A Prospective, Multicenter Evaluation of Safety and Diagnostic Outcomes With Robotic-Assisted Bronchoscopy

Results of the Transbronchial Biopsy Assisted by Robot Guidance in the Evaluation of Tumors of the Lung (TARGET) Trial

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BACKGROUND: It remains challenging to safely and reliably biopsy peripheral pulmonary lesions (PPLs). Robotic-assisted bronchoscopy (RAB) is gaining adoption for navigation to PPLs. However, evidence from large studies remains limited.

RESEARCH QUESTION: What is the clinical safety, navigational success, and diagnostic yield of RAB for biopsy of PPLs in a broad range of patients in a real-world setting?

STUDY DESIGN AND METHODS: This multicenter, prospective, single-arm study enrolled patients aged > 21 years with 8- to 50-mm lung lesions requiring bronchoscopic diagnosis. The primary end point was the incidence of the following device- or procedure-related events: (1) pneumothorax requiring intervention; (2) bleeding requiring intervention; or (3) respiratory failure. Secondary end points included individual components of the primary end point, procedure time, pneumothoraces, radial probe endobronchial ultrasound confirmation, conversion to an alternative biopsy procedure, complications, and diagnostic yield.

RESULTS: Among 715 patients at 21 sites, 679 met study criteria and underwent RAB (mean age 68.7 years; 55.4% female; 86.5% White; 77.5% with current/past tobacco use). Mean (range) lesion size was 20.9 (7.0-63.0) mm; median (interquartile range) distance from the pleural surface was 5 (0-16) mm. Most lesions were solid (n = 587 [86.6%]) and within the outer two-thirds of the lung (n = 593 [87.5%]). The primary end point was observed in 26 (3.8%) patients (19 pneumothorax, 7 bleeding, and 0 respiratory failure). Users reported that RAB reached the lesion in 670 (98.7%) of 679 cases, and lesion location was confirmed with radial probe endobronchial ultrasound in 607 (91.7%) of 662 cases; sampling through the bronchoscope was performed in 675 (99.4%) of 679 cases. Prevalence of malignancy was 64.1% through 12 months. Adjudicated diagnostic yield was 61.6% when calculated with the American Thoracic Society/American College of Chest Physicians (CHEST) definition for strict reporting criteria. Sensitivity for malignancy was 78.8%.

INTERPRETATION: This multicenter prospective study of RAB—to our knowledge, the largest to date—showed that RAB-guided sampling of PPLs is safe and compares favorably to results from sizable non-robotic bronchoscopy studies.

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KEY WORDS: biopsy; bronchoscopy; Monarch; lung cancer; lung nodule; navigation bronchoscopy; peripheral pulmonary lesions; robotic; robotic bronchoscopy

Take-Home Points

Study Question: What is the clinical safety and navigational success of robotic-assisted bronchoscopy (RAB) for biopsy of peripheral pulmonary lesions (PPLs) in a broad range of patients in a real-world setting?

Results: The adjudicated primary safety end point was observed in 3.8% of participants (19 pneumothorax, 7 bleeding, and 0 respiratory failure). Users reported that RAB reached the lesion in 98.7% of cases. Diagnostic yield was adjudicated and was 61.6% when calculated according to the American Thoracic Society/American College of Chest Physicians reporting guidelines, whereas investigator-reported diagnostic yield was 83.2%.

Interpretation: This multicenter prospective study of RAB—to our knowledge, the largest to date—showed that RAB-guided sampling of PPLs is safe and compares favorably to results from sizable non-robotic bronchoscopy studies.

Although progress has been made in prevention, early detection, and treatment, lung cancer remains the leading cause of cancer mortality, accounting for 1 in 4 cancer deaths[1] and totaling > 2 million deaths worldwide annually.[2] Most patients with lung cancer are identified with their disease at an advanced stage, and diagnosis is often established on small biopsy or cytology specimens. Advances in molecular biology have improved the understanding of lung cancer and have changed treatment approaches.[3] Biopsies that enable histologic characterization and mutation analysis are becoming increasingly important.[4] However, biopsy of peripheral pulmonary lesions (PPLs) remains a challenge due to the ability to gain access to the periphery of the lung, lesion size, locations that are difficult to access via standard bronchoscopy, and acquisition of an adequate sample once the lesion is reached.[5] Despite technological development over the past 2 decades, the diagnosis of pulmonary nodules remains suboptimal, with diagnostic yield (DY) reported between 40% and 70%.[6-11] Robotic-assisted bronchoscopy (RAB) was developed to overcome the challenges of reaching and sampling PPLs. RAB systems allow users to control robotic arms with a remote device to navigate to the PPLs for biopsy.

A robotic-assisted endoscopy system (MONARCH Platform; Johnson & Johnson MedTech) was designed to provide bronchoscopic visualization and airway access for diagnostic and therapeutic procedures. The system aids in navigation, combining continuous bronchoscopic visualization with a three-dimensional reconstruction of the lung. It has been assessed in small clinical feasibility studies.[12,13] This prospective multicenter study was conducted to evaluate the safety, navigational success, and diagnostic yield of RAB with biopsy in a broad range of participants with PPLs.

Study Design and Methods

This prospective, multicenter, single-arm observational study evaluated the safety and diagnostic outcomes of RAB performed in patients with pulmonary lesions. Applicable parts of the Consolidated Standards of Reporting Trials guidance were followed for the study, and the study was registered on ClinicalTrials.gov.[14] The study was industry sponsored, and sponsors participated in study design, data analysis, and reporting under the guidance of an independent steering committee. However, the adjudication process was conducted by the independent steering committee. The

ABBREVIATIONS: AE = adverse event; ATS = American Thoracic Society; CBCT = cone-beam CT; CHEST = American College of Chest Physicians; DY = diagnostic yield; EBUS = endobronchial ultrasound; ENB = electromagnetic navigational bronchoscopy; PPL = peripheral pulmonary lesion; R-EBUS = radial endobronchial ultrasound; RAB = robotic-assisted bronchoscopy

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study enrolled 715 participants across 21 sites in the United States and Hong Kong. The trial was designed to adhere to the bioethical guidelines established in the Declaration of Helsinki. Institutional review board approval was obtained; details about institutional review board information, including the approving organization and approval numbers, are included in e-Appendix A.

Each site obtained informed consent from qualified participants. Individuals were given an opportunity to review and sign documentation of Health Insurance Portability and Accountability Act compliance and authorization. Patients were followed up until a definitive diagnosis was established or for up to 24 months after the procedure. A schedule of assessments is presented in e-Table 1.

Study Population

Individuals were included in the study if they were: (1) > 21 years of age; (2) capable and willing to give informed consent; (3) an acceptable candidate for an elective, nonemergent bronchoscopic procedure; and (4) had 8- to 50-mm lung lesion(s) eligible for bronchoscopic diagnosis identified from a CT scan within 28 days of the intended bronchoscopy.

Participants meeting any of the following criteria were not eligible to participate: (1) medical contraindication to bronchoscopy as assessed by the investigator; (2) presence of uncorrectable bleeding disorders; (3) indwelling medical devices interfering with electromagnetic navigation, including but not limited to pacemakers; (4) target lesion having endobronchial involvement identified on chest CT imaging; (5) lack of fitness to undergo flexible bronchoscopy as determined by the bronchoscopist prior to the procedure; (6) participation in any other clinical trial within 30 days of enrollment that would interfere with this study; (7) uncontrolled or irreversible coagulopathy; (8) female individuals who were pregnant or nursing at the time of the procedure or those of childbearing potential refusing a pregnancy test prior to the procedure; and (9) CT scan performed > 28 days prior to the bronchoscopy procedure. In addition, individuals were excluded from the study for any presenting condition discovered intraoperatively that, in the opinion of the investigator, would make participating in this study not in the participants' best interest. Reasons included, but were not limited to, the presence of an unexpected endobronchial lesion, adequate tissue acquisition obtained via endobronchial ultrasound-guided transbronchial fine needle aspiration during the procedure, and the individual's unstable clinical status during general anesthesia (e-Appendix B).

Investigators recorded the procedural results of a single target lesion. CT findings were collected that included identification of a bronchus sign (visible bronchus observed on axial, coronal, or sagittal view in contact with any portion of the lesion), lesion morphology (CT pattern), and lesion location (inner, middle, outer third of hemithorax, with thirds defined by concentric lines arising from the hilum[15,16]). Ability to reach the lesion was defined as effectively maneuvering the bronchoscope to the target lesion based on feedback from the navigation system (alignment and proximity to the target).

Safety and Effectiveness Outcomes

The primary composite end point was the incidence of 1 or more of the following device- or procedure-related events: pneumothorax requiring intervention; bleeding requiring medical intervention; or respiratory failure, device or procedure related. The device- or procedure-related events were adjudicated by one of the authors (D. H. S.); details on the Common Terminology Criteria for Adverse Events Scale Severity Classification are presented in e-Table 2.

Secondary end points included the individual components of the primary end point; the incidence of all pneumothoraces; radial probe endobronchial ultrasound (R-EBUS) confirmation (proportion of participants who achieved either concentric or eccentric R-EBUS confirmation); total procedure time from introduction to removal of the bronchoscope; conversion to conventional bronchoscopic procedure; complications unrelated to device or procedure; DY; and post-bronchoscopy infections. Pathology reports for patients were adjudicated by authors who were independent of the sponsor (A. C. C., D. H. S., G. A. S., S. M., and K. Y.) into prespecified diagnostic categories (e-Table 3), and disagreements were resolved by consensus among non-sponsor authors.

Strict DY was calculated according to the research statement from the American Thoracic Society (ATS)/American College of Chest Physicians (CHEST).[17] In this approach, all patients with a malignant or specific benign diagnosis based on a review of the pathology reports were categorized as diagnostic. All participants in whom a procedure was performed were included in the denominator.

Statistical Methods

Summary statistics as appropriate for categorical or continuous variables are provided for all demographic, clinical, and procedural characteristics. A 95% CI for the primary end point was estimated via the normal approximation to the binomial distribution. DY was calculated at index and through at least 12 and up to 24 months after the procedure. Summary statistics for demographic and clinical characteristics are presented by whether the biopsy sample from previous RAB was considered diagnostic. Identification of variables significantly associated with DY used univariate (χ^2 test) and multivariate (logistic regression) approaches in an exploratory analysis. Multivariate models only included variables measured prior to the index procedure as covariates. For stepwise logistic regression, entry and exit significance levels were 0.20 and 0.05, respectively.

Unadjusted P values $< .05$ were considered significant. Statistical analysis was performed by using SAS version 9.4 (SAS Institute, Inc).

Results

From December 2019 to September 2022, a total of 715 patients were screened at 21 centers, and 36 were excluded due to screen failure (n = 28) or as training cases per protocol (n = 8). Screen failure reasons included lesion size not 8 to 50 mm (5 participants), lack of fitness to undergo procedure (1 participant), CT scan completed > 28 days prior to procedure (3 participants), and intraoperative exclusions (19 participants) such as distorted anatomy, endobronchial lesions, and diagnostic EBUS.

Sites enrolled an average of 3.4 patients per month. Follow-up occurred until October 2023. Fifty-two patients (7.7%) discontinued during the 12-month follow-up window due to loss to follow-up (5.4%), death classified as unrelated to the procedure or the device by the investigator (1.0%), patient refusal to continue or withdrawal of consent (0.7%), early termination at physician's discretion (0.3%), or other (0.1%). Baseline demographic characteristics are presented in Table 1.

Lesion Characteristics

Lesion characteristics are presented in Table 1 and e-Tables 4 and 5. Mean (range) lesion size was 20.9 (7.0-63.0) mm; lesion size was > 3 cm in 114 participants (16.8%) and > 5 cm in 2 participants (0.3%). Median (interquartile range) distance from the pleural surface was 5 (0-16) mm, with 37% of lesions abutting a pleural surface (Fig 1). Subsolid nodules represented 13.4% of targeted nodules, of which 78 (85.7%) were semi-solid, and 13 (14.3%) were pure ground-glass. Bronchus sign was present in 59.9% of targeted nodules. Most lesions were located in the outer two-thirds of the lung (87.5%) (Fig 2). PET was performed on 53.5% of patients (n = 361), with the majority of lesions (n = 267 [75.4%]) considered hypermetabolic by the investigator.

Procedural Characteristics

Procedural characteristics are summarized in Table 2. R-EBUS was available and used in 97.5% of cases and cone-beam CT (CBCT) imaging in 16.6%. Transbronchial needle aspiration was performed in 97.1% of cases and transbronchial biopsy using forceps in 81.1% of cases. Brushes were used in 39.8% of cases, and rapid on-site evaluation was used in 542 (79.8%) cases. EBUS staging of lymph nodes was performed for 398 patients (58.6%) and occurred prior to RAB in 56 cases (14.1%). Cases were converted to non-robotic bronchoscopic procedures in 14 patients (2.1%).

Safety

Twenty-six (3.8%) of 679 patients experienced device- or procedure-related adverse events (AEs) that met the adjudicated safety primary end point. Pneumothorax requiring intervention was the most commonly occurring component of the primary safety end point (19 of 679 [2.8% of patients]). These were classified as Grade 2 (1 of 679 [0.1%]) and Grade 3 (18 of 679 [2.7%]) events with 15 patients receiving a chest tube (15 of 679 [2.2%]). Device-related bleeding contributing to the primary safety end point occurred as Grade 2 (6 of 679 [0.9%]) and Grade 4 (1 of 679 [0.1%]) events. No patients experienced respiratory failure of Grade 4 or higher related to the study device or procedure. Table 3 presents the results for the adjudicated primary safety end point. Ninety-seven patients experienced ≥ 1 AE (97 of 679 [14.3%]; 127 AEs total); 75 (75 of 679 [11.0%]) reported a peri-procedural AE (ie, within 7 days), and 28 (28 of 679 [4.1%]) reported a peri-procedural serious AE. A summary of all AEs and serious AEs is presented in e-Table 6.

Effectiveness

Users reported that RAB reached the lesion in 98.7% (670 of 679) of cases. Localization of the target

TABLE 1] Baseline Demographic and Clinical Characteristics

Characteristic	Value[a] (N = 679)
Age, y	
Mean ± SD	68.7 ± 10.1
Median (minimum, maximum)	69.0 (31, 92)
Sex	
Male	303 (44.6)
Female	376 (55.4)
Race and ethnicity	
White	587 (86.5)
Black	48 (7.1)
Asian	30 (4.4)
Hispanic or Latino	12 (1.8)
Other	14 (2.0)
Medical history condition	
COPD/emphysema	286 (42.2)
Asthma	97 (14.3)
Myocardial infarction	41 (6.0)
Unstable angina	10 (1.5)
Congestive heart failure	35 (5.2)
History of lung cancer	89 (13.1)
History of extrathoracic malignancies	241 (35.5)
Smoking history	
Prior	381 (56.1)
Current	145 (21.4)
Never	149 (21.9)
Unknown	4 (0.6)
Pack years[b]	
Mean ± SD	38.1 ± 27.2
Median (minimum, maximum)	35.0 (0.3, 228.0)
Estimated preprocedure probability of malignancy	
Low (0%-10%)	18 (2.7)
Intermediate (11%-60%)	261 (38.5)
High (61%-100%)	399 (58.8)
Lesion characteristics	
Targeted lesion size (long axis), mm	
Mean ± SD	23.8 ± 11.0
Median (minimum, maximum)	21.0 (8.0, 75.0)
Targeted lesion size (short axis), mm	
Mean ± SD	18.0 ± 8.9
Median (minimum, maximum)	15.0 (4.7, 55.0)
Bronchus sign	406 (59.9)
Lung zone	
Proximal	85 (12.5)
Middle	273 (40.3)
Peripheral	320 (47.2)
Distance from closest edge of nodule to closest pleura surface, mm[c]	
Mean ± SD	10.0 ± 12.2
Median (minimum, maximum)	5.0 (0.0, 88.0)
Morphologic features	
Solid nodule	587 (86.6)
Subsolid nodule	91 (13.4)
Subsolid nodule type[d]	
Pure ground-glass	13 (14.3)
Semi-solid	78 (85.7)

Data are presented as No. (%) unless otherwise indicated. CHF = congestive heart failure.
[a]Denominator and percentages were based on patients with non-missing data.
[b]Pack years was summarized only with patients indicating "prior" or "current" in smoking history (n = 500, 26 unknown).
[c]Distance from the closest edge of the nodule to closest pleura surface was defined as the smaller value of distance from the closest edge of the nodule to closest fissure or distance from the closest edge of the nodule to pleura for each individual.
[d]Subsolid nodule type was summarized with number of patients indicating subsolid nodule under morphologic features (n = 45).

lesion and R-EBUS confirmation occurred in 91.7% of the patients (607 of 662) (Table 2). Investigators classified 377 (55.5%) cases as malignant, 188 (27.7%) as benign, and 114 (16.8%) as nondiagnostic according to their institution's pathology report, resulting in an investigator-reported DY of 83.2%. Adjudication of reports by the steering committee (A. C. C., D. H. S., G. A. S., S. M., and K. Y.) according to the categorization provided in e-Table 3 classified 54.4% as malignant, 9.3% as specific benign, 15.9% as nonspecific benign, and 20.3% as nondiagnostic at index (Table 4). Strictly defined DY recommended by the ATS/CHEST research statement was 61.6% (95% CI, 57.9%-65.2%). Details are presented in Figure 3.[17] Cancer prevalence was 64.1% through 12 months. Sensitivity for malignancy was 78.8%.

Subgroups of Interest and Predictors of Yield

Using the strict definition, DY was 68.8% for lesion size > 20 mm, 56.2% for lesion size ≤ 20 mm, 66.7% when bronchus sign was present, and 61.1% when CBCT imaging was used. DY was 63.0% for solid lesions and 51.6% for subsolid lesions. DY was 70.9% for concentric

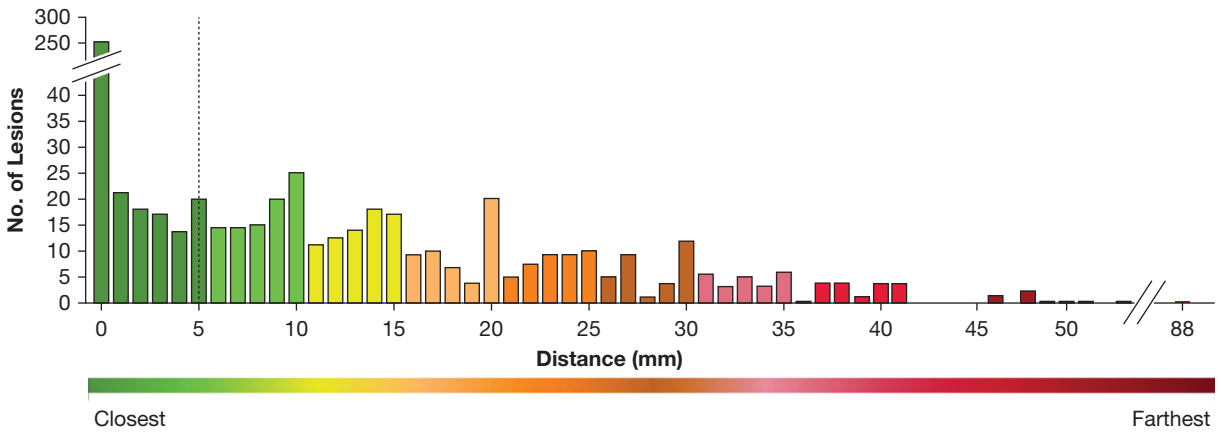

Figure 1 – *Distance of nodule to pleural surface in millimeters.*

lesions and 58.5% for eccentric lesions as determined by R-EBUS (e-Table 2). Variables found to be significantly associated with higher DY using the strict definition in multivariate analysis included history of COPD/emphysema, presence of bronchus sign, lesion size > 20 mm, and higher estimated probability of malignancy (Table 5).

Discussion

The introduction of robotic bronchoscopy has led to questions regarding its safety, diagnostic ability, utility, and cost effectiveness. Several smaller trials have suggested that robotic bronchoscopy can accomplish all of these goals[12,17,18]; however, larger, prospective trials have yet to be reported. The data presented here from this large, multicenter, prospective trial show that robotic bronchoscopy is safe, with a side effect profile similar to that of other navigational bronchoscopy trials.

The AE rate was low. The rate of procedure-related pneumothorax (2.8%) and tube thoracostomy (2.2%) was low, despite a substantial proportion of the targeted lesions close to or touching the pleural surface. The pneumothorax rate mirrors rates of pneumothorax in many previously reported bronchoscopy studies.[8,13,19-24] This minimal pneumothorax rate is favorable compared with reported CT-guided biopsy pneumothorax rates of 15% to 30% and 6% chest tube placement.[25] In addition, transthoracic needle aspiration does not offer staging information of primary lung lesions and has been associated with postprocedure hospitalization.[25,26] There were no procedure- or device-related reports of respiratory failure or infection.

The diagnostic yield of RAB was 61.6% according to strict reporting criteria, defined recently by the ATS/CHEST reporting guidelines.[17,27,28] A previous multicenter pilot study of RAB (the Robotic Bronchoscopy for Peripheral Pulmonary Lesions: A Multicenter Pilot and Feasibility Study [BENEFIT] trial) reported a DY of 74% or, using the strict criteria,[17] a DY of 66.7%, which was substantiated by a retrospective study reporting a yield of 77%.[29] The larger prospective multicenter trial presented here corroborates these results; using the BENEFIT calculation, DY in this trial was 73.1%. The results reported here compare favorably to the ACCP Quality Improvement Registry, Evaluation, and Education registry (581 patients), in which the yield of navigational bronchoscopy was 53.7% using the strict definition.[24] Despite innovations in bronchoscopic techniques, the diagnosis of PPLs remains a significant clinical challenge. A meta-analysis of guided bronchoscopy, including robotic bronchoscopy, reported an aggregate DY of 70% in > 16,000 patients, reflecting heterogeneous DY definitions.[11] Interestingly, despite innovations, this yield had not improved over the previous decade compared with a prior, similar meta-analysis.[9]

Debate continues on how to evaluate new diagnostic technology in bronchoscopy. Vachani et al[27,28] have shown that using various reporting methods and differing populations can have dramatic effects on the DY that has been described by bronchoscopy trials in the past. In this trial, DY ranged from 61.6% to 84.6% with different DY definitions. It has recently been shown that the strict definition of DY is highly predictive of diagnostic accuracy through 2 years.[30] With the publication of the new ATS/CHEST guideline, we have for comparison re-analyzed the results of another large, prospective trial of electromagnetic navigational bronchoscopy (ENB), the Clinical

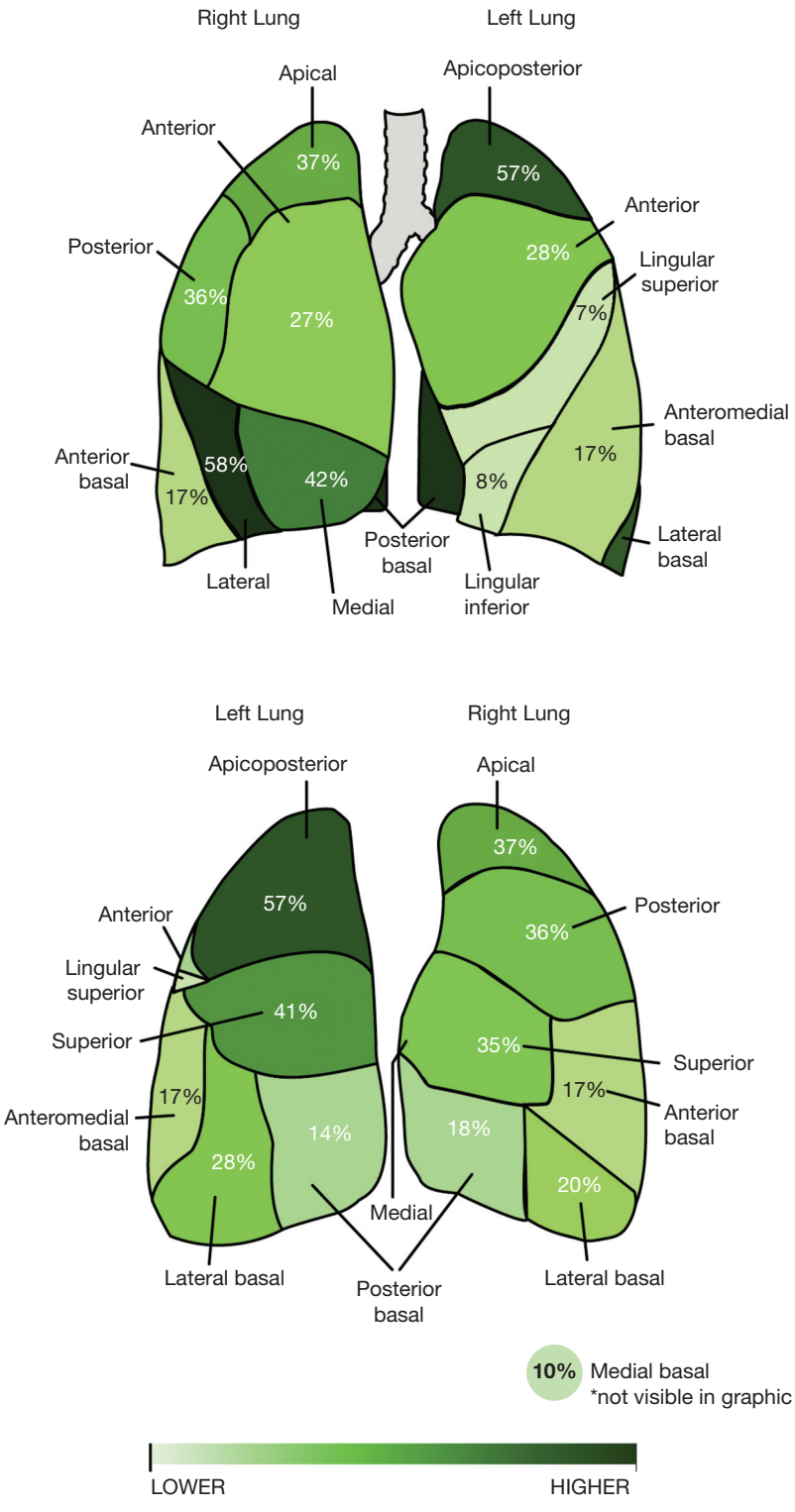

Figure 2 – *Lesion frequency by lobe.*

Evaluation of superDimension Navigation System for Electromagnetic Navigation Bronchoscopy (NAVIGATE) trial.[19] Using the ATS/CHEST strict reporting guidelines, the DY within the NAVIGATE trial was 48.7% (613 of 1,260), which is striking compared with the reported liberal DY after 12-month follow-up of 73%. In comparison, the DY in the study reported here using the ATS strict calculation was 61.6%, and using the NAVIGATE definition it was 84.6%.

TABLE 2] Bronchoscopy Procedure and Biopsy

Lesion Localization	No. of Patients (%)[a] (N = 679)
General anesthesia	679 (100.0)
CBCT imaging used	113 (16.6)
Biopsy tools	
Needle	65 9 (97.1)
Forceps	551 (81.1)
Brushes	270 (39.8)
Ability to reach to targeted lesion	670 (98.7)
Ability to localize targeted lesion with R-EBUS[b]	607 (91.7)
Ability to localize targeted lesion with R-EBUS for solid nodule[b,c]	541 (93.6)
Ability to localize targeted lesion with R-EBUS for subsolid nodule[b,d]	65 (78.3)
R-EBUS used	662 (97.5)
R-EBUS image pattern[d]	
Concentric	289 (48.0)
Eccentric	313 (52.0)
Bronchoscopic biopsy	
Ability to take samples by passing instruments through working channel of robotic bronchoscope	675 (99.4)
EBUS staging biopsy of lymph nodules performed	398 (58.6)
Salvage procedure performed	14 (2.1)

CBCT = cone-beam CT; EBUS = endobronchial ultrasound; R-EBUS = radial endobronchial ultrasound.
[a]Denominator and percentages were based on patients with non-missing data.
[b]R-EBUS localization summaries excluded 1 site (n = 17) where confirmation was performed only with CBCT imaging (n = 662).
[c]Ability to localize targeted lesion with R-EBUS for solid nodule was summarized with number of patients with solid nodules in morphologic features (n = 578).
[d]Ability to localize targeted lesion with R-EBUS for subsolid nodule was summarized with number of patients with subsolid nodules in morphologic features (n = 83).

TABLE 3] Adjudicated Postprocedural AEs Contributing to the Primary End Point

Postprocedural AE	No. of Patients (%)[a] (N = 679)
Patients with procedure or device-related AE during or following procedure contributing to safety composite end point	26 (3.8)
Pneumothorax ≥ grade 2[b]	19 (2.8)
Bleeding ≥ grade 2	7 (1.0)
Respiratory failure ≥ grade 4	0 (0.0)
CTCAE grade of procedure- or device-related pneumothorax[a]	
Grade 1	9 (1.3)
Grade 2	1 (0.1)
Grade 3	18 (2.7)[c]
CTCAE grade of procedure- or device-related bleeding[d]	
Grade 1	6 (0.9)
Grade 2	6 (0.9)
Grade 4	1 (0.1)

Data on AEs reported within 7 days of the procedure are included; serious AEs were monitored from enrollment through study exit. AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.
[a]All percentages were calculated by using the number of patients in the full analysis set as the denominator.
[b]CTCAE version 5.0 grades (abbreviated; full details are provided in e-Table 2): Grade 1: Mild, intervention not indicated; Grade 2: Moderate, minimal, local, or noninvasive intervention indicated; Grade 3: Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; Grade 4: Life-threatening consequences, urgent intervention indicated; and Grade 5: Death related to AE.
[c]Hospitalizations all categorized as Grade 3.
[d]CTCAE Grades were only applicable for patients who experienced procedure- or device-related pneumothorax, significant bleeding, respiratory failure, or infections.

Initial evaluations in human cadaver lungs revealed that RAB, despite having diameter dimensions similar to standard flexible bronchoscopes, was able to access further into the lung periphery and into locations that were difficult to access with flexible bronchoscopy due to angulation.[31] Cadaver studies have also reported that RAB was superior to ENB and standard bronchoscopy with R-EBUS in its ability to localize and precisely puncture the lesion.[32] The ability to manipulate the scope seems important when factors such as scope-to-lesion distance and R-EBUS probe localization are likely related to increased DY. The ability to reach the lesion and identify the lesion via R-EBUS in > 90% of this cohort are both indicators of successful navigation. The results reported here, however, like other trials, have presented a rate of DY that is lower than the rate of localization.[33] This discordance has also been found in older studies of fluoroscopy-guided R-EBUS, in which successful lesion localization was reported in > 95% of the cases; however, DYs were 58% to 69%.[10,34] This discordance may reflect a variety of factors, including variation in tools.

Factors associated with DY are not surprising when looking across DY definitions and considering univariate or multivariate exploratory analyses. History of COPD/emphysema, presence of bronchus sign, and

TABLE 4] Index Diagnoses

Category	Subcategory	Count	Percentage of Total (N = 679)
Malignant (n = 356)	NSCLC (adenocarcinoma)	193	28.4
	NSCLC (squamous cell carcinoma)	74	10.9
	Metastatic malignancy	30	4.4
	Neuroendocrine tumor	18	2.7
	Small cell carcinoma	15	2.2
	NSCLC NOS	14	2.1
	Other malignant (eg, squamous and small cell, mixed small cell, and NSCLC)	12	1.8
Benign specific (n = 62)	Necrotizing (caseating) granulomatous inflammation	14	2.1
	Non-necrotizing granulomatous inflammation	14	2.1
	Organizing pneumonia	13	1.9
	Infection/abscess (bacterial, fungal, and viral)	9	1.3
	Granuloma	8	1.2
	Hamartoma	2	0.3
	Other specific benign (eg, amyloid, mixed granuloma and inflammation)	2	0.3
Benign nonspecific (n = 105)	Inflammation (acute/benign inflammation, chronic inflammation, inflammatory tissue, neutrophilic inflammation, and lymphocytes)	88	13.0
	Multinucleated giant cell(s)	6	0.9
	Fibroelastic scar	5	0.7
	Other nonspecific benign (eg, necrosis, rare histiocytic aggregate)	3	0.4
	Interstitial lung disease	1	0.1
	Radiotherapy changes	1	0.1
	Squamous dysplasia/metaplasia	1	0.1
Nondiagnostic (n = 156)	Benign/normal lung tissue	56	8.2
	Atypical cells (insufficient evidence for malignant diagnosis)	43	6.3
	Bronchial epithelium	22	3.2
	Other nondiagnostic (eg, rare detached atypical mucus glands and inflammation, acellular, insufficient material)	12	1.8
	Reactive bronchial cells	9	1.3
	Blood clots/hemorrhage	6	0.9
	Biopsy by other procedure	5	0.7
	Macrophages	3	0.4

NOS = not otherwise specified; NSCLC = non-small cell lung cancer.

lesion size > 20 mm were associated with DY. Nodule diameter and bronchus sign were also found to be associated with DY within the most comprehensive meta-analysis published on this subject.[11] When using the strict DY definition, a higher probability of cancer was associated with increased DY, a factor previously reported in a secondary analysis of another trial.[35] Solid nodule CT pattern was associated with increased DY when using the intermediate DY definition. This raises the question of how the probability of cancer and solid nodule CT patterns in Transbronchial Biopsy Assisted by Robot Guidance in the Evaluation of Tumors of the Lung Trial (TARGET) compare with NAVIGATE as well as other navigational bronchoscopy trials. Ability to obtain concentric R-EBUS images of the lesion was associated with DY in univariate analysis but was not

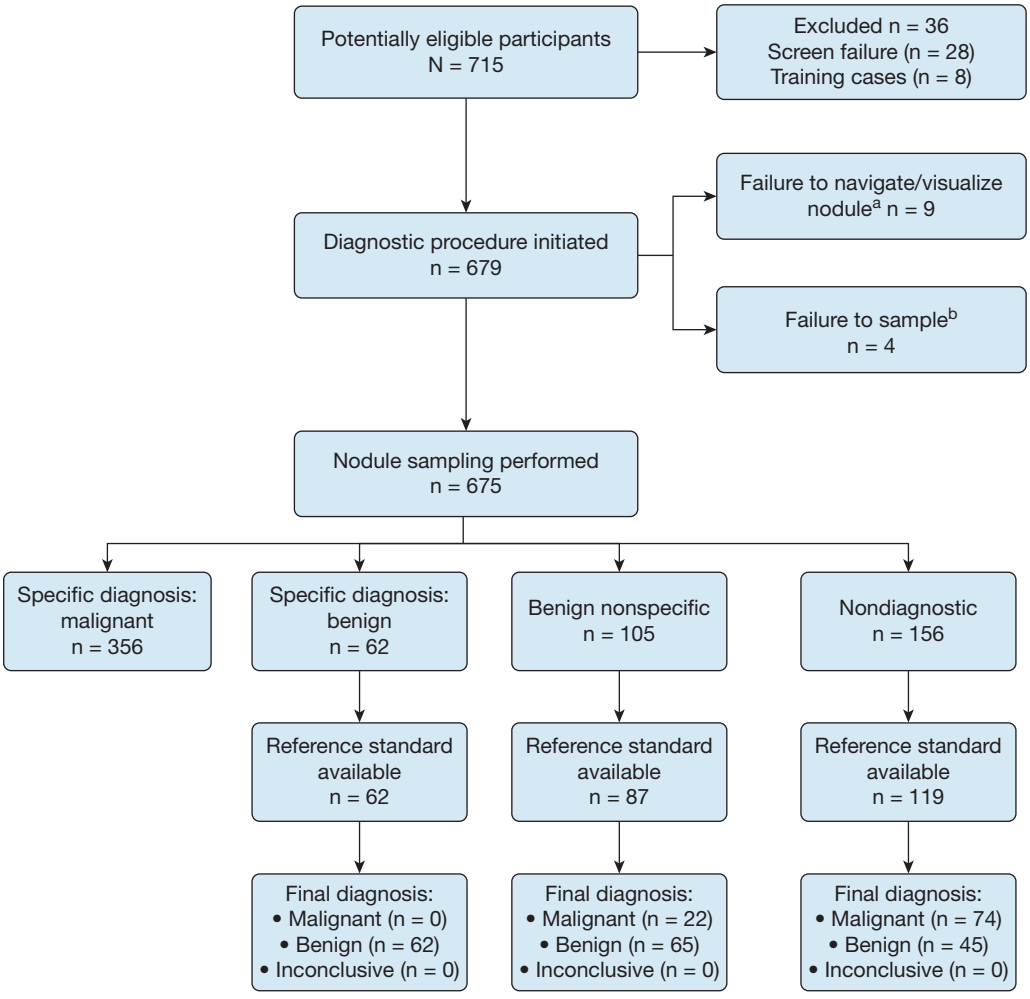

Figure 3 – *Flowchart illustrating the patient population for the TARGET study. This diagram adheres to the ATS/American College of Chest Physicians guidelines.*[17] *[a]Failure to navigate/visualize identified by answering "No" to "Ability to reach targeted lesion with Monarch?" This did not prevent a sample from being taken, and these individuals were not immediately excluded from diagnostic yield analyses. [b]Failure to sample with Monarch responses were converted to salvage procedures and are included as nondiagnostic at index and during follow-up so as to only enter the denominator for diagnostic yield calculation. ATS = American Thoracic Society; TARGET = Transbronchial Biopsy Assisted by Robot Guidance in the Evaluation of Tumors of the Lung Trial.*

included in multivariate analyses due to missing data. The use of CBCT guidance (113 patients [17%]) was not associated with an increased DY. It is unclear whether CBCT imaging may have been used selectively in more challenging lesions, limiting the conclusions that can be drawn from this result. In addition, nodule to pleural distance and lung zone location (proximal, middle, or peripheral) did not affect DY.

To our knowledge, the current study is the largest RAB study to date and includes academic and community centers, providing generalizable estimates of safety and effectiveness in real-world clinical practice. This study was prospectively designed and included adjudication by independent steering committee members of both safety and key efficacy end points, including prespecified categorization of index pathology reports. We are not aware of other large multicenter DY studies that included adjudication. Adjudication adds rigor, as evidenced by a differential estimate of DY. The investigator-reported DY was 83.2%, compared with the adjudicated DY of 61.6% (strict definition). There was high agreement between adjudicators and investigators on malignant diagnoses. Most discrepancies were related to benign abnormalities. For example, patients with nonspecific inflammation or atypical cells were adjudicated as nondiagnostic, whereas in some cases, local investigators had considered such findings diagnostic. The ATS/CHEST consensus statement, which recommends that nonspecific inflammation and atypical cells should be considered nondiagnostic, was

TABLE 5] Summary of Predictors of DY

Variable Category	Strict Definition Index Only (n = 679)			Intermediate DY Definition Follow-up on NSB (n = 679)			Liberal DY Definition Follow-up on NSB and ND (n = 679)		
	No (n = 261)	Yes (n = 418)	Univariate *P* Value/ Logistic *P* Value[a]	No (n = 196)	Yes (n = 483)	Univariate *P* Value/ Logistic *P* Value[a]	No (n = 151)	Yes (n = 528)	Univariate *P* Value/ Logistic *P* Value[a]
Age			.046			.050			.012/.012
< 65 y	92 (44.0)	117 (56.0)		71 (34.0)	138 (66.0)		59 (28.2)	150 (71.8)	
≥ 65 y	169 (36.0)	301 (64.0)		125 (26.6)	345 (73.4)		92 (19.6)	378 (80.4)	
Sex			.48			.27			.32
Female	149 (39.6)	227 (60.4)		115 (30.6)	261 (69.4)		89 (23.7)	287 (76.3)	
Male	112 (37.0)	191 (63.0)		81 (26.7)	222 (73.3)		62 (20.5)	241 (79.5)	
Race			.80			.91			.94
White	225 (38.3)	362 (61.7)		168 (28.6)	419 (71.4)		129 (22.0)	458 (78.0)	
Black	17 (35.4)	31 (64.6)		15 (31.3)	33 (68.7)		11 (22.9)	37 (77.1)	
Asian	12 (40.0)	18 (60.0)		8 (26.7)	22 (73.3)		8 (26.7)	22 (73.3)	
Other	7 (50.0)	7 (50.0)		5 (35.7)	9 (64.3)		3 (21.4)	11 (78.6)	
Ethnicity			.21			.19			.28
Hispanic or Latino	5 (41.7)	7 (58.3)		5 (41.7)	7 (58.3)		4 (33.3)	8 (66.7)	
Not Hispanic or Latino	239 (37.6)	396 (62.4)		178 (28.0)	457 (72.0)		137 (21.6)	498 (78.4)	
Unknown	17 (53.1)	15 (46.9)		13 (40.6)	19 (59.4)		10 (31.3)	22 (68.7)	
BMI			.65			.30			.39
< 30 kg/m^2	190 (37.8)	312 (62.2)		139 (27.7)	363 (72.3)		107 (21.3)	395 (78.7)	
≥ 30 kg/m^2	70 (39.8)	106 (60.2)		56 (31.8)	120 (68.2)		43 (24.4)	133 (75.6)	
COPD/emphysema			.036/.0093			.012/.0008			.029/.0029
No	164 (41.8)	228 (58.2)		128 (32.7)	264 (67.3)		99 (25.3)	293 (74.7)	
Yes	97 (33.9)	189 (66.1)		68 (23.8)	218 (76.2)		52 (18.2)	234 (81.8)	
Asthma			.88			.80			.87
No	223 (38.4)	358 (61.6)		169 (29.1)	412 (70.9)		130 (22.4)	451 (77.6)	
Yes	38 (39.2)	59 (60.8)		27 (27.8)	70 (72.2)		21 (21.6)	76 (78.4)	
Cardiovascular			.082			.49			.85
No	224 (39.9)	337 (60.1)		165 (29.4)	396 (70.6)		124 (22.1)	437 (77.9)	
Yes	37 (31.4)	81 (68.6)		31 (26.3)	87 (73.7)		27 (22.9)	91 (77.1)	
History of lung cancer			.68			.11			.0052/.0010
No	225 (38.1)	365 (61.9)		164 (27.8)	426 (72.2)		121 (20.5)	469 (79.5)	

(Continued)

TABLE 5] *(Continued)*

Variable Category	Strict Definition Index Only (n = 679)			Intermediate DY Definition Follow-up on NSB (n = 679)			Liberal DY Definition Follow-up on NSB and ND (n = 679)		
	No (n = 261)	Yes (n = 418)	Univariate *P* Value/ Logistic *P* Value[a]	No (n = 196)	Yes (n = 483)	Univariate *P* Value/ Logistic *P* Value[a]	No (n = 151)	Yes (n = 528)	Univariate *P* Value/ Logistic *P* Value[a]
Yes	36 (40.4)	53 (59.6)		32 (36.0)	57 (64.0)		30 (33.7)	59 (66.3)	
History of other cancer			.44			.53			.62
No	173 (39.5)	265 (60.5)		130 (29.7)	308 (70.3)		100 (22.8)	338 (77.2)	
Yes	88 (36.5)	153 (63.5)		66 (27.4)	175 (72.6)		51 (21.2)	190 (78.8)	
History of any cancer			.95			.75			.32
No	148 (38.5)	236 (61.5)		109 (28.4)	275 (71.6)		80 (20.8)	304 (79.2)	
Yes	113 (38.3)	182 (61.7)		87 (29.5)	208 (70.5)		71 (24.1)	224 (75.9)	
Family history of lung cancer			.66			.56			.87
No	217 (38.8)	342 (61.2)		164 (29.3)	395 (70.7)		125 (22.4)	434 (77.6)	
Yes	44 (36.7)	76 (63.3)		32 (26.7)	88 (73.3)		26 (21.7)	94 (78.3)	
Family history of other cancer			.90			.31			.44
No	143 (38.2)	231 (61.8)		102 (27.3)	272 (72.7)		79 (21.1)	295 (78.9)	
Yes	118 (38.7)	187 (61.3)		94 (30.8)	211 (69.2)		72 (23.6)	233 (76.4)	
Family history of any cancer			.98			.37			.21
No	124 (38.4)	199 (61.6)		88 (27.2)	235 (72.8)		65 (20.1)	258 (79.9)	
Yes	137 (38.5)	219 (61.5)		108 (30.3)	248 (69.7)		86 (24.2)	270 (75.8)	
Smoking status			.60			.98			.93
Current	51 (35.2)	94 (64.8)		42 (29.0)	103 (71.0)		30 (20.7)	115 (79.3)	
Prior	146 (38.3)	235 (61.7)		108 (28.3)	273 (71.7)		88 (23.1)	293 (76.9)	
Never	63 (42.3)	86 (57.7)		45 (30.2)	104 (69.8)		32 (21.5)	117 (78.5)	
Unknown	1 (25.0)	3 (75.0)		1 (25.0)	3 (75.0)		1 (25.0)	3 (75.0)	
Tobacco use			.33			.71			.82
No	64 (41.8)	89 (58.2)		46 (30.1)	107 (69.9)		33 (21.6)	120 (78.4)	
Yes	197 (37.5)	325 (62.5)		150 (28.5)	376 (71.5)		118 (22.4)	408 (77.6)	
Bronchus sign			.0006/.022			.0015/.012			.050
No	126 (46.3)	146 (53.7)		97 (35.7)	175 (64.3)		71 (26.1)	201 (73.9)	
Yes	135 (33.3)	271 (66.7)		99 (24.4)	307 (75.6)		80 (19.7)	326 (80.3)	

(Continued)

TABLE 5] *(Continued)*

Variable Category	Strict Definition Index Only (n = 679)			Intermediate DY Definition Follow-up on NSB (n = 679)			Liberal DY Definition Follow-up on NSB and ND (n = 679)		
	No (n = 261)	Yes (n = 418)	Univariate *P* Value/ Logistic *P* Value[a]	No (n = 196)	Yes (n = 483)	Univariate *P* Value/ Logistic *P* Value[a]	No (n = 151)	Yes (n = 528)	Univariate *P* Value/ Logistic *P* Value[a]
Lung zone			.23			.32			.48
Proximal	31 (36.5)	54 (63.5)		21 (24.7)	64 (75.3)		15 (17.6)	70 (82.4)	
Middle	96 (35.2)	177 (64.8)		74 (27.1)	199 (72.9)		60 (22.0)	213 (78.0)	
Peripheral	134 (41.9)	186 (58.1)		101 (31.6)	219 (68.4)		76 (23.8)	244 (76.2)	
Lobe location			.55			.34			.70
Left lower	38 (40.0)	57 (60.0)		33 (34.7)	62 (65.3)		24 (25.3)	71 (74.7)	
Left upper	61 (35.7)	110 (64.3)		44 (25.7)	127 (74.3)		36 (21.1)	135 (78.9)	
Right lower	59 (39.6)	90 (60.4)		43 (28.9)	106 (71.1)		31 (20.8)	118 (79.2)	
Right middle	16 (30.2)	37 (69.8)		11 (20.8)	42 (79.2)		9 (17.0)	44 (83.0)	
Right upper	87 (41.4)	123 (58.6)		65 (31.0)	145 (69.0)		51 (24.3)	159 (75.7)	
Upper lobe location			.83			.85			.69
No	113 (38.0)	113 (38.0)		87 (29.3)	210 (70.7)		64 (21.5)	233 (78.5)	
Yes	148 (38.8)	148 (38.8)		109 (28.6)	272 (71.4)		87 (22.8)	294 (77.2)	
Cone-beam CT usage			.90			.59			.34
No	217 (38.3)	349 (61.7)		161 (28.4)	405 (71.6)		122 (21.6)	444 (78.4)	
Yes	44 (38.9)	69 (61.1)		35 (31.0)	78 (69.0)		29 (25.7)	84 (74.3)	
Nodule attenuation			.038			.0016/.0045			.036
Solid	217 (37.0)	370 (63.0)		157 (26.8)	430 (73.2)		123 (21.0)	464 (79.0)	
Subsolid	44 (48.4)	47 (51.6)		39 (42.9)	52 (57.1)		28 (30.8)	63 (69.2)	
Nodule to pleura distance			.39			.66			.63
0-5 mm	135 (39.6)	206 (60.4)		97 (28.4)	244 (71.6)		77 (22.6)	264 (77.4)	
6-15 mm	55 (34.0)	107 (66.0)		44 (27.2)	118 (72.8)		32 (19.8)	130 (80.2)	
> 15 mm	71 (40.6)	104 (59.4)		55 (31.4)	120 (68.6)		42 (24.0)	133 (76.0)	
Procedure duration			.0072			.014			.036
< 30 min	54 (29.2)	131 (70.8)		39 (21.1)	146 (78.9)		29 (15.7)	156 (84.3)	
≥ 30–< 60 min	163 (42.9)	217 (57.1)		125 (32.9)	255 (67.1)		96 (25.3)	284 (74.7)	
≥ 60 min	44 (38.6)	70 (61.4)		32 (28.1)	82 (71.9)		26 (22.8)	88 (77.2)	
R-EBUS image[b]			.0014			.0007			.016
Concentric	84 (29.1)	205 (70.9)		55 (19.0)	234 (81.0)		44 (15.2)	245 (84.8)	

(Continued)

TABLE 5] *(Continued)*

Variable Category	Strict Definition Index Only (n = 679)			Intermediate DY Definition Follow-up on NSB (n = 679)			Liberal DY Definition Follow-up on NSB and ND (n = 679)		
	No (n = 261)	Yes (n = 418)	Univariate *P* Value/ Logistic *P* Value[a]	No (n = 196)	Yes (n = 483)	Univariate *P* Value/ Logistic *P* Value[a]	No (n = 151)	Yes (n = 528)	Univariate *P* Value/ Logistic *P* Value[a]
Eccentric	130 (41.5)	183 (58.5)		97 (31.0)	216 (69.0)		72 (23.0)	241 (77.0)	
Lesion size			.0009/.039			<.0001/ < .0001			.00030/.00030
≤ 20 mm	172 (43.8)	221 (56.2)		139 (35.4)	254 (64.6)		107 (27.2)	286 (72.8)	
> 20 mm	89 (31.2)	196 (68.8)		57 (20.0)	228 (80.0)		44 (15.4)	241 (84.6)	
Estimated malignancy probability			< .0001/< .0001			.0011			.23
0-10	11 (61.1)	7 (38.9)		6 (33.3)	12 (66.7)		3 (16.7)	15 (83.3)	
11-60	134 (51.3)	127 (48.7)		96 (36.8)	165 (63.2)		67 (25.7)	194 (74.3)	
61-100	116 (29.1)	283 (70.9)		94 (23.6)	305 (76.4)		81 (20.3)	318 (79.7)	
Scope to lesion distance			.13			.12			.18
≤ 10 mm	30 (29.7)	71 (70.3)		20 (19.8)	81 (80.2)		15 (14.9)	86 (85.1)	
> 10 - ≤ 20 mm	89 (37.4)	149 (62.6)		70 (29.4)	168 (70.6)		56 (23.5)	182 (76.5)	
> 20 mm	136 (40.7)	198 (59.3)		100 (29.9)	234 (70.1)		76 (22.8)	258 (77.2)	
EBUS staging biopsy of lymph nodules performed			.20			.18			.11
No	116 (41.3)	165 (58.7)		89 (31.7)	192 (68.3)		71 (25.3)	210 (74.7)	
Yes	145 (36.4)	253 (63.6)		107 (26.9)	291 (73.1)		80 (20.1)	318 (79.9)	
Rapid on-site evaluation			.096			.80			.63
No	59 (44.4)	74 (55.6)		39 (29.3)	94 (70.7)		31 (23.3)	102 (76.7)	
Yes	198 (36.5)	344 (63.5)		153 (28.2)	389 (71.8)		116 (21.4)	426 (78.6)	

Data are presented as No. (%). Percentages are calculated by using the row total for each variable presented. *P* values are presented for all variables for univariate comparison (χ^2 test) and for those that remained significant in multivariate logistic regression analyses with stepwise variable selection. No adjustments for multiplicity have been applied. DY = diagnostic yield; EBUS = endobronchial ultrasound; ND = nondiagnostic; NSB = nonspecific benign.

[a]R-EBUS image is excluded from multivariable analysis given missing data on 74 participants.

[b]Only reported for variables that remained significant after stepwise selection in logistic regression model. Candidate set of predictors included in the stepwise logistic model: age category, sex, race, ethnicity, BMI category, COPD/emphysema, cardiovascular medical history, personal history of lung cancer, personal history of extrathoracic malignancy, family history of lung cancer, tobacco use, bronchus sign, lung zone, upper lobe location, nodule attenuation, baseline size category, and estimated probability of malignancy.

not available when investigators were making their initial assessments. These observations highlight the need for more consistency in reporting biopsy findings in future bronchoscopy studies. We provide DY results based on multiple approaches commonly used in the literature, allowing comparison of our study results and aligned with the statement by ATS/CHEST on the Assessment of Advanced Diagnostic Bronchoscopy Outcomes for Peripheral Lung Lesions.[17]

A substantial proportion of patients had both staging EBUS and RAB, an advantage of a single bronchoscopy procedure, with most patients having staging EBUS following RAB. Future research may explore whether positive rapid on-site evaluation on linear EBUS affects the decision to proceed with RAB, and whether there may be a resulting impact to cost-effectiveness or atelectasis.

There are limitations to the current trial, including that this was a single-arm observational study. In addition, although there were both academic and community-based centers in this study, making the findings generalizable, the decision to proceed with bronchoscopic diagnosis of lung lesions may not have been uniform among sites, and there was varying experience of investigators with the RAB technology. Sites began enrolling at various times during the enrollment period, and sites enrolled an average of 3.4 patients per site per month; 5% of screened patients were excluded, and it is possible that some eligible patients may have been omitted due to limited investigator time or research support during the pandemic years. The small number of CBCT users makes interpretation of the DY associated with this technology premature. Future studies should consider randomized trials comparing RAB vs other bronchoscopic platforms (eg, R-RBUS) or CT-guided biopsy for diagnosis of PPLs.

The field continues to struggle with increasing the DY for peripheral bronchoscopy reliably $> 70\%$, particularly in those with small lesions.[11] Future research efforts should remain directed at methods that help with tissue acquisition as well as evaluation of the most appropriate tools for diagnostic biopsy. A randomized trial of ENB vs CT-guided biopsy of PPL, the Navigation Endoscopy to Reach Indeterminate Lung Nodules vs Transthoracic Needle Aspiration (VERITAS) trial,[36] has completed enrollment and has reported noninferiority of ENB. As we work to improve DY of pulmonary nodules, additional outcomes are likely more important to patients and overall care goals. There are currently very few studies assessing the need for salvage procedures, delay in patient care, and overall costs to patients and the health care system.

Interpretation

In this large multicenter prospective study performed across diverse patient populations at academic and community medical centers, robotic bronchoscopy showed safe localization, access, and sampling of peripheral nodules. Successful navigation and localization by radial ultrasound were high, and DY varied depending on the definitions reported by current guidelines and compares favorably to results from large non-robotic bronchoscopy studies. This study adds clarity on lesion and imaging factors that affect diagnostic yield of robotic bronchoscopy.

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Role of sponsors: The sponsor participated in the design of the study, conducting the study, data collection, data management, data analysis, interpretation of the data, and preparation, and review and approval of the manuscript.

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Additional information: The e-Appendixes and e-Tables are available online under "Supplementary Data."

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