Augmented Fluoroscopy

A New and Novel Navigation Platform for Peripheral Bronchoscopy

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Background: **The diagnosis of lung nodules continues to be a challenge. Confirmed diagnosis allows appropriate treatment for cancers and allows avoidance of more invasive procedures for proven noncancers. Currently, available lung biopsy technologies each have their own limitations, which affect the ability to successfully navigate to a suspicious nodule and to collect a diagnostic sample. Additional advancements in endobronchial navigation, localization, and guided biopsy are needed to obtain higher rates of definitive diagnosis for lung nodules.**

Methods: **This is a prospective, multicenter study that assessed the localization success rate and diagnostic yield of bronchoscopies guided only by the LungVision platform. Physicians navigated to pulmonary nodules according to a proposed pathway and verified nodule location using radial endobronchial ultrasound before the biopsy.**

Results: **Fifty-five patients were enrolled in the study. Two patients had >1 nodule that was evaluated on the day of the procedure. During bronchoscopy, the nodule localization success rate was 93%. The overall diagnostic yield measured the day of the procedure, based on the immediate rapid on-site pathology report, was 75.4%.**

Conclusion: **LungVision provides reliable navigation and ability to biopsy pulmonary nodules with an acceptable success rate. The platform demonstrates a high localization rate of pulmonary nodules.**

Key Words: bronchoscopy, navigational bronchoscopy, augmented imaging, augmented fluoroscopy, lung nodule

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The solitary pulmonary nodule represents a diagnostic dilemma.[1–5] The ideal lung nodule biopsy approach should be the most minimally invasive technique that yields an excellent diagnostic sample and introduces a few complications.[5] Bronchoscopic access to nodules is advantageous in that it is associated with less risk of pneumothorax that percutaneous techniques, however, yield may not be as good. The addition of navigational technologies to standard bronchoscopy has increased the yield of bronchoscopy. However, each of the current commercially available lung biopsy techniques and hardware/software solutions have their own strengths and limitations.

Navigational bronchoscopy platforms have primarily relied upon small diameter extended working channel (EWC) catheters to reach targets in the periphery of the lung. Procedural yield, however, has been highly variable, averaging 70% success. Several factors have been identified that contribute to this suboptimal yield, some of which are related to the type of navigation used, whereas others are related to the EWC itself. These include computed tomography (CT)-to-body divergence for electromagnetic navigation bronchoscopy (ENB) and the presence or absence of a bronchus sign.[6]

The LungVision platform (Body Vision Medical LTD, Ramat Ha Sharon, Israel) was developed to enable augmented endobronchial navigation and guided biopsy of peripheral pulmonary nodules, combining data from standard imaging modalities available in bronchoscopy with common endoscopic biopsy instruments. The real-time imaging platform uses a 3-dimensional structural map of the lungs generated from preoperative CT images paired with real-time fluoroscopic and ultrasound images, to assist in identifying the nodule location and a potential pathway to the nodule. The pathway is provided as an augmented overlay to the standard fluoroscopic screen, guiding the endobronchial tools to the nodule in real time. The platform integrates images from CT,

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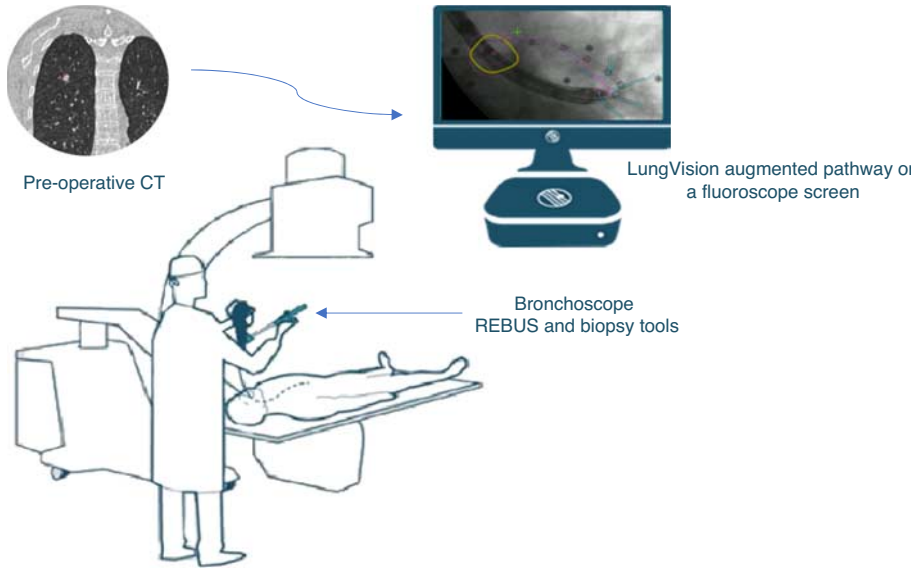

FIGURE 1. LungVision Platform. The platform integrates with available endobronchial modalities including bronchoscope, fluoroscope, and radial endobronchial ultrasound (REBUS) to present an augmented real-time pathway to a suspicious lung nodule. CT indicates computed tomography.

fluoroscopy, and radial endobronchial ultrasound (REBUS) (Fig. 1) during the case.

This is the first report of a multicenter study using the LungVision platform for nodule navigation and biopsy. The primary purpose of this study was to assess the performance of the LungVision platform to guide lung biopsy during bronchoscopy.

METHODS

This is a prospective, multicenter registry utilizing the first generation of the LungVision system for navigational bronchoscopy and biopsy of suspicious pulmonary nodules performed at 5 clinical sites, both academic and community hospitals. The participating sites were: Cleveland Clinic Foundation, (Cleveland OH), Catholic Health Initiative (Chattanooga, TN), Cancer Treatment Center of America (Tulsa, OK), OSF Saint Francis Medical Center (Peoria, IL), and University of Chicago Medicine (Chicago, IL). This study protocol was approved by the Institutional Review Board at each study site and informed consent was obtained from all patients before the procedure.

All patients evaluated for pulmonary nodules that were assigned to undergo bronchoscopy for the intent of biopsy were eligible for the study.

Procedure Flow

Before bronchoscopy, preprocedural CT scans were imported into the LungVision planning software to reconstruct the tracheobronchial tree and identify the targeted nodule. Standard chest CT scans with a slice thickness of ≤ 1.5 mm were used, with at least 50% slice overlap. The nodule was marked on a CT scan in 3 dimensions (axial, coronal, and sagittal views; Fig. 2) and the preferred pathway to the nodule was selected.

Bronchoscopy occurred under general anesthesia or conscious sedation, according to each institution's standard approach. Before every procedure, a location board with radio-opaque markers on it is placed on the procedure table under the cushion and is used for location analytics. A visual inspection of the airway is performed before every procedure to identify endobronchial lesions (that could potentially obviate the need for a nodule biopsy) and clear the airway of secretions. After inspection, the LungVision catheter is inserted through the bronchoscope into the airways. The catheter is a modified working channel scored with radio-opaque markers used for location analytics; its distal tip is curved and used for steering (Fig. 3). Using LungVision guidance CT-to-body registration is first performed. Once registration occurs, navigation to the targeted nodule is undertaken according to LungVision guidance. This guidance consists of a fluoroscopic overlay of the airway pathway and the target itself. Navigation along this pathway was performed under live fluoroscopic imaging. Once the tip of

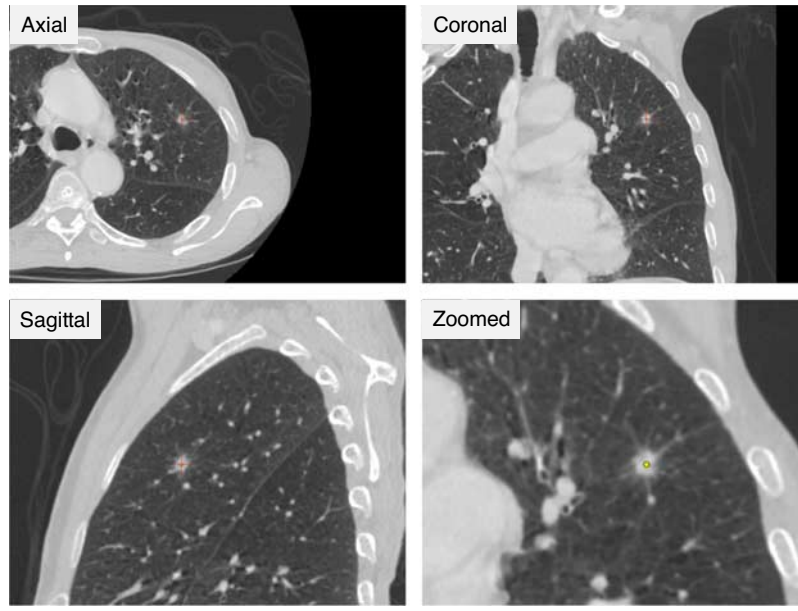

FIGURE 2. A snapshot from the planning software that shows a suspicious 8-mm LUL nodule in 3-dimensional. An axial, coronal, and sagittal views of the nodule and a zoomed view are evaluated.

the catheter is at the augmented target (ie, the lung nodule) as displayed by LungVision, REBUS is inserted through the catheter to evaluate the articulation of the catheter with the nodule. Articulation was graded as either within the nodule, adjacent to the nodule or not articulating at all with the nodule. The biopsy was then performed, with biopsy tool selection at the discretion of the proceduralist. A biopsy was performed under live fluoroscopic guidance, using the nodule overlay on the fluoroscopic image as a guide (Fig. 4). Rapid on-site evaluation (ROSE) of the sample was used in all cases.

If the LungVision procedure was not successful in reaching the nodule or making a diagnosis through ROSE, then the protocol will allow for the

FIGURE 3. The LungVision catheter. From right, the inner stylet, the modified working channel without stylet, the working channel with a stylet inserted.

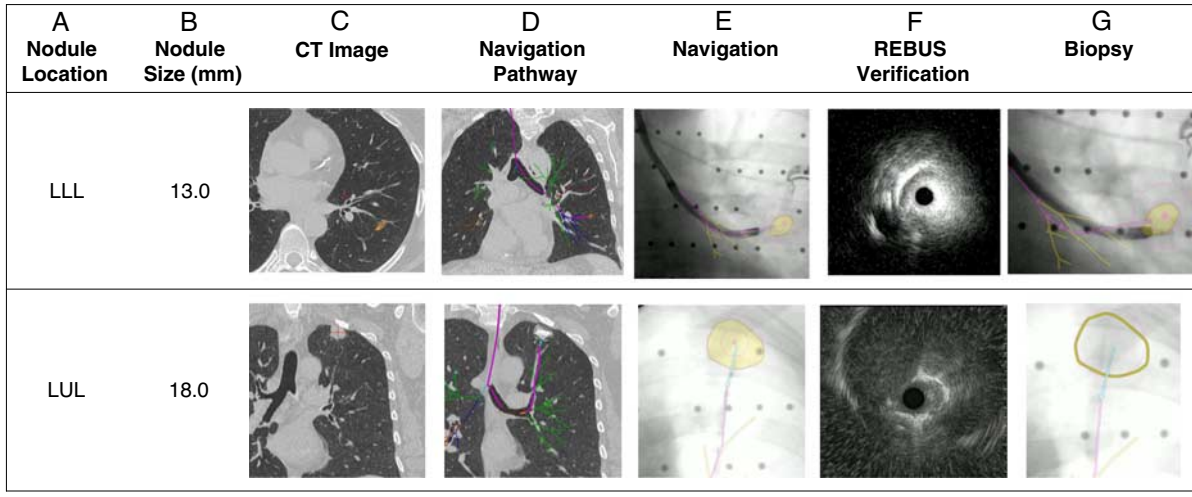

FIGURE 4. Procedure flow. Pulmonary nodules were identified in different sizes and lobes (A and B) and marked on computed tomography (C). The proposed navigation pathway proposed by the system was presented on the physician screen, shown in purple, the nodule was marked in yellow (D). The physician navigated with a steerable catheter through the working channel of the bronchoscope to the nodule with real-time augmented visualization of the nodule (E). Once the catheter reached the proposed PN location, localization was confirmed by a radial endobronchial ultrasound (REBUS) (F) and then a biopsy was collected under real-time guidance (G).

proceduralist to convert to other peripheral modalities available at the respective center. However, this did not occur in any of the procedures.

Endpoints

Several endpoints were defined by the protocol and included the following: (1) positive localization of the nodule as defined by confirmation with REBUS of the nodule at the location specified by the navigation parameters given by LungVision. (2) Diagnostic yield is defined as a definitive histologic diagnosis (malignant or benign) on the day of the procedure through ROSE and on the basis of results in the final pathology report. No long-term follow-up pathology results were used to calculate the final diagnostic yield. (3) Safety and adverse events as defined as bleeding requiring intervention (beyond standard suctioning), pneumothorax, respiratory failure postprocedure, and postprocedure hospitalization. (4) Total fluoroscopy time and radiation dose.

RESULTS

A total of 55 patients were enrolled in the study between February 2017 and September 2018. The mean (SD) age was 70 (±9.3) years, and 51% of the patients were female individuals. Two patients had 2 separate suspicious nodules that were examined during the same procedure for a total of 57 endobronchial navigations. Nodules in all lung lobes were represented in the study. Almost half of the nodules were smaller than 20 mm in size (n = 26, 46.0%). Median and mean nodule size was 20.0 and 27.6 mm, respectively, with a range of 5.0 to 80.0 mm. No adverse events were reported. Patients and nodules characteristics are summarized in Table 1. The average procedure time was 51.3 minutes.

Navigation to the target nodule was determined exclusively by LungVision. Of the 57 nodules targeted, 53 nodules (93%) were successfully localized and verified by REBUS (Table 2). Nodule localization was not shown to

TABLE 1. Patient and Nodule Characteristics

Characteristic	Patients, n (%)
Sex	
Male	27 (49)
Female	28 (51)
Age (y)	
< 55	3 (5.5)
> 55	52 (94.5)
Smoking habits	
Current	18 (32.7)
Former	27 (49.1)
None	10 (18.2)
Nodule distribution	
Upper lobes	30 (52.6)
RML	5 (8.8)
Lingula	2 (3.5)
Lower lobes	20 (35.1)
Nodules size (mm)	
≤ 20	26 (45.6)
> 21	31 (54.4)

TABLE 2. Total Localization Success Verified With REBUS and Diagnostic Yield

	n (%)
No. patients	55 (100)
No. navigations	57 (100)
Total number of nodules localized	53 (93)
Total diagnostic yield	43 (75.4)

REBUS indicates radial endobronchial ultrasound.

be dependent on nodule size, showing similar localization success of 88.5% for nodules that were smaller than 20 mm, 92.3% for nodules between 21 and 30 mm, and 100% verification for masses over 30 mm in size (Table 3).

Guided biopsy sampling was performed solely under the guidance of the LungVision platform. The overall diagnostic yield of nodules sampled in the study was 75.4% (Table 2). The biopsies were considered definitively diagnostic if the pathology results, generated from the samples at the day of the procedure, were determined to be malignant or confirmed benign samples (such as fungal elements on biopsy). Of the 4 patients with acute inflammation, 1 patient grew Actinomyces species from the specimen, and was subsequently treated and improved on a short-term follow-up CT scan; this patient was considered a definitive benign sample. The other results of acute inflammation were considered nondiagnostic for this analysis.

Diagnostic yield varied with nodule size. The diagnostic yield for nodules smaller than 20 mm was 73.1%, for nodules between 21 and 30 mm was 61.5%, for masses between 31 and 40 mm was 85.7%, and the diagnostic yield for masses that were larger than 40 mm was 90.9% (Table 3). Specific diagnoses are listed in Table 4. The average fluoroscopy time was 9.4 ± 6.9 minutes, with the average radiation dose being 248.7 mGy.

TABLE 4. Pathology Results Based on Nodule Size

	n (%)	
Diagnosis	**Nodules ≤ 20 mm**	**Nodules > 20 mm**
Adenocarcinoma	11 (42.3)	8 (25.8)
Squamous cell carcinoma	2 (7.7)	5 (16.1)
Non–small cell carcinoma	2 (7.7)	3 (9.7)
Small cell carcinoma	1 (3.8)	2 (6.5)
Carcinoma	0.0	2 (6.5)
Metastatic chondrosarcoma	0.0	1 (3.2)
Carcinoid	0.0	1 (3.2)
Fungus	3 (11.5)	0.0
Acute inflammation	2 (7.7)	2 (6.5)
Granuloma	0.0	1 (3.2)
Nondiagnostic	5 (19.3)	6 (19.3)

DISCUSSION

Proof of malignancy in solitary peripheral lung nodules can allow for targeted management of benign disease, earlier cancer diagnosis, and potentially avoid unnecessary surgical interventions for benign disease. However, only 10% to 18% of small lung nodules (10 to 20 mm in size) are malignant.[7] Thus, the importance of a minimally invasive way to accurately biopsy these nodules is evident. Though bronchoscopy is a safe and minimally invasive approach to biopsy nodules, its clinical performance has been modest, especially for peripherally located lesions, even with the advent of new technology, such as electromagnetic navigation, REBUS, and virtual CT.[1]

Currently, available navigation and biopsy techniques show a high localization rate, above 90%.[4,8,9] However, their diagnostic yield is much lower. For REBUS, the reported diagnostic yield is ~57% to 58.9%,[2,8] and for electromagnetic navigation, it is between 38.5% and 73% after a 12-month follow-up as was reported in the NAVIGATE study.[2,9] The gap between the high values of localization success and the low values of the diagnostic yield may be explained by several factors. First, some techniques lack real-time confirmation of the biopsy instrument in the nodule at the time of sampling. Tip movement away from the nodule during a biopsy can allow

TABLE 3. Nodule Size and Rate of Localization Success Verified With REBUS and Diagnostic Yield Determined Based on Pathology Report at Day of Procedure

	n (%)				
Nodule Size	**≤ 10 mm**	**11-20 mm**	**21-30 mm**	**31-40 mm**	**> 40 mm**
No. nodules, n	7	19	13	7	11
Localization verification with REBUS	6 (85.7)	17 (89.5)	12 (92.3)	7 (100.0)	11 (100.0)
Diagnostic yield	5 (71.4)	14 (73.7)	8 (61.5)	6 (85.7)	10 (90.9)

REBUS indicates radial endobronchial ultrasound.

instruments to "slide" past the target. As the nodule is not being visualized in real time, it is hard to ascertain the exact relationship of the instrument to the nodule. Even in cases where ultrasound verification of the nodule is obtained, the ultrasound probe is removed before sample collection, and the biopsy is performed under blinded conditions. The challenge of placing the biopsy instruments exactly where the ultrasound probe had been may also affect the diagnostic yield, especially in curved tip catheters that may straighten when biopsy tools, which are more rigid than ultrasound probes, are placed through it.

Second, currently available biopsy instruments, including the most frequently used, needle, brush, and forceps, each has their own limitations in obtaining an informative sample. These limitations include the instrument's ability to collect a sample of sufficient size for analysis, the instrument's flexibility to reach the nodule, the dependence on a positive bronchus sign for a higher yield, and risks of complications, such as pneumothorax and hemorrhage. The ability of each biopsy instrument to obtain a diagnostic tissue is affected by the nodule's type, size, location, and accessibility.[2,5] Physician and pathologist experience are also a factor in obtaining a successful biopsy sample.

Third, limitations of the navigation technology can also result in poor yield, especially for those depending on electromagnetic guidance. Recently published studies suggest that ENB is highly sensitive to CT-to-body divergence and to respiratory motion.[10,11] Significant variance in nodule location between the planning CT and the procedural lung has been shown to occur, and are thought to be because of changes in lung size and orientation that occur at the time of the procedure.[10] The observed variance may reduce the ability to diagnose early stage nodules that are <20 mm in diameter. Thus, variability in the diagnostic yield of ENB may be in part because of the discrepancy between the calculated nodule location and the actual physical location of the nodule, plus the lack of real-time information/visualization of the sampling location.[12] Using adjunctive imaging to improve localization has been met with mixed results. Though the majority of physicians utilize fluoroscopy during peripheral bronchoscopy, regardless of the modality used to reach the periphery.[13,14] However, unless the nodule is radiopaque, fluoroscopy provides only nominal value to the procedure. REBUS provides visualization of the nodule in real time, providing verification for its location, but its ability to identify the nodule depends on the nodule's characteristics, such as size and location, and the articulation of the probe to the nodule (eccentric vs. concentric).[8,15]

One possible way to improve the diagnostic yield of peripheral lung nodules is to confirm that the sampling instrument is in the nodule during a biopsy. The LungVision platform provides a real-time augmented fluoroscopy view that visualizes the nodule in question during a biopsy.[2,5]

In this study, we assessed the navigation success and biopsy collection of pulmonary nodules guided by LungVision. Navigation to the targeted nodule location was verified simultaneously with REBUS and LungVision, with combined success of 93%. Localization verification ranged between 88.5% for small nodules (< 20 mm in diameter) and 100% verification success for masses over 30 mm size. A similar localization verification success rate was reported by Chen et al in a study that used CT–anatomic correlation and REBUS confirmation to reach pulmonary nodules. With a reported localization success of 95.4%, nodule localization was not shown to be size dependent, but was influenced by the presence of bronchus sign and when a concentric view was obtained.[8]

The diagnostic yield obtained in this study was determined from pathology results on the day of the procedure. No follow-up was performed after the initial pathology report. Follow-up data could have influenced the diagnostic yield; however, this study was not designed to follow patients out to 2 years radiographically or to follow patients prospectively to see if they had a surgical biopsy. Here, the overall same-day diagnostic yield was 75.4% and it was size dependent, ranging from 73.1% for nodules <20 mm in size to 90.9% for masses > 40 mm. In our study, the diagnostic yield for nodules between 21 and 30 mm size was less than that for those nodules <20 mm. The reasons for this are unclear but may be related to the relatively small sample size. Larger studies would be able to evaluate this in a more detailed manner.

Chen and colleagues showed a high localization success rate of CT–anatomic correlation with REBUS confirmation, however, with a diagnostic yield of only 58.9%. The diagnostic yield in that study was also dependent on nodule size and ranged between 50% (nodules of 10 to 20 mm) and 72% (for nodules over 50 mm). This lower yield was explained by the high number of small nodules included in the study and by the

distribution of eccentric versus concentric views, and by the presence or absence of bronchus sign in these procedures.[8]

Another explanation for the disparity between the localization rate and the diagnostic yield in Chen and colleagues may be related to the blinded conditions of sampling. After REBUS confirmation of the nodule location, the ultrasound probe was removed to insert the biopsy instruments. The biopsy step itself was performed under unguided conditions. As bronchoscopy is a dynamic procedure and the patient continues breathing throughout the entire procedure, chest motion can alter the nodule location on an average of 17.6 mm, with significantly higher displacement in the lower lobes.[10] This movement can lead to a biopsy being collected from a different area than where the nodule was seen by REBUS.

Advanced ENB technologies, which were introduced a decade ago, improved the diagnostic yield of bronchoscopy, and opened a new approach for guided bronchoscopy. These technologies guide physicians to the lung periphery by providing a suggested pathway derived from preoperative CT images. The pathway is presented as a static image on the endobronchial tree that does not take into consideration tissue displacement from CT to real-time anatomy or breathing movement. Lung displacement may arise for a variety of preprocedural and periprocedural reasons. Though navigation modalities have increased the localization rate during bronchoscopy, the diagnostic yield has not significantly risen in parallel. In most ENB-oriented technologies, once the physician has reached the nodule, whether an ultrasound is used to verify the location or not, the biopsy is performed under unguided conditions unless it can be visualized on fluoroscopic imaging. The ability to show the biopsy instruments in the nodule during biopsy together with real-time lung motion tracking can increase the chances of adequate sample acquisition and potentially increase the diagnostic yield.

Limitations

There are several limitations to this study. As this is the first study with the LungVision platform, the algorithm of the LungVision platform was continuously updated and improved throughout the study, which may have had an impact on performance. Patient selection was determined by the participated physicians without restrictions on nodule size, location, and stage of the disease. ROSE was performed in all procedures locally and variability in cytology review might have contributed to the diagnostic yield. Further clinical studies are needed to assess the efficacy of the LungVision platform.

CONCLUSIONS

Successful bronchoscopy relies on accurate navigation through the bronchial tree to the location of the nodule and collection of an informative sample. Current modalities lack the ability to provide a combined real-time guidance experience during both navigation and biopsy. The results from this study show that successful localization of a pulmonary nodule and real-time visualization of the biopsy instrument in the nodule, combined with real-time tracking of pulmonary-related motion, provide a high degree of localization with a diagnostic yield that is comparable with other diagnostic modalities. As this technology evolves, further studies with a larger patient population will help characterize its performance and role in nodule biopsy management.

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The authors undertook the review of data, drafted and revised the manuscript. They personally reviewed the efficacy data, understood the statistical methods used for efficacy analysis, and confirmed an understanding of this analysis that the methods are clearly described and that they are a fair way to report the results.

REFERENCES

1. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. *Chest*. 2012;142:385–393.
2. Ost DE, Ernst A, Lei X, et al. Diagnostic yield and complications of bronchoscopy for peripheral lung lesions. Results of the AQuIRE registry. *Am J Respir Crit Care Med*. 2016;193:68–77.
3. Ernst A, Silvestri GA, Johnstone D. American College of Chest P. Interventional pulmonary procedures: guidelines from the American College of Chest Physicians. *Chest*. 2003;123:1693–1717.
4. Khandhar SJ, Bowling MR, Flandes J, et al. Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: first results of the prospective, multicenter NAVIGATE study. *BMC Pulm Med*. 2017; 17:59.
5. Latimer KM, Mott TF. Lung cancer: diagnosis, treatment principles, and screening. *Am Fam Physician*. 2015;91:250–256.
6. Khan KA, Nardelli P, Jaeger A, et al. Navigational bronchoscopy for early lung cancer: a road to therapy. *Adv Ther*. 2016;33:580–596.
7. Xu C, Hao K, Song Y, et al. Early diagnosis of solitary pulmonary nodules. *J Thorac Dis*. 2013;5:830–840.
8. Chen AC, Loiselle A, Zhou L, et al. Localization of peripheral pulmonary lesions using a method of

computed tomography-anatomic correlation and radial probe endobronchial ultrasound confirmation. *Ann Am Thorac Soc*. 2016;13:1586–1592.
9. Folch EE, Pritchett MA, Nead MA, et al. Electromagnetic navigation bronchoscopy for peripheral pulmonary lesions: one-year results of the prospective, multicenter NAVIGATE study. *J Thorac Oncol*. 2019; 14:445–458.
10. Chen A, Pastis N, Furukawa B, et al. The effect of respiratory motion on pulmonary nodule location during electromagnetic navigation bronchoscopy. *Chest*. 2015;147:1275–1281.
11. Pritchett MA. Augmented endobronchial fluoroscopic navigation and localization system: comparison with cone beam CT. A poster presentation. *Am J Respir Crit Care Med*. 2018;197:A6156.
12. Gildea TR. Lung lesion localization and the diagnostic drop. *Ann Am Thorac Soc*. 2016;13:1450–1452.
13. Baaklini WA, Reinoso MA, Gorin AB, et al. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. *Chest*. 2000;117:1049–1054.
14. Hautmann H, Henke MO, Bitterling H. High diagnostic yield from transbronchial biopsy of solitary pulmonary nodules using low-dose CT-guidance. *Respirology*. 2010;15:677–682.
15. Zaric B, Eberhardt R, Herth F, et al. Linear and radial endobronchial ultrasound in diagnosis and staging of lung cancer. *Expert Rev Med Devices*. 2013;10:685–695.