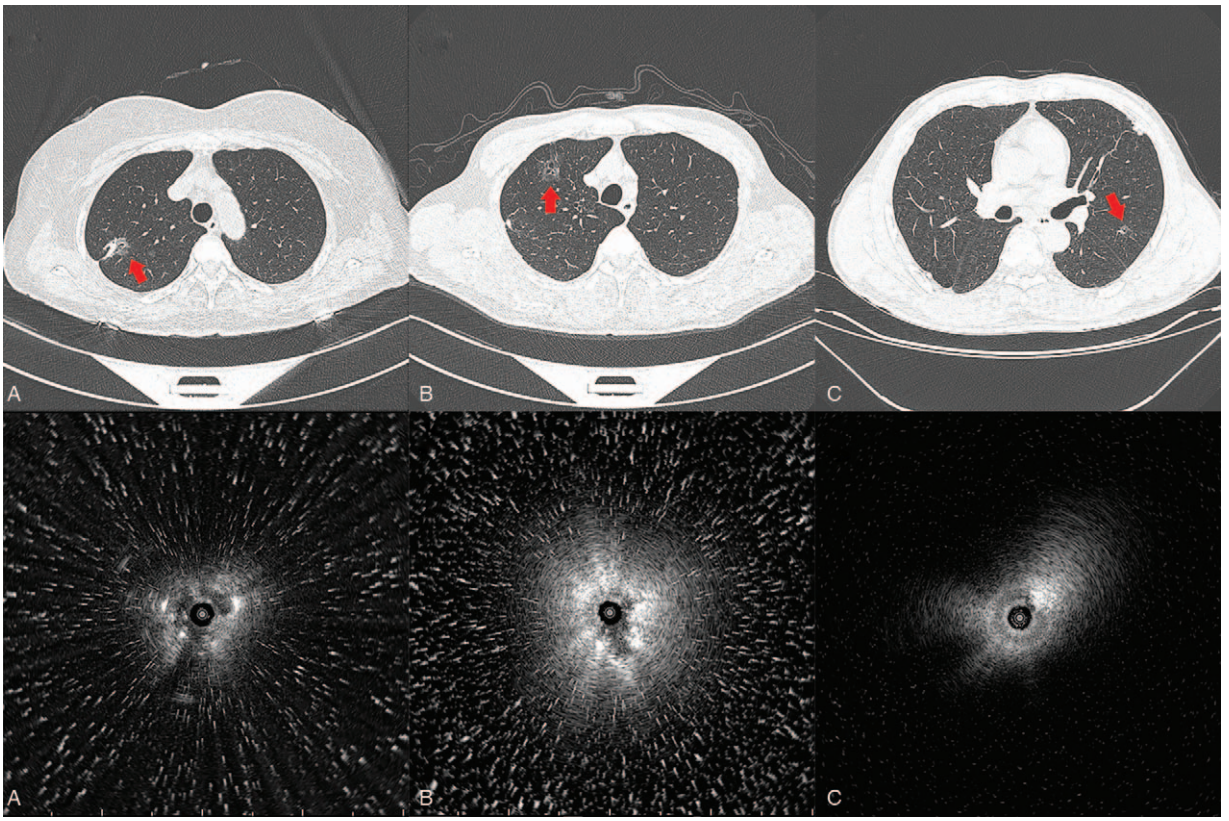

Figure 1. Imaging characteristics in different density lung lesions. All 3 cases had confirmed pathological diagnoses of invasive adenocarcinoma by VATS biopsy. A, PSN with imaging changing on R-EBUS; B, pGGO with imaging changing on R-EBUS; C, pGGO without imaging changing on R-EBUS.

by 2 thoracic surgeons. The pathological examination was diagnosed and reviewed by 2 pathologists.

2.4. Pathological examination

Pathological tissues obtained by brush biopsy were used to make smears. After air-drying, smears were placed in anhydrous alcohol for exfoliative cytological examination and acid-fast bacillus test. Tissues obtained by bronchoalveolar lavage were used for liquid-based cytological testing. Tissues obtained by biopsy forceps were fixed by formalin solution, paraffin embedded, sectioned and stained with hematoxylin eosin for pathological examination. Then, according to the pathological test results, the next treatment plan was determined according to the flow chart (Fig. 2).

2.5. Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. The enumeration data are represented as n/N (%). The measurement data are represented as the mean ± standard deviation (mean ± SD). The Pearson's chi-squared test was used for comparison between the groups. A 2-tailed $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics of patients and nodules

A total of 37 lesions were biopsied in 25 patients, including 14 males and 11 females, with an average age of 66.8 (±7.57) years and an average lesion size of 23.3 (±10.08) mm. Fourteen lesions were SSNs, and 23 were SNs. Among them, 10 lesions were in the posterior area of the right upper lobe, 3 lesions were in the apical area of the right upper lobe, 2 lesions were in the anterior area of the right upper lobe, 3 lesions were in the posterior basal area of the right lower lobe, 2 lesions were in the medial basal area of the right lower lobe, 3 lesions were in the lateral basal area of the right lower lobe, 4 lesions were in the apicoposterior area of the left upper lobe, 4 lesions were in the superior lingular area of the left upper lobe, 2 lesions were in the posterior area of the left lower lobe, 2 lesions were in the anterior basal area of the left lower lobe and 2 lesions were in the lateral basal area of the left lower lobe (Table 1).

Navigation was completed for all lesions, and the success rate of navigation was 37/37 (100%). The diagnostic accuracy (success rate of ENB combined with R-EBUS to obtain meaningful pathology tissues) was 34/37 (91.6%). The pathological diagnoses of the biopsies were as follows: 7 cases of adenocarcinoma, 1 case of atypical adenomatous hyperplasia, 3 cases of non-small cell lung cancer, 3 cases of undetermined pathological classification of malignant tumor cells, 3 cases of heterocysts, 16 cases of inflammation, 1 case of tuberculosis and 3 cases of normal epithelial cells (Table 2).

Notably, we found that during the navigation when the sensor head was withdrawn and the biopsy tool was outstretched, the angle of the biopsy tool between the original angle of the sensor was changed due to the different component material of the biopsy tools (Fig. 3). The main reason for this deviation is that rubber is the main material constituting the EWC, and the biopsy tools are made of metal. During surgery, the biopsy tool passing

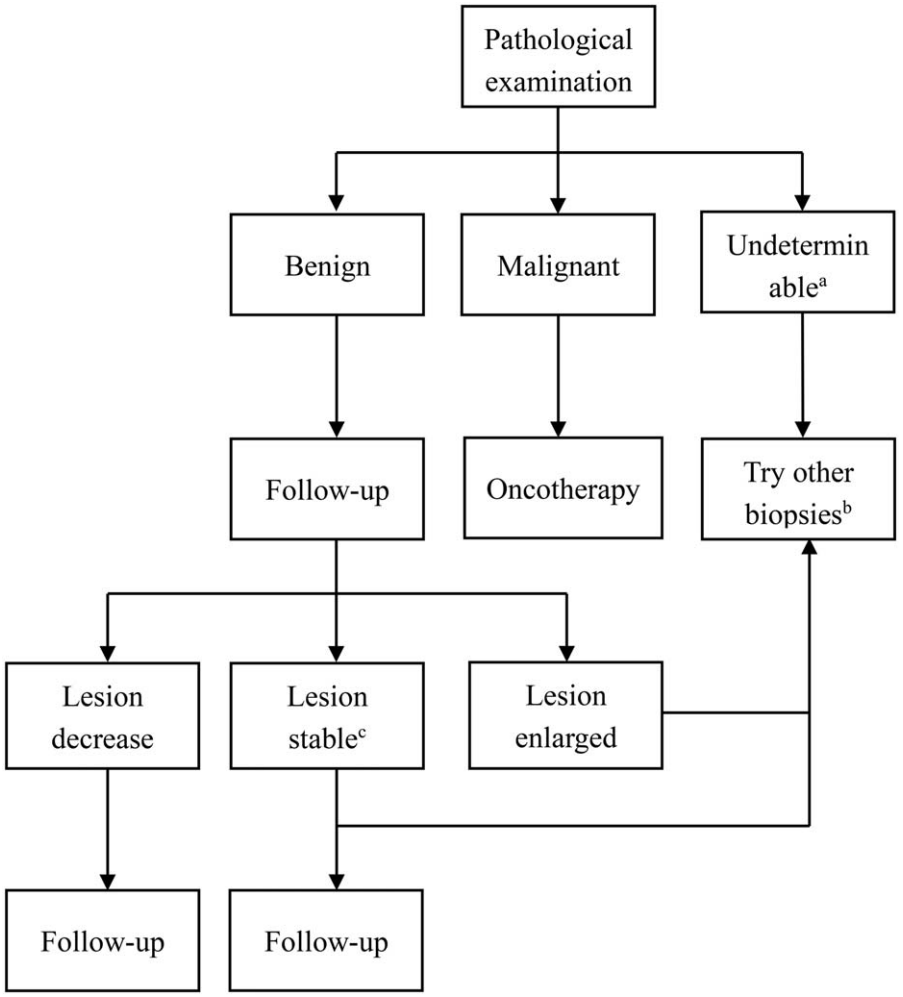

Figure 2. ENB postoperative procedure. [a]undeterminable including: pathological examination was benign or normal epithelial cells obtained, but the imaging findings were highly suspicious of malignancy; normal epithelial cells were detected, but could not be diagnosed because of the little cells amount. [b]other biopsies including: video-assisted thoracoscopic surgery biopsy, percutaneous lung biopsy, bronchoscopy and etc. [c]patient diagnosed as nonmalignant and lesion stable, but had high-risk nodules based on imaging findings would be recommended try other biopsies.

through the EWC will inevitably deform the EWC slightly. Especially after the biopsy forceps pass through the EWC in the closed state, it needs to be reopened to obtain tissue, and then return to the closed state to exit the EWC. In this case, using the handle to control the opening and closing of the biopsy forceps makes the tension change of the material more obvious, and the material deformation of the EWC is also more obvious.

Table 1

Clinical characteristics of SNs and SSNs.

Variables	SN (n = 23)	SSN (n = 14)	Total (n = 37)	*P* value
Age (yr) (±SD)	67.21 (±7.5)	66.14 (±7.95)	66.81 (±7.57)	.264
Gender, n (%)				.515
Male	12 (56.52)	9 (64.28)	21 (56.75)	
Female	11 (47.82)	5 (35.71)	16 (43.24)	
Nodule size (cm)(±SD)	23.98 (±8.11)	22.17 (±13.07)	23.3 (±10.08)	.383
Nodule location, n (%)				.772
RUL	9 (39.13)	6 (42.85)	14 (37.83)	
RML	0 (0)	0 (0)	0 (0)	
RLL	6 (26.08)	2 (14.28)	8 (21.62)	
LUL	4 (17.39)	4 (28.57)	8 (21.62)	
LLL	4 (17.39)	2 (14.28)	6 (16.21)	

LLL = left lower lobe, LUL = left upper lobe, RLL = right lower lobe, RML = right middle lobe, RUL = right upper lobe, SD = standard deviation, SN = solid nodule, SSN = subsolid pulmonary nodule.

Table 2

ENB combined with R-EBUS results.

Variables	SN (n = 23)	SSN (n = 14)	Total (n = 37)	*P* value
Pathological type, n (%)				
Adenocarcinoma	5 (21.73)	2 (14.28)	7 (18.91)	
AAH	0 (0)	1 (7.14)	1 (2.7)	
NSCLC	3 (13.04)	0 (0)	3 (8.1)	
Atypical cells	3 (13.04)	0 (0)	3 (8.1)	
Inflammation	6 (26.08)	10 (71.42)	16 (43.24)	
Normal epithelial cells	2 (8.69)	1 (7.14)	3 (8.1)	
Tuberculosis	1 (4.34)	0 (0)	1 (2.7)	
Unclassified malignant tumors	3 (13.04)	0 (0)	3 (8.1)	
Sensitive of biopsy tools, n (%)				.462
Brush biopsy	10 (50)	2 (28.57)	12 (44.44)	
Biopsy forceps	11 (55)	5 (71.42)	16 (59.25)	
Bronchoalveolar lavage	10 (50)	1 (14.28)	11 (40.74)	
Undiagnosed cases*, n (%)	2 (8.69)	1 (7.14)	3 (8.1)	.373
Diagnostic accuracy, n (%)	21 (91.3)	13 (92.85)	34 (91.89)	1
FN†, n (%)	2 (4.34)	7 (50)	9 (25)	.17
Diagnostic yield[2], n (%)	20 (90.9)	7 (50)	27 (75)	.014

AAH = atypical adenomatous hyperplasia, FN = false negative, NSCLC = non-small cell lung cancer, SN = solid nodule.

* normal epithelial cell considered as undiagnosed.

† excluded, lost to follow-up in 1 case.

3.2. ENB-related adverse events

No death due to lung cancer or ENB-related adverse events occurred within 12 months of follow-up. Pneumothorax occurred in 1 case (1/37, 2.7%). In this patient, the lesion was adjacent to the pleura and diaphragm, which suggests a relative contraindication of PTLB. The thoracic pleura was punctured because of unsatisfactory depth control during the biopsy. Closed thoracic drainage was performed immediately. One day after the operation, the patient recovered and was discharged from the hospital.

3.3. Diagnostic outcomes

We classified the lesions that met the following criteria as true positive (TP) results: the pathological diagnosis after subsequent diagnostic test was consistent with ENB biopsy. True negative results were other biopsy tests confirming a nonmalignant diagnosis or without lesion progression on imaging examination after at least 12 months of follow-up. False negative (FN) results showed that the ENB pathology diagnosis was nonmalignant after at least 12 months of follow-up, or there was lesion growth or malignancy confirmed by other biopsy methods. Treatment without a confirmed diagnosis or death due to lung carcinoma within 12 months follow-up procedure was also considered an FN result.

A follow-up procedure was performed in 20 patients after ENB biopsy diagnosis of nonmalignancy. One patient was excluded due to being lost to follow-up after at least 12 months. The total diagnostic yield (true positive rate+ true negative rate) was 27/36 (75%) and the diagnostic yield between SN and SSN group was statistically significant ($P = .006$). The FN rate of ENB was 9/19 (47.3%) ($P = .26$). The sensitivity rates of the 3 biopsy tools were 12/27 (44.4%) for brush biopsy, 11/27 (40.7%) for bronchoalveolar lavage and 16/27 (59.2%) for biopsy forceps. In the SSN group, the diagnostic accuracy was 13/14 (92.8%), the diagnostic yield was 7/14 (50%) and the FN rate was 7/14 (50%). In the SN group, the diagnostic accuracy was 21/23 (91.3%), the diagnostic yield was 20/22 (90.9%) and the FN rate was 2/22 (9.1%) (Fig. 4).

4. Discussion

This single-center retrospective study demonstrated the feasibility and accuracy of ENB combined with R-EBUS biopsy for different density peripheral pulmonary nodules. The diagnostic accuracy of PTLB in pulmonary nodules has been reported to range from 59 to 96%,[17] which may be even worse in SSNs. A recent meta-analysis reported that the diagnostic accuracy was only 60% when using PTLB biopsy for SSNs, and few of these studies reported the long-term follow-up of negative results. In 1 study, the FNR of PTLB was approximately 49%.[18] Baaklini et al. found that for peripheral lung lesions less than 2 cm, the diagnostic yield of conventional fiberoptic bronchoscope was only 14%.[19] In recent years, many reports have used ENB with or without R-EBUS to perform biopsy of lung nodules. Most of the lung nodules in these studies are SNs, and there are few studies on SSNs or pGGOs. Very few studies analyzing the correlation between the density of lesion and diagnostic yield.[20] A recent prospective multicenter clinical study showed that the diagnostic yield of ENB was 72.9% and the false negative rate was 45.4% after 1-year follow-up completed.[21] However, in this high credibility study only 6.3% of the enrolled cases were SSNs, and the diagnostic yield subgroup analysis of SN and SSN were not performed. Therefore, the clinical significance of these study would be reduced in specific patients.

In our study, we used ENB combined with R-EBUS to achieve a diagnostic yield of 75% and a false negative rate of 36.3%. Especially in SNs, radial endobronchial ultrasound can sensitively detect abnormal echoes around the airway, so ENB navigation would be more in real-time and more accurate. Even in the lower lobe that exhibits high respiratory mobility, ENB navigation can realize dynamic real-time positioning. As a result, the diagnostic accuracy and the diagnostic yield had reached a high level. However, in SSNs, the imaging changes were not obvious; some pure ground glass nodules even had no imaging changes on B-ultrasound or C-arm X-ray.[22,23] Although 92.8% of the cases were diagnosed by ENB biopsy, the diagnostic yield was not satisfying. We believed that the diagnostic yield for SSNs could be

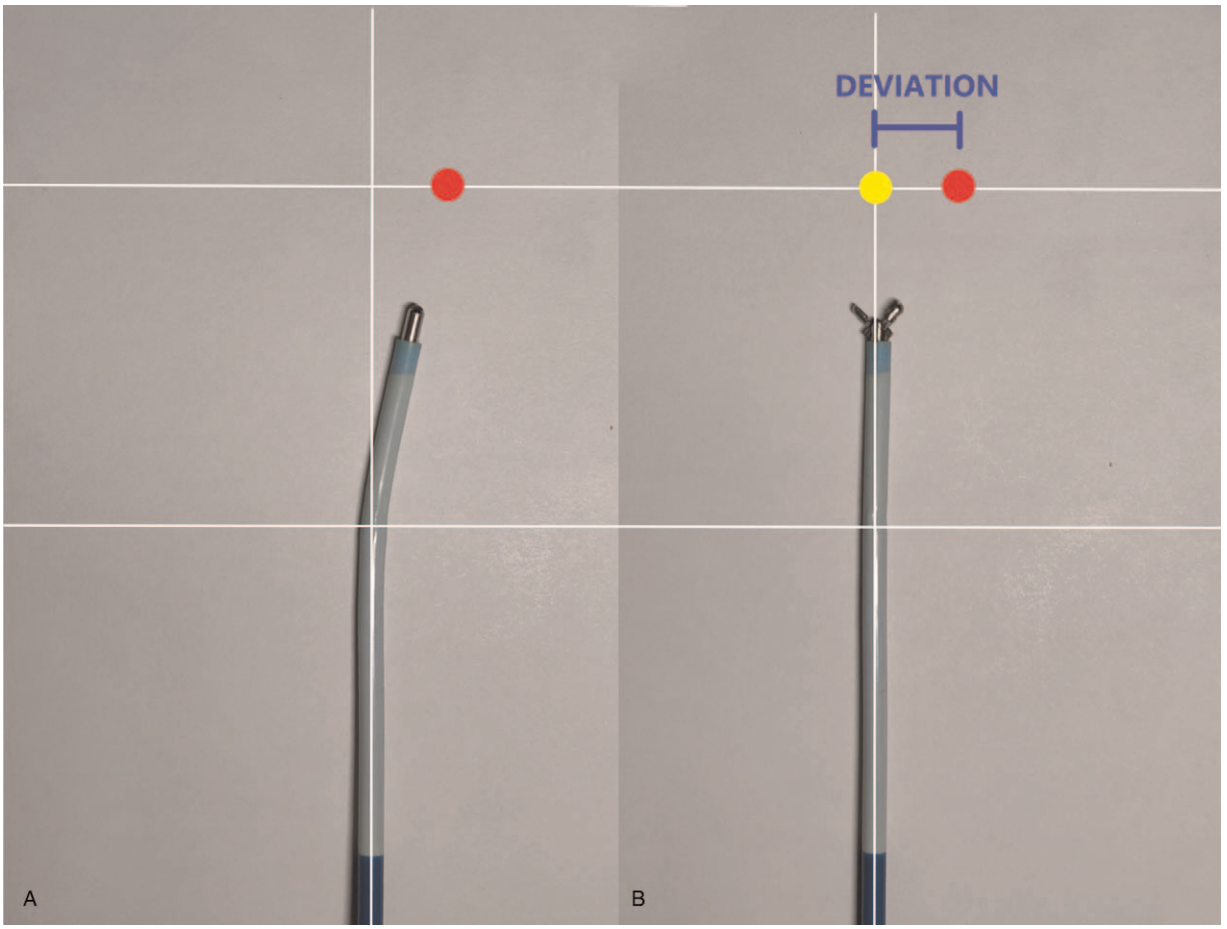

Figure 3. Deviation between sensor head and biopsy tool. A, the simulated sensor head reaches the lesion in tension-free conditions; B, the simulated angle change when the sensor head is withdrawn and the biopsy tool is outstretched.

improved by using Cone Beam CT to identify EWC and lesion location immediately during the operation.[24–26]

It is worth noting that, according to the flow chart, we performed other biopsies in a few patients who were diagnosed as nonmalignant with ENB biopsy but had lesion growth during follow-up or were evaluated as high-risk nodules based on imaging findings. We found that the traditional "ENB diagnostic accuracy," that is, the success rate of ENB to obtain meaningful pathology tissues, cannot be equated with pathological diagnosis. Long-term follow-up studies of ENB patients are still needed to rule out false negative results.

In operation, due to respiratory motion or other unavoidable navigation deviations, it is likely that the biopsy tools can reach the tissues surrounding lesions instead of the central cells, which may lead to higher rates of false-negative results in small-diameter lesions. At the same time, we found that during navigation, although the software showed that the sensor head had already precisely reached the lesion, when the sensor head was withdrawn and the biopsy tool was outstretched, the angle of the biopsy tool between the original angle of the sensor was changed because of the different component material of the biopsy tools. The angle change was confirmed by intraoperative C-arm X-ray.[21] This is also likely to be the reason for a significant reduction in the diagnostic yield of ENB biopsy for small-diameter lesions. We believe that using EWC with higher stiffness or making the stiffness of the biopsy tool and sensor head similar will reduce this deviation.

Most SSNs are early lung adenocarcinomas originating from alveolar epithelial cells. The tumor cells grow in the pulmonary parenchyma around the trachea, and the proportion of tumor cells is small.[27,28] Comparing the positive rate of 3 biopsy tools we used in this study, the differences were not significant. It does not seem that the biopsy method, which can obtain more pathological tissues, would have a higher diagnostic yield. Thus, using multiple biopsy tools was necessary, especially bronchoalveolar lavage and brush biopsy, which may have wider biopsy ranges than forceps or needles do.[29] However, these 3 biopsy tools used in our study cannot effectively or accurately penetrate the trachea to biopsy the lesions in the lung parenchyma. This could also be the reason for the low pathological diagnostic rate of SSNs. Perhaps a higher diagnostic yield will be achieved by using a puncture biopsy needle or the latest ENB combined with transthoracic percutaneous fine needle aspiration technique (TPNA).[25,30,31] This technology also provides the possibility for the subsequent use of ENB combined with TPNA for radiofrequency ablation of lung tumors. After completing the puncture of the trachea, the radiofrequency ablation probe can be inserted around the lesion located in the lung parenchyma to achieve simultaneous completion of biopsy and tumor ablation. This technology is especially suitable for patients who cannot tolerate surgery or suffer from multiple primary lung cancer. For the latter, performing multiple operations to remove the lesion will cause a large loss of lung function and a significant decrease in exercise tolerance. Using ENB combined

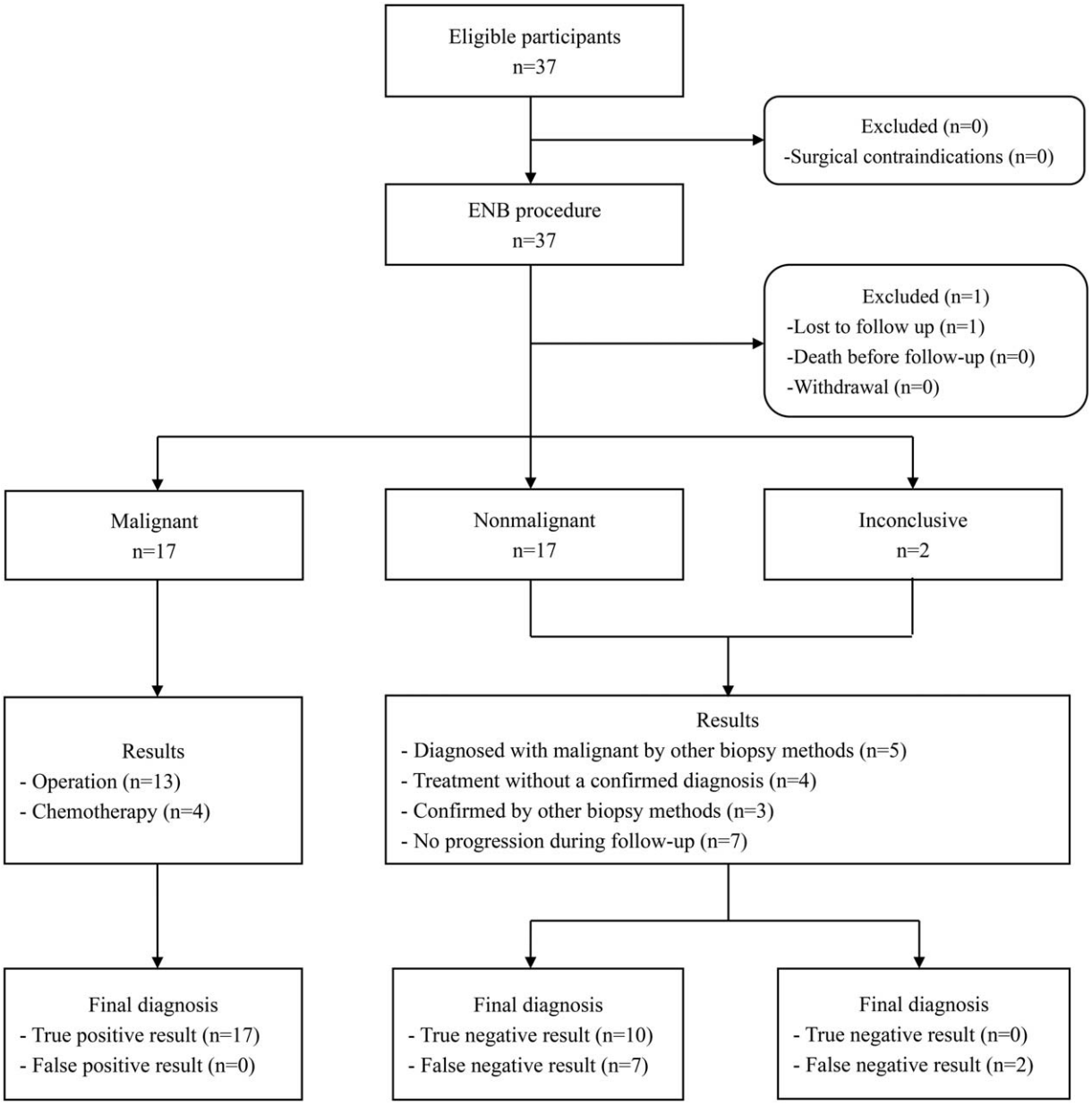

Figure 4. STARD flow diagram of ENB procedure.

with TPNA for radiofrequency ablation can avoid multiple operations and greatly reduce the loss of lung function. This technology also has a wider operating area than conventional transthoracic radiofrequency ablation. In the past, the location of the lesion that was relatively contraindicated can now also be completed by ENB-TPNA. The research on this innovative technology is ongoing in our medical center and will be published after the subsequent data collection is completed. We believe that as more studies confirm the feasibility and safety of this method in the future, ENB combined with radiofrequency ablation will become a new method for the treatment of early lung cancer.[32]

5. Conclusion

ENB combined with R-EBUS for performing biopsy of peripheral lung nodules is safe and effective, especially for solid nodules, but the diagnostic yield for the biopsy of subsolid nodules still requires improvement. In this study, we found that the main factors affecting the diagnostic yield are the density of the lesions and the deviations caused by the different materials of the biopsy tools. Therefore, appropriate patients should be carefully selected for ENB biopsy. We recommend avoiding ENB combined with R-EBUS biopsy for SSNs, especially pGGOs. Given the current technical limitations, for this type of lesions, it is a better choice to complete a biopsy and resection at the same time during VATS surgery. In patients with SNs, since ENB combined with R-EBUS can sensitively identify the location of the lesion, achieving a higher diagnostic yield. Therefore, we recommend that ENB combined with R-EBUS be considered as a first-line biopsy method, especially when the patient refuses or cannot complete the VATS operation due to physical limitations.

Author contributions

Conceptualization: Nan Wang.
Data curation: Nan Wang.
Funding acquisition: Haitao Ma, Haitao Huang, Yu Feng.
Resources: Yu Feng.
Software: Yu Feng.
Supervision: Haitao Ma.
Validation: Haitao Ma.
Visualization: Haitao Huang.
Writing – original draft: Nan Wang.
Writing – review & editing: Haitao Huang.

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