ORIGINAL ARTICLE

Diagnostic Yield and Complications of Bronchoscopy for Peripheral Lung Lesions

Results of the AQuIRE Registry

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Abstract

Rationale: Advanced bronchoscopy techniques such as electromagnetic navigation (EMN) have been studied in clinical trials, but there are no randomized studies comparing EMN with standard bronchoscopy.

Objectives: To measure and identify the determinants of diagnostic yield for bronchoscopy in patients with peripheral lung lesions. Secondary outcomes included diagnostic yield of different sampling techniques, complications, and practice pattern variations.

Methods: We used the AQuIRE (ACCP Quality Improvement Registry, Evaluation, and Education) registry to conduct a multicenter study of consecutive patients who underwent transbronchial biopsy (TBBx) for evaluation of peripheral lesions.

Measurements and Main Results: Fifteen centers with 22 physicians enrolled 581 patients. Of the 581 patients, 312 (53.7%) had a diagnostic bronchoscopy. Unadjusted for other factors, the diagnostic yield was 63.7% when no radial endobronchial ultrasound (r-EBUS) and no EMN were used, 57.0% with r-EBUS alone, 38.5% with EMN alone, and 47.1% with EMN combined with r-EBUS. In multivariate analysis, peripheral transbronchial needle aspiration (TBNA), larger lesion size, nonupper lobe location, and tobacco use were associated with increased diagnostic yield, whereas EMN was associated with lower diagnostic yield. Peripheral TBNA was used in 16.4% of cases. TBNA was diagnostic, whereas TBBx was nondiagnostic in 9.5% of cases in which both were performed. Complications occurred in 13 (2.2%) patients, and pneumothorax occurred in 10 (1.7%) patients. There were significant differences between centers and physicians in terms of case selection, sampling methods, and anesthesia. Medical center diagnostic yields ranged from 33 to 73% ($P = 0.16$).

Conclusions: Peripheral TBNA improved diagnostic yield for peripheral lesions but was underused. The diagnostic yields of EMN and r-EBUS were lower than expected, even after adjustment.

Keywords: bronchoscopy; transbronchial biopsy; endobronchial ultrasound; electromagnetic navigation; lung cancer

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At a Glance Commentary

Scientific Knowledge on the Subject: Advanced bronchoscopy techniques for peripheral lung lesions such as electromagnetic navigation (EMN) have been studied in clinical trials, but there are no randomized controlled trials comparing EMN with standard bronchoscopy. Existing studies are limited by the uncertain representativeness of the study populations and by the lack of conventional bronchoscopy controls.

What This Study Adds to the Field: This multicenter registry-based clinical effectiveness study shows that bronchoscopy for peripheral lesions provides moderately high diagnostic yield at relatively low risk. Peripheral transbronchial needle aspiration improved diagnostic yield but was underused. The diagnostic yields of EMN and radial endobronchial ultrasound were lower than expected even after adjustment for other factors.

Diagnosis of peripheral lung nodules and masses can be achieved with a variety of techniques, including bronchoscopy, computed tomography (CT)-guided needle biopsy, and video-assisted thoracoscopic surgery (1–4). Advances in bronchoscopy, including electromagnetic navigation (EMN) and radial endobronchial ultrasound (r-EBUS), have made transbronchial biopsy (TBBx) approaches more appealing (5–8). Diagnostic yields for these advanced bronchoscopic techniques, when used in carefully selected patients in clinical trials, have ranged from 46 to 88% (3, 5, 9, 10). The American College of Chest Physicians (CHEST; formerly known as ACCP) evidence-based lung cancer guidelines recommend that the type of biopsy selected should be based on nodule size, location, relationship to a patent airway, risk of complications, and available expertise (3). However, although these studies of advanced bronchoscopic techniques are promising, much of the data comes from clinical research studies conducted at centers of excellence that examined carefully selected and relatively small populations of patients. One of the acknowledged limitations identified in the CHEST lung cancer guidelines evidence review was that existing studies were limited by the uncertain representativeness of the study populations (3). Whether these results can be generalized to everyday practice is unknown.

Registries offer the benefit of providing clinical effectiveness data that are more generalizable than that obtained from more focused clinical trials (11–13). We used the AQuIRE (ACCP Quality Improvement Registry, Evaluation, and Education) program to evaluate all bronchoscopies performed for diagnosis of peripheral lung nodules and masses. Our primary objective was to quantify the diagnostic yield of different types of bronchoscopy in everyday clinical practice and to identify the factors that affect the diagnostic yield.

Methods

Consecutive patients who underwent bronchoscopy with TBBx of a peripheral nodule or mass from February 2009 to March 2013 were entered into AQuIRE (14). Not all centers started participating at the same time; some participated for the entire duration of the study, whereas others participated for ⩾1 year. Participating physicians agreed to enter all consecutive subjects for the duration of their participation. Data were collected prospectively and entered via a Web-based interface using standardized definitions, quality control checks, and protocols as previously described (11–13). The study was approved by institutional review board committee 4, protocol DR09-0101, at the University of Texas MD Anderson Cancer Center (*see* online supplement for details).

Subjects with peripheral lung nodules and masses were included. The lung periphery was defined as the segmental bronchus or beyond, such that the lesion required TBBx rather than endobronchial biopsy. Information extracted from AQuIRE included patient demographic characteristics, clinical characteristics, physician and hospital information, procedural information, laboratory results, complications, and adverse events.

The primary outcome was the diagnostic yield of bronchoscopy for peripheral lesions, irrespective of the sampling method that established the diagnosis, provided that the technique targeted the peripheral lesion. A bronchoscopy procedure was considered diagnostic if a specific malignant or benign diagnosis of the peripheral lesion was made by any of the following: TBBx, transbronchial brush, bronchoalveolar lavage (BAL), or a peripheral transbronchial needle aspiration (TBNA). If only inflammatory tissue or lymphocytes was obtained, the procedure was considered nondiagnostic. If mediastinal lymph node sampling was done concurrently with sampling of the peripheral lesion, only those techniques that targeted the peripheral lesion were counted. Secondary outcomes included diagnostic yield of each technique separately (i.e., TBBx, brush, BAL, and TBNA), complications, and practice pattern variations (*see* the online supplement for details).

In a subset analysis, follow-up data were collected for subjects who had a nondiagnostic bronchoscopy to establish what the true diagnosis was (*see* Figure E1 in the online supplement). This was used to calculate the sensitivity of bronchoscopy for primary lung cancer. Not all centers participated in this subset analysis; however, participating centers collected follow-up data on all subjects enrolled at their centers. These follow-up data were not part of the standard data set in AQuIRE, and hence, were not required of all centers. All bronchoscopic results that showed lung cancer were considered true positives (TP). If initial bronchoscopy failed to reveal a specific diagnosis, and follow-up data demonstrated that lung cancer was eventually diagnosed, the subject was considered a false negative (FN). If the follow-up data demonstrated that a specific diagnosis was never made, but there was no evidence of growth on serial CT for 1 year, then this subject was considered a true negative (TN). Sensitivity of bronchoscopy for primary lung cancer was defined as TP/(TP + FN). Because some subjects were lost to follow-up, we conducted a sensitivity analysis to determine the possible minimum and maximum diagnostic sensitivities (15). To determine the minimum sensitivity, all subjects lost to follow-up were considered FN. To determine the maximum sensitivity, all subjects lost to follow-up were considered TN.

Statistical Analysis

For each outcome, associations with the corresponding set of variables were checked

Table 1. Patient and Clinical Characteristics

Characteristic	Value (*N* = *581*)
Age, yr, mean ± SD	67.1 ± 12.6
Male:female sex, n (%)	295 (50.8): 286 (49.2)
Inpatient, n (%)	60 (10.3)
Used tobacco, n (%)	470 (80.9)
ASA score, n (%)	
1	6 (1)
2	246 (42.3)
3	309 (53.2)
4	20 (3.4)
Deep sedation or general anesthesia, n (%)	191 (32.9)
Size of largest nodule or mass, n (%)	
⩽2 cm	272 (46.8)
>2 cm	309 (53.2)
Air bronchograms of nodule/mass, n (%)	277 (47.7)
GGO present in the nodule/mass, n (%)	27 (4.6)
Location of nodule/mass, n (%)	
Central 2/3 of the lung on CT	236 (40.6)
Peripheral 1/3 of the lung on CT	345 (59.4)
Upper lobe location of target lesion, n (%)	341 (58.7)
No. of nodules/masses, n (%)	
Single	507 (87.3)
Multiple	74 (12.7)
Procedures performed as part of bronchoscopy, n (%)	
BAL	254 (43.7)
TBBX	581 (100)
Cytology brush	458 (78.8)
Wash	325 (55.9)
TBNA on peripheral nodule / mass	95 (16.4)
Concurrent EBUS-TBNA of mediastinal lymph nodes	299 (51)
BAL location, n (%)	
High yield†	98 (38.6)
Lobar	38 (15)
Low yield†	118 (46.5)
No. of TBBx specimens, n (%)	
<6 specimens taken	188 (32.4)
⩾6 specimens taken	393 (67.6)
Guidance of TBBX, n (%)	
Single-plane fluoroscopy	416 (71.6)
Any EMN/virtual bronchoscopy/CT fluoroscopy*	266 (45.8)
Radial EBUS	385 (66.3)
Biplane fluoroscopy	55 (9.5)
TBNA done in an upper lobe location, n (% based on total N = 95)	50 (52.6)
No. of TBNA passes at peripheral site, n (% based on total N = 95)	
0	486 (83.6)
1–3	72 (12.4)
4–20	23 (4)
Guidance of peripheral TBNA, n (% based on total N = 95)	
Unguided/blind	10 (10.5)
Convex EBUS	22 (23.2)
Conventional fluoroscopy	52 (54.7)
EMN to guide peripheral TBNA*	44 (46.3)
Radial EBUS	47 (49.5)
Onsite cytology	29 (30.5)
Needle gauge used for TBNA of peripheral lesion n (% based on total N = 95)	
19	47 (49.5)
20	1 (1.1)
21	22 (23.2)
22	25 (26.3)

Definition of abbreviations: ASA = American Society of Anesthesiology physical status classification system; BAL = bronchoalveolar lavage; CT = computed tomography; EBUS = endobronchial ultrasound; EMN = electromagnetic navigation; GGO = ground-glass opacity; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; TBBX = transbronchial biopsy; TBNA = transbronchial needle aspiration.

*EMN systems included SuperDimension (n = 252), Veran Medical Technologies (St. Louis, Missouri) (n = 4), Lung point (Broncus Technologies, Mountain View, California) (n = 4), and CT fluoroscopy (n = 14), with a few cases using more than one of these techniques.

†High yield for BAL was defined based on an *a priori* definition of segments that were believed to be likely to have high fluid return based on their anterior locations. High yield was any RUL anterior, RML medial segment, RML lateral segment, RML segment not specified, or RLL anterior basal segment. All other segments were considered low yield.

by χ^2 test or Fisher's exact test (for categorical variables), or checked by Wilcoxon-Mann-Whitney test, as appropriate. We used multivariable hierarchical logistic regression, with subjects nested within physicians nested within centers (*see* the online supplement). We evaluated the interaction between r-EBUS and EMN, based on previous work that suggested that the combination might be better than either alone (10). *P* values <0.05 were considered significant; all tests were two-sided. All statistical analyses were performed in SAS (version 9.3; SAS Institute, Cary, North Carolina) or STATA/IC (12.1; StataCorp, College Station, Texas).

Results

Fifteen centers with 22 physicians enrolled 581 subjects. Clinical characteristics are listed in Table 1, and the bronchoscopic diagnoses are listed in Table 2.

Diagnosis Made by Bronchoscopy

Bronchoscopy was diagnostic in 312 (53.7%) of 581 peripheral lesions. Unadjusted for other factors, the diagnostic yield of bronchoscopy was 63.7% with no r-EBUS and no EMN, 57.0% with r-EBUS alone, 38.5% with EMN alone, and 47.1% with EMN plus r-EBUS. Univariate and multivariate analyses of factors associated with diagnostic yield are listed in Tables 3 and 4. TBNA, larger lesion size, nonupper lobe location, and tobacco use were associated with a higher diagnostic yield. The interaction term to evaluate the effect of r-EBUS, EMN, or their combination was significant, indicating that adding r-EBUS to EMN improved performance more than expected.

Diagnosis Made by Transbronchial Biopsy

TBBx of the peripheral lesions was diagnostic in 251 (43.2%) of the 581 subjects. TBBx was the sole diagnostic test in 11.1% of cases when TBBx, TBNA, brushing, and BAL were all performed. Univariate and multivariate analyses of factors associated with TBBx yield are provided in Tables E8 and E9.

Diagnosis Made by Transbronchial Needle Aspiration

TBNA of the peripheral lesions was diagnostic in 45 (47.4%) of the 95 subjects in whom it was performed. TBNA was

Table 2. Diagnosis Made by Bronchoscopy of Peripheral Pulmonary Lesions

Diagnosis	No. of Patients	
	n	%
Non–small cell lung cancer		
Adenocarcinoma	120	38.5
Squamous	79	25.3
Nonspecified (undifferentiated)	21	6.7
Large cell	1	0.3
Small cell lung cancer	12	3.8
Other primary lung cancer	6	1.9
Carcinoid tumor of the lung	5	1.6
Metastatic to the lung		
From a hematological origin*	7	2.2
Originating from a solid tumor	14	4.5
Epithelioid hemangioendothelioma	1	0.3
Hamartoma	1	0.3
Infection		
Bacterial	16	5.1
Prototheca wickerhamii (an algae)	1	0.3
Fungal		
Aspergillus	3	1.0
Histoplasmosis	2	0.6
Other	4	1.3
Tuberculosis	1	0.3
Viral: other	1	0.3
Sarcoidosis†	9	2.9
Granulomatous inflammation†	2	0.6
Bronchiolitis obliterans organizing pneumonia	3	1.0
Interstitial lung disease: other	1	0.3
Foreign body aspiration	1	0.3
Lipid pneumonia	1	0.3

*Hematologic origin refers to any lymphomas, leukemia, or myeloma.
†Sarcoidosis was a combined clinical–pathologic diagnosis. If the physician found granulomatous inflammation without evidence of infection, but was not certain, this was also clinically consistent with sarcoidosis and termed granulomatous inflammation.

diagnostic, whereas TBBx was nondiagnostic in 9.5% of cases in which both tests were performed. TBNA was the sole positive test in 6.3% of cases when TBBx, TBNA, brushing, and BAL were all performed. Univariate analysis of factors associated with TBNA yield are provided in Table E10. On multivariate analysis, only a peripheral lesion of >2 cm (odds ratio [OR], 2.96; 95% confidence interval [CI], 1.17–7.49; $P = 0.026$) was associated with higher diagnostic yield.

Diagnosis Made by Transbronchial Brush

Transbronchial brushing was diagnostic in 173 (37.8%) of the 458 subjects in whom it was performed. Brushing was diagnostic, whereas TBBx was nondiagnostic in 8.1% of cases in which both tests were performed. Brushing was the sole positive test in 7.4% of subjects when TBBx, TBNA, brushing, and BAL were all performed. Univariate and multivariate analyses of factors associated with transbronchial brush yield are provided in Tables E1 and E2. On multivariate analysis, only tobacco use and lesion size >2 cm were associated with a higher diagnostic yield.

Diagnosis Made by Bronchoalveolar Lavage

BAL was diagnostic in 49 (19.3%) of the 254 subjects in whom it was performed. BAL was positive, whereas TBBx was nondiagnostic in 8.7% of cases in which both tests were performed. BAL was the sole positive test in 2% of subjects when TBBx, TBNA, brush, and BAL were all performed. Univariate analyses of factors associated with BAL yield are provided in Table E3. However, none of these variables had a significant association with diagnostic yield after controlling for the hierarchical structure of the data.

Sensitivity for Lung Cancer

Four centers collected follow-up data on 336 subjects to calculate diagnostic sensitivity. Bronchoscopy was positive for lung cancer in 144 peripheral lesions (*see* Figure E1). A specific diagnosis other than lung cancer was made either by bronchoscopy or subsequent biopsy in 97 subjects (*see* Table E4). There were 51 FN results in which bronchoscopy was negative for lung cancer in the peripheral lesion, but lung cancer was proven in these FN cases by EBUS of the mediastinal lymph nodes during the same bronchoscopy (n = 8), subsequent CT-guided biopsy (n = 14), video-assisted thoracoscopic surgery or thoracotomy (n = 17), repeat bronchoscopy (n = 8), mediastinoscopy (n = 1), and distant biopsy (e.g., adrenal biopsy showing lung cancer) (n = 3). Bronchoscopy did not arrive at a specific diagnosis in 44 subjects who were subsequently lost to follow-up. These subjects were considered indeterminate. We excluded indeterminate cases when calculating the maximum sensitivity, which was 144 of 195 subjects (74%) (95% CI, 67%–80%). We considered indeterminate cases to be FN when calculating the minimum sensitivity, which was 144 of 239 subjects (60%) (95% CI, 54%–67%). *See* Table 5 for stratified analysis.

Complications during the Bronchoscopy

Complications occurred in 13 (2.2%) of the 581 subjects. Complications included pneumothorax (n = 10), bleeding (n = 1), refractory hypoxemia (n = 1), and respiratory failure (n = 1). On univariate analysis, a lesion size of <2 cm ($P = 0.04$) was associated with increased risk of complications (*see* Table E5). However, after controlling for the hierarchical structure of the data, none of the variables had a significant association with complications. A secondary analysis that evaluated pneumothorax is available (*see* Table E6).

Practice Pattern Variations

There were significant differences between centers and between physicians in terms of case selection, as reflected in the size of

Table 3. Patient and Clinical Characteristics by Diagnostic Yield of Bronchoscopy for Peripheral Lesions

	DX Yield by Bronchoscopy		
	No (*N* = *269*)	Yes (*N* = *312*)	*P* Value
Used tobacco, n (%)			
No	64 (57.7)	47 (42.3)	
Yes	205 (43.6)	265 (56.4)	0.008
Size of nodule/mass, n (%)			
⩽2 cm	155 (57)	117 (43)	
>2 cm	114 (36.9)	195 (63.1)	<0.0001
Air bronchograms, n (%)			
Absent	155 (57)	117 (43)	
Present	114 (36.9)	195 (63.1)	0.01
GGO of nodule, n (%)			
False	252 (45.5)	302 (54.5)	
True	17 (63)	10 (37)	0.07
Location of nodule/mass, n (%)			
Central 2/3 of the lung on CT	101 (42.8)	135 (57.2)	
Peripheral 1/3 of the lung on CT	168 (48.7)	177 (51.3)	0.16
No. of nodules/masses, n (%)			
Single	228 (45)	279 (55)	
Multiple	41 (55.4)	33 (44.6)	0.09
Procedure: BAL, n (%)			
No	152 (46.5)	175 (53.5)	
Yes	117 (46.1)	137 (53.9)	0.92
Procedure: cytology brush, n (%)			
No	59 (48)	64 (52)	
Yes	210 (45.9)	248 (54.1)	0.68
Procedure: wash, n (%)			
No	116 (45.3)	140 (54.7)	
Yes	153 (47.1)	172 (52.9)	0.67
Upper lobe location, n (%)			
No	99 (41.3)	141 (58.8)	
Yes	170 (49.9)	171 (50.1)	0.04
No. of TBBx specimens, n (%)			
<6 specimens taken	89 (47.3)	99 (52.7)	
⩾6 specimens taken	180 (45.8)	213 (54.2)	0.79
Guidance of TBBX: single-plane fluoroscopy, n (%)			
No	79 (47.9)	86 (52.1)	
Yes	190 (45.7)	226 (54.3)	0.63
Guidance of TBBX: any EMN or virtual bronchoscopy, n (%)			
No	125 (39.7)	190 (60.3)	
Yes	144 (54.1)	122 (45.9)	0.0005
Guidance of TBBX: radial EBUS, n (%)			
No	81 (41.3)	115 (58.7)	
Yes	188 (48.8)	197 (51.2)	0.09
Guidance of TBBX: biplane fluoroscopy, n (%)			
No	244 (46.4)	282 (53.6)	
Yes	25 (45.5)	30 (54.5)	0.89
TBNA on peripheral nodule/mass, n (%)			
No	236 (48.6)	250 (51.4)	
Yes	33 (34.7)	62 (65.3)	0.01
No. of TBNA passes at peripheral site, n (%)			
1–3	24 (33.3)	48 (66.7)	
⩾4	9 (39.1)	14 (60.9)	0.61
Conventional unguided peripheral TBNA, n (%)			
No	268 (46.9)	303 (53.1)	
Yes	1 (10)	9 (90)	0.02
Guidance of peripheral TBNA: convex EBUS, n (%)			
No	263 (47)	296 (53)	
Yes	6 (27.3)	16 (72.7)	0.07

(Continued)

lesions biopsied and the methods of tissue sampling used (Table 6). Anesthesia methods also varied significantly, with seven centers using moderate sedation in ⩾85% of cases, five centers using deep sedation/general anesthesia in ⩾85% of cases, and three centers using an intermediate case mix of moderate sedation versus general anesthesia. We did not find evidence of an association between type of anesthesia and diagnostic yield or complications.

Of the 15 centers, 3 had access to r-EBUS only, 2 had access to EMN only, 8 had access to both r-EBUS and EMN, and 2 had access to neither. The median number of TBBx per year per physician was 55 (range 4–341). In the 11 centers that used r-EBUS, the median number of r-EBUS TBBx cases per year per physician was 35 (range 3–100), and in the 10 centers that used EMN, the median number of EMN TBBx cases per year per physician was 14 (range 3–50). Of note, this included all centers that a physician worked at. A participating physician might work at two hospitals, but only one hospital might participate in the registry. The cases done at the nonparticipating hospital would not be in AQuIRE. However, in terms of physician experience, we counted any TBBx done at any hospital during the year. In centers that had r-EBUS, size was not related to r-EBUS use (lesion size ⩽2 cm 49% use, lesions >2 cm 51% use; $P = 0.41$). In centers that had EMN, EMN was used more frequently for smaller lesions (⩽2 cm 62% use vs. >2 cm 38% use; $P < 0.001$). When EMN was performed, the average number of TBBx samples taken was slightly higher (6.8 ± 2.2 vs. 5.5 ± 2.1; $P < 0.001$). Similarly, when r-EBUS was performed, more TBBx samples were taken (6.6 ± 2.2 vs. 5.3 ± 2.0; $P < 0.001$). *See* Table E7 for additional comparisons between EMN and r-EBUS. Center diagnostic yields ranged from 33 to 73% ($P = 0.16$).

Discussion

In this study, we quantified the clinical effectiveness of bronchoscopy for peripheral lesions and identified factors associated with diagnostic yield and complications. The overall diagnostic yield of bronchoscopy was 53.7%, whereas the sensitivity for lung cancer was in the 60 to 74% range. Our data were consistent with previous studies of

Table 3. (*Continued*)

	DX Yield by Bronchoscopy		
	No (*N* = *269*)	Yes (*N* = *312*)	*P* Value
Guidance of peripheral TBNA: fluoroscopy, n (%)			
No	251 (47.4)	278 (52.6)	
Yes	18 (34.6)	34 (65.4)	0.08
Guidance of peripheral TBNA: EMN, n (%)			
No	251 (46.7)	286 (53.3)	
Yes	18 (40.9)	26 (59.1)	0.45
Guidance of peripheral TBNA: radial EBUS, n (%)			
No	251 (47)	283 (53)	
Yes	18 (38.3)	29 (61.7)	0.25
Onsite cytology, n (%)			
No	254 (46)	298 (54)	
Yes	15 (51.7)	14 (48.3)	0.55
Deep sedation or general anesthesia, n (%)			
No	185 (47.4)	205 (52.6)	
Yes	84 (44)	107 (56)	0.43

Definition of abbreviations: BAL = bronchoalveolar lavage; CT = computed tomography; DX = diagnostic; EBUS = endobronchial ultrasound; EMN = electromagnetic navigation; GGO = ground-glass opacity; TBBX = transbronchial biopsy; TBNA = transbronchial needle aspiration.

bronchoscopy for peripheral lesions in which the sensitivity of bronchoscopy ranged from 36 to 88% (1, 4, 16). After adjusting for covariates, we found that advanced imaging and guidance with EMN were associated with lower diagnostic yields. The factor most amenable to physician control that improved diagnostic yield was use of peripheral TBNA. This was particularly relevant because there were significant practice pattern variations in terms of case selection, anesthesia, and methods of tissue sampling. Reassuringly, complications remained rare, occurring in 2.2% of subjects, even though a wide variety of techniques were used.

Our registry data also allowed us to evaluate current practice patterns and provided insights into how technologies might affect the clinical effectiveness of bronchoscopy. Previous studies showed that using TBNA to sample peripheral lesions increased yield (16–24). When r-EBUS demonstrated an "eccentric" lesion, which is defined as the probe being largely biased toward one side of the lesion without the lesion completely surrounding the probe, TBNA might theoretically be particularly useful, because other techniques such as brush and TBBx might bypass the lesion (25, 26). Our data confirmed that peripheral TBNA increases yield, but it also showed that the technique is only being used in approximately 16% of cases. However, peripheral TBNA does have limitations; lesions in the upper lobes and in the superior segment of the lower lobes may not be amenable to TBNA because the needle may not be able to navigate the sharp turns required. This may explain some of the underuse of peripheral TBNA (17, 19, 20, 22). On balance, although it is not reasonable to expect 100% use of peripheral TBNA, the 16% use rate observed probably indicates that there is opportunity for improvement.

This study also provides information on the clinical effectiveness of EMN and r-EBUS. A previous metaanalysis of 39 studies found a pooled diagnostic yield of 70% for advanced diagnostic techniques, but there was marked heterogeneity ($P < 0.0001$), with yields ranging from 46% to 86.2% (5). Analysis of EMN studies and r-EBUS studies have arrived at similar results (4). However, there have been no randomized controlled trials (RCTs) that have compared EMN with conventional bronchoscopy, so the incremental benefit of EMN compared with conventional bronchoscopy cannot be determined. One RCT compared EMN with r-EBUS and with the combination of EMN and r-EBUS, but there was no conventional bronchoscopy arm (10). Our diagnostic yield of 57.0% with r-EBUS alone is toward the low end of reported values, whereas our yield of 38.5% with EMN alone is lower than that in previous studies (4). In 14 studies of EMN that involved 932 subjects, the diagnostic yield was 68% in prospective studies and 71% in retrospective studies (4). Our registry results suggest that when EMN and r-EBUS are applied outside of the research setting, they do not perform as well as previously reported in clinical trials.

What can account for the observed differences in diagnostic yield between studies that use EMN and r-EBUS? Publication bias may explain some of the discordance, because small studies with positive results (i.e., higher yield) would be more likely to get published than small studies with negative results. Other possibilities could include differences in the prevalence and types of disease present in the population being studied. The prevalence of cancer in a small focused clinical trial, whether prospective or retrospective, in which only a subset of subjects are chosen for evaluation, may be significantly higher than the prevalence of cancer in consecutive patients who are undergoing TBBx in everyday practice. Similarly, the distribution of diseases encountered in a clinical trial may be much narrower or different than in everyday practice. This probably explains some of the heterogeneity of results in previous metaanalyses (5). For instance, in the one previous RCT of EMN versus r-EBUS versus combination, 70% of subjects had lung cancer, and all subjects were deemed to be good surgical candidates, which is not the case in routine clinical practice, which is what was studied in our registry (10). In other studies of r-EBUS, the prevalence of lung cancer ranged from 67 to 87% (26, 26–28), whereas in our registry, it was 58%. This is not to say that more narrowly targeted studies are incorrect, merely that it is important to consider differences in patient selection when assessing how a technology will actually perform in practice. Our registry study differs from previous investigations of EMN and r-EBUS, because a single standard definition was developed prospectively and was used across multiple centers to capture data on all consecutive subjects who underwent TBBx from a broad range of practices. Therefore, this is more reflective of how this technology performs in everyday practice than in more focused but less representative clinical trials.

However, although issues of publication bias and patient selection could explain differences in diagnostic yield among studies, the more concerning issue is the sensitivity of EMN and r-EBUS. Although diagnostic yield can be significantly affected by patient selection and the prevalence of disease, the data on sensitivity for lung cancer suggest that EMN and r-EBUS performance was worse than expected (Table 5). Comparing the best case scenario of EMN sensitivity versus the worst case scenario of bronchoscopy without EMN shows little difference in sensitivity. The same is true for r-EBUS. Based on the previous literature, we would have expected both EMN and r-EBUS to be associated with significantly higher sensitivity (4–6, 29). The absence of benefit seen with EMN and r-EBUS may have been due to patient selection, with more difficult cases being selected for EMN and r-EBUS. This is supported by the relatively high sensitivity of conventional bronchoscopy observed and the observation that patients with smaller lesions were more likely to undergo EMN.

In multivariate models of diagnostic yield, after adjustment for size, location, TBNA use, and tobacco use, EMN was still associated with lower diagnostic yields (Table 4). Of note, r-EBUS was not associated with lower yield in either univariate or multivariate analysis, but in contrast to the previous literature, we found no evidence of benefit either (4–6). Even so, there may be residual confounding that has not been accounted for in the multivariate models. For example, in those centers that have both EMN and r-EBUS, it may be that when r-EBUS visualizes the lesion, EMN is not used. This would result in EMN being preferentially used on the hardest cases, even after adjusting for size. It is important to emphasize that the magnitude of the effect of such unmeasured factors on the observed sensitivity and yield of EMN and r-EBUS could be large.

In addition, factors other than patient selection and residual confounding may be at work. If we view EMN as essentially conventional bronchoscopy plus EMN, then it seems counter-intuitive to believe that EMN could ever be worse than conventional bronchoscopy alone. However, for this to be true, the bronchoscopist would need to do a conventional bronchoscopy and take the same number of biopsies as usual and then take additional biopsies using EMN guidance. Therefore, the number of biopsies would double, and the combination could not then be worse than conventional bronchoscopy alone. However, that is not what happens. Instead, with EMN, the number of biopsies is roughly equal to that of a conventional bronchoscopy, and all the biopsies are done with EMN. Therefore, it is possible that EMN or any other technique can be worse than conventional bronchoscopy when the routine conventional biopsies are not done. In addition, there are other technologies that are integral to EMN that may affect yield—specifically, extended working channels (EWC). When the bronchoscopist arrives at the target using EMN, they withdraw the EMN probe, but leave the EWC in place. The EWC is essentially a catheter that ensures the same place will be sampled. The bronchoscopist passes the forceps through the EWC and takes the first biopsy outside the EWC. The forceps are removed while leaving the EWC in the same place. The second biopsy is done using the same method, so it will be almost on top of the first biopsy; there is very little variation. All biopsies are in a tight cluster. If the EWC is in the target, there will be many "hits," but if it is not in the target, then everything is likely to be negative; therefore, an all or none phenomenon occurs. Conversely, with conventional bronchoscopy, the between-pass variation is significant; hitting the same spot exactly is rare. However, the same spot does not always need to be hit, because only one or two hits of the 6 to 8 passes are needed. Thus, conventional bronchoscopy samples different areas in the region of interest. The result is that conventional bronchoscopy samples a larger volume than EWC biopsies, because each pass is distinct. How bronchoscopists use the EWC may be driving outcomes and may explain some of the differences in EMN yield. EWC use in this study tracks exactly with r-EBUS and EMN use; therefore, we cannot separate the effects of EWC from EMN.

This also explains the synergy observed between r-EBUS with EMN. With EMN/r-EBUS, if the bronchoscopist sees that they are not in precisely the correct area with r-EBUS, they are more likely to go back and sample a different area. Hence, it is quite plausible that EMN plus r-EBUS performs better than EMN alone; this is what we found and what has been reported previously (10). Even then, the use of the EWC means that sampling will be in a very tight cluster. This can be an advantage if r-EBUS shows that the EWC is surrounded by the lesion (i.e., concentric); however, at other times, this tight clustering may be a disadvantage (25, 26). Therefore, it is really the aggregate performance of the entire system that drives outcome. The individual parts interact (e.g., EMN/r-EBUS/EWC), and bronchoscopy is the platform that delivers these systems. However, EMN is not "conventional bronchoscopy plus"; it is a system unto itself. The observed performance of EMN is probably

Table 4. Multivariate Logistic Regression Model for Diagnostic Yield of Bronchoscopy for Peripheral Lesions

	Odds Ratio	95% CI	*P* Value*
Model without interaction terms			
Use tobacco: yes vs. no	1.95	1.25–3.03	0.003
Size >2 cm vs. ⩽2 cm	2.05	1.44–2.93	<0.001
Upper lobe: yes vs. no	0.67	0.47–0.96	0.028
Guidance: any EMN or virtual bronchoscopy: yes vs. no	0.59	0.41–0.85	0.004
TBNA with fluoroscopy: yes vs. no	2.23	1.19–4.19	0.013
Model with interaction terms			
Use tobacco: yes vs. no	2.00	1.28–3.13	0.002
Size >2 cm vs. ⩽2 cm	2.18	1.52–3.12	<0.001
Upper lobe: yes vs. no	0.67	0.47–0.96	0.03
Guidance: any EMN: yes vs. no	0.33	0.16–0.71	0.005
Guidance: r-EBUS: yes vs. no	0.61	0.38–0.99	0.04
Guidance: combination of EMN and r-EBUS	2.40	1.00–5.74	0.05
TBNA with fluoroscopy: yes vs. no	2.30	1.22–4.33	0.01

Definition of abbreviations: CI = confidence interval; EMN = electromagnetic navigation; r-EBUS = radial endobronchial ultrasound; TBNA = transbronchial needle aspiration.
**P* value for testing for homogeneity in hierarchical models is 1.0.

Table 5. Sensitivity of Bronchoscopy for Peripheral Diagnosis of Lung Cancer

Variable	Minimum Sensitivity* (*N = 239*)	Maximum Sensitivity† (*N = 195*)
Bronchoscopy, all cases	60%	74%
Size		
⩽2 cm	50%	67%
>2 cm	71%	79%
Location		
Central 2/3 of the lung on CT	60%	71%
Peripheral 1/3 of the lung on CT	60%	76%
EMN status		
Used	54%	69%
Not used	68%	79%
r-EBUS status		
Used	56%	70%
Not used	73%	85%
No r-EBUS or EMN used	78%	91%

Definition of abbreviations: CT = computed tomography; EMN = electromagnetic navigation; r-EBUS= endobronchial ultrasound.
*Minimum sensitivity was based on the assumption that all patients lost to follow-up (n = 44) actually had lung cancer (i.e., were false negative).
†Maximum sensitivity was based on the assumption that all patients lost to follow-up did not have lung cancer (i.e., were true negatives).

determined partially by how the bronchoscopist uses the EWC, whether r-EBUS is used, whether TBNA is performed, and other residual confounding and patient selection factors.

The data from the AQuIRE registry can provide some insight into how these complex systems perform in everyday practice, but it is also important to recognize the limitations of this study. These include its retrospective design and the limited ability to use surgery as a gold standard to establish diagnostic sensitivity. This limits our ability to arrive at precise estimates of sensitivity, but this is a necessary tradeoff if we are to measure clinical effectiveness in routine practice, in which a significant portion of patients cannot undergo a surgical biopsy. Another issue is context variables. These are an important consideration when studying bronchoscopy because they affect patient selection and yield. The decision to proceed with bronchoscopy and the resulting diagnostic yield are contingent on the alternative strategies available to physicians. If interventional radiology is not strong, then bronchoscopy may be used more often than it would otherwise be in centers that have access to quality interventional radiology services. This may affect diagnostic yield significantly, because it affects patient selection, although it is difficult to know in which direction this would lead (i.e., higher or lower yields). Other examples of relevant context variables include the availability of anesthesia services for bronchoscopy and the quality of pathology and cytology services (12, 30). We controlled for center-level effects in the model, and there were no center-level effects evident; however, the number of institutions involved was relatively small, so these results should be viewed as exploratory. Finally, as with all registry studies, the associations observed are not necessarily causal; therefore, caution should be used when interpreting the results.

However, because of these limitations, we believe that the data from this registry calls into question whether or not the system of EMN/EWC is truly superior to conventional bronchoscopy. Most previous EMN studies did not have a direct comparator, but rather compared the diagnostic yield of EMN to that reported in the literature (4, 5). However, when the only comparator is historical controls, publication bias and selection bias can lead to a false sense of security and overestimation of how well new technologies perform. In addition, if EMN is superior to conventional bronchoscopy, it is important to ask whether the magnitude of the benefit is worth the cost. This requires quantification of the marginal benefit of EMN versus conventional bronchoscopy. Without high-quality RCTs, this is difficult to tell. Unfortunately, there are no RCTs of EMN versus conventional bronchoscopy.

In summary, this registry-based clinical effectiveness study shows that bronchoscopy provides moderately high diagnostic yield at relatively low risk. Peripheral TBNA improved diagnostic yield but was underused. Appropriate use of TBNA for peripheral lesions represents a quality improvement opportunity. In addition, the diagnostic yield of EMN and r-EBUS were lower than expected even after adjustment for other factors. Although selection bias and study design issues limit the strength of the inferences that can be drawn, based on these results, it is apparent that further systematic study of these technologies is needed. Because patient selection varies between those who receive CT-guided biopsy and those who receive EMN and/or r-EBUS or conventional bronchoscopy (5), the diagnostic yield and complication rate of these alternatives need to be studied prospectively. Publication bias and selection bias combined with single arm cohort studies may have led to a

Table 6. Center- and Physician-Level Practice Pattern Variations

Variable	Center-Level Range of Values	*P* Value	Physician-Level Range of Values	*P* Value
Percentage of cases with lesions ⩽2 cm in size	17–71%	<0.001	13–67%	0.002
Use of deep sedation or general anesthesia	0–100%	<0.001	0–100%	<0.001
Peripheral TBNA use	4–40%	<0.001	0–40%	<0.001
EMN use	0–83%	<0.001	0–75%	<0.001
r-EBUS use	0–86%	<0.001	0–100%	<0.001

Definition of abbreviations: EMN = electromagnetic navigation; r-EBUS= endobronchial ultrasound; TBNA = transbronchial needle aspiration.

systematic overestimation of how well EMN performs in relation to conventional bronchoscopy. Because of the performance of the technology and the costs associated with it, RCTs are necessary to more accurately quantify the magnitude of the risks and the benefits. Clinical effectiveness studies can be complementary to these RCTs, because they provide insights into how well these techniques perform in actual practice. However, both are needed, and in the case of EMN in particular, what is lacking is multicenter RCT data that demonstrates superiority. ■

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