ORIGINAL ARTICLE

Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: One-Year Results of the Prospective, Multicenter NAVIGATE Study

Erik E. Folch, MD,[a,*] Michael A. Pritchett, DO,[b] Michael A. Nead, MD,[c]
Mark R. Bowling, MD,[d] Septimiu D. Murgu, MD,[e] William S. Krimsky, MD,[f]
Boris A. Murillo, MD,[g] Gregory P. LeMense, MD,[h] Douglas J. Minnich, MD,[i,j]
Sandeep Bansal, MD,[k] Blesilda Q. Ellis, MD,[l] Amit K. Mahajan, MD,[m]
Thomas R. Gildea, MD,[n] Rabih I. Bechara, MD,[o] Eric Sztejman, MD,[p]
Javier Flandes, MD,[q] Otis B. Rickman, DO,[r] Sadia Benzaquen, MD,[s]
D. Kyle Hogarth, MD,[t] Philip A. Linden, MD,[u] Momen M. Wahidi, MD,[v]
Jennifer S. Mattingley, MD,[w,x] Kristin L. Hood, PhD,[x] Haiying Lin, MS,[x]
Jennifer J. Wolvers, BSc,[x] Sandeep J. Khandhar, MD,[m] for the NAVIGATE Study
Investigators

[a]Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
[b]Pulmonary Department, Pinehurst Medical Clinic and FirstHealth Moore Regional Hospital, Pinehurst, North Carolina
[c]University of Rochester Medical Center, Rochester New York
[d]Department of Internal Medicine, Division of Pulmonary Critical Care and Sleep Medicine, Brody School of Medicine, East Carolina University, Greenville, North Carolina
[e]Interventional Pulmonology Program, The University of Chicago Medicine, Chicago, Illinois
[f]Pulmonary and Critical Care Associates of Baltimore, Baltimore, Maryland
[g]Providence Health Center and Waco Lung Associates, Waco, Texas
[h]Blount Memorial Physicians Group, Alcoa, Tennessee
[i]Division of Cardiothoracic Surgery, University of Alabama at Birmingham, Birmingham, Alabama
[j]Princeton Baptist Medical Center, Birmingham, Alabama
[k]Penn Highlands Healthcare, DuBois, Pennsylvania
[l]Pulmonary Associates of Mobile PC, Mobile, Alabama
[m]Inova Health System, Falls Church, Virginia
[n]Department of Pulmonary, Allergy, and Critical Care Medicine and Transplant Center, Cleveland Clinic, Cleveland, Ohio
[o]Morehouse School of Medicine, and Cancer Treatment Centers of America, Newnan, Georgia

PVirtua Pulmonary Group, Marlton, New Jersey
qPulmonary Department, IIS-Fundacion Jimenez Diaz University Hospital, CIBERES, Madrid, Spain
rDepartment of Medicine and Thoracic Surgery, Vanderbilt University Medical Center, Ingram Cancer Center, Nashville, Tennessee
sUniversity of Cincinnati Physicians Company LLC, Cincinnati, Ohio
tThe University of Chicago Medicine, Chicago, Illinois
uDivisions of Thoracic and Esophageal Surgery, Department of Surgery, University Hospitals Cleveland Medical Center and Case Western Reserve School of Medicine, Cleveland, Ohio
vDepartment of Medicine, Duke University Medical Center, Durham, North Carolina
wGundersen Health System, La Crosse, Wisconsin
xMedtronic, Minneapolis, Minnesota

ABSTRACT

Introduction: Electromagnetic navigation bronchoscopy (ENB) is a minimally invasive technology that guides endoscopic tools to pulmonary lesions. ENB has been evaluated primarily in small, single-center studies; thus, the diagnostic yield in a generalizable setting is unknown.

Methods: NAVIGATE is a prospective, multicenter, cohort study that evaluated ENB using the superDimension navigation system (Medtronic, Minneapolis, Minnesota). In this United States cohort analysis, 1215 consecutive subjects were enrolled at 29 academic and community sites from April 2015 to August 2016.

Results: The median lesion size was 20.0 mm. Fluoroscopy was used in 91% of cases (lesions visible in 60%) and radial endobronchial ultrasound in 57%. The median ENB planning time was 5 minutes; the ENB-specific procedure time was 25 minutes. Among 1157 subjects undergoing ENB-guided biopsy, 94% (1092 of 1157) had navigation completed and tissue obtained. Follow-up was completed in 99% of subjects at 1 month and 80% at 12 months. The 12-month diagnostic yield was 73%. Pathology results of the ENB-aided tissue samples showed malignancy in 44% (484 of 1092). Sensitivity, specificity, positive predictive value, and negative predictive value for malignancy were 69%, 100%, 100%, and 56%, respectively. ENB-related Common Terminology Criteria for Adverse Events grade 2 or higher pneumothoraces (requiring admission or chest tube placement) occurred in 2.9%. The ENB-related Common Terminology Criteria for Adverse Events grade 2 or higher bronchopulmonary hemorrhage and grade 4 or higher respiratory failure rates were 1.5% and 0.7%, respectively.

Conclusions: NAVIGATE shows that an ENB-aided diagnosis can be obtained in approximately three-quarters of evaluable patients across a generalizable cohort based on prospective 12-month follow-up in a pragmatic setting with a low procedural complication rate.

Introduction

Guidelines recommend the least invasive method possible for the evaluation of suspicious lung nodules based on the pre-test probability of malignancy.[1] Electromagnetic navigation bronchoscopy (ENB) is recommended for peripheral lesions difficult to reach with conventional bronchoscopy alone.[2] However, as with all diagnostic modalities, the diagnostic yield, sensitivity, and negative predictive value (NPV) of ENB must be established to achieve sufficient confidence in a nonmalignant result and guide further evaluation based on patient comorbidities and cancer risk.

More than 100 ENB studies have been published (Supplemental Data 1); however, most were retrospective, single-center, and conducted by expert users. Furthermore, long-term follow-up of initially negative or indeterminate diagnoses is often incomplete. Thus, the generalizability of diagnostic yield data in the ENB literature is unknown.

NAVIGATE is a large, multicenter cohort study that prospectively evaluated the diagnostic yield of ENB with rigorous follow-up to ensure that negative or indeterminate results are truly negative.[3] One-month safety and usage patterns of the first 1000 subjects enrolled have been published.[4] The current analysis of the full United States cohort is the first opportunity to assess ENB diagnostic yield across diverse settings in a real-world, patient-centered design. This 12-month analysis has broad and immediate applicability given the current challenges in the management of nodules detected incidentally and through low-dose computed tomography (CT) screening.

Materials and Methods

NAVIGATE is a prospective, multicenter, global, single-arm, pragmatic cohort study of ENB using the superDimension navigation system, version

6.0 or higher (Medtronic, Minneapolis, Minnesota).[5] Consecutive adult subjects presenting with a lung lesion requiring evaluation and who were candidates for an elective ENB procedure according to physician judgment were enrolled. There were no protocol-specified restrictions on procedural technique, complementary tools, or imaging (planning or surveillance); these were subject to the clinician's discretion, but were prospectively captured. Biopsy tools used by the NAVIGATE investigators were aspirating needles, biopsy forceps, cytology brushes, needle-tipped cytology brushes, the superDimension triple-needle cytology brush (Medtronic), the GenCut core biopsy system (Medtronic), and bronchoalveolar lavage (considered a tool for the purposes of this analysis).[4] Lymph node staging by linear endobronchial ultrasound (EBUS) could occur before, during, or after the index procedure at physician discretion. Any patients initially considered for ENB who obtained a diagnosis by linear EBUS that precluded the need for ENB evaluation of a lung lesion were not enrolled. A maximum of 75 subjects per site was allowed to ensure diversity. Source-data verification was conducted in 25% of subjects using risk-based monitoring. Twenty-four–month follow-up was pre-specified at all sites. The study is registered on ClinicalTrials.gov (NCT02410837) and the full study design has been published.[3]

In the overall study, subjects were enrolled at 37 sites in the United States and Europe. The focus herein is on the 12-month follow-up of the United States cohort. Twelve-month follow-up in Europe is ongoing.

The primary endpoint was ENB-related pneumothorax requiring intervention or hospitalization, which was chosen as a safety endpoint applicable to ENB-guided lung lesion biopsy, fiducial placement, or dye marking. Safety endpoints were defined according to the validated Common Terminology Criteria for Adverse Events scale (CTCAE) and adjudicated by an independent medical monitor.[3]

For the purposes of this 12-month analysis, pathology results of ENB-aided biopsy samples that were diagnostic of a nonmalignant condition or indeterminate were referred to as negative for malignancy or negative, for brevity. Follow-up was then conducted to determine the true diagnosis (malignant or nonmalignant). All cases were followed according to the practitioner's judgment (e.g., surgical tissue biopsy, repeat ENB, CT-guided transthoracic needle biopsy or aspiration [TTNA], serial CT imaging, and lung health visits). Cases with subsequent diagnostic tests confirming a nonmalignant diagnosis or without lesion progression on radiographic follow-up were considered true-negative as of 12 months, consistent with prior ENB studies (Supplemental Data 2). If the follow-up diagnostics revealed malignancy or if lesion growth was observed on repeat imaging with appropriate follow-up diagnostic testing, this was considered a false-negative. The following were also considered false-negative: death due to lung cancer within 12 months; treatment without a confirmed diagnosis; and new diagnoses of cancer in the lung from any site (including non-index lesions, or lymph nodes diagnosed as malignant by linear EBUS during or after the index procedure).

Twelve-month diagnostic yield was calculated per subject as the rate of true-positives (for malignancy) plus true negatives (for malignancy) of all subjects with attempted lung lesion biopsies. Negative cases with insufficient information to evaluate 12-month diagnostic yield were deferred for analysis at 24 months. These cases were included in a sensitivity analysis, assuming all were false-negative and then true-negative, to provide low and high estimates of 12-month diagnostic yield, sensitivity, and NPV. All subjects will be followed through 24 months in accordance with guideline recommendations.[6]

Analyses were performed using SAS Version 9.4 (SAS Inc., Cary, North Carolina). Data are summarized by descriptive statistics, including frequency distributions and cross-tabulations for discrete variables and mean, standard deviation, median, interquartile range, minimum, and maximum values for continuous variables. Univariate and multivariate logistic regression models were conducted to determine predictors of 12-month diagnostic yield. After selecting candidate variables, multivariate logistic regression analyses were conducted using stepwise selection procedures with an entry significance level of 0.20 and an exit significance level of 0.05.

Ethics

This study is being conducted in accordance with the Declaration of Helsinki and all local regulatory requirements. The protocol was approved by the institutional review board of all participating sites. All subjects provided written informed consent.

Role of the Funding Source

Results

Subjects Included in the Analysis

At the 12-month snapshot, 1215 subjects were enrolled at 29 United States sites (11 academic, 12 private, and 6 mixed centers) (Supplemental Data 3) from April 2015 to August 2016. ENB aided in lung lesion biopsy (n = 1157 subjects), fiducial placement (n = 258), pleural dye marking (n 2 3), and/or lymph node biopsy (n = 30) (Fig. 1). Linear EBUS-guided lymph node staging was conducted during the ENB procedure in 448 subjects. Results of ENB-aided dye marking and fiducial placement to localize lesions for surgical resection or stereotactic body radiation therapy have been published.[4]

Follow-up was completed in 98.9% (1202 of 1215) at 1 month and 80.3% (976 of 1215) at 12 months (±30 days) (Fig. 2). Including all available information through 395 days post-procedure, follow-up regarding the initial ENB-aided diagnosis was obtained in 91.0% of biopsy subjects.

Subject, Lesion, and Procedural Characteristics

Subject, lesion, and procedural characteristics are shown in Table 1. The average age was 67.6 ± 11.3 years (range: 21.0–93.0 years). Fifteen percent had a history of lung cancer. The median lesion size was 20 mm; most lesions were between 14 mm (quartile 1) and 30 mm (quartile 3) (Supplemental Data 4). Lesions were 10 mm or greater from the pleura in 48.8% (649 of 1329); 25% were on the pleura (Fig. 3). General anesthesia was used in 81.4% of procedures (989 of 1215) and moderate sedation was used in 18.6%. One to five lesions were sampled per subject (average: 1.2 lesions). The pre-test probability of malignancy was greater than 65% in 59.0% of subjects by physician assessment and 51.9% using a validated risk model.[7] Concurrent imaging included fluoroscopy in 91.0% (lesions visible in 60% by physician reports), radial EBUS (rEBUS) in 57.4%, and cone-beam CT in 4.9%. The median ENB planning time was 5.0 minutes (Q1, 4.0 min – Q3, 9.0 min). The median total procedure time (bronchoscope in to bronchoscope out) was 52.0 minutes, which included 25.0 minutes of ENB-specific navigation and sampling time (first entry to last exit of the locatable guide or extended working channel [EWC]). The median ENB-specific procedure time was 30.0 minutes with rapid on-site evaluation (ROSE) and 18.0 minutes without ROSE.

ENB-Related Adverse Events

Pneumothorax requiring hospitalization or intervention (CTCAE grade 2 or greater) occurred in 2.9% (35 of 1215). Any-grade pneumothorax occurred in 4.3%.
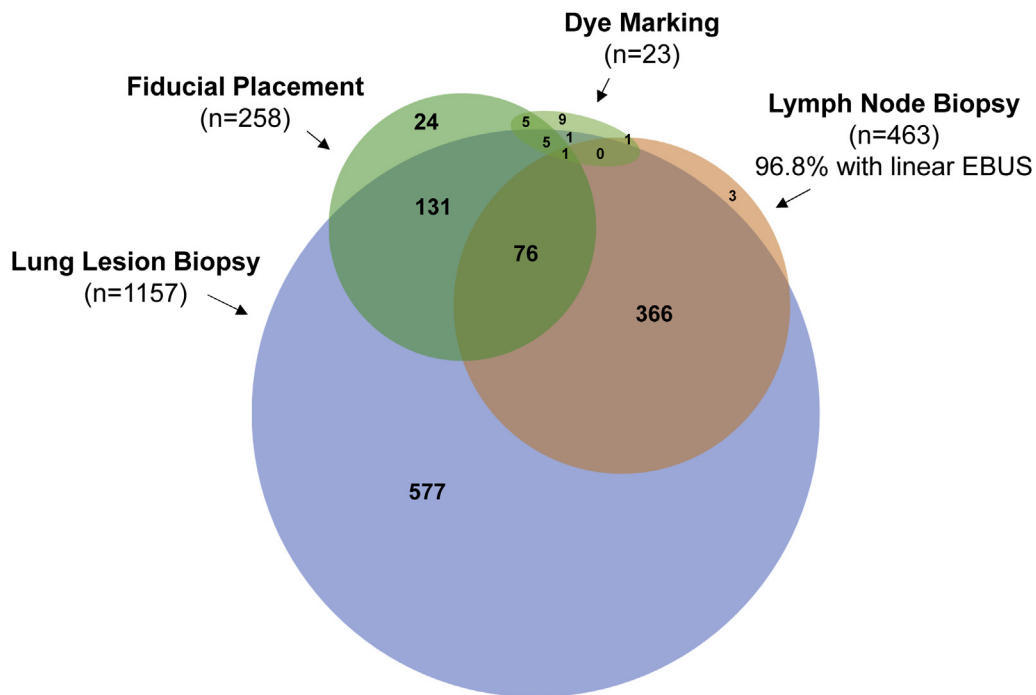
Figure 1. Reasons for conducting ENB in NAVIGATE. The NAVIGATE ENB index procedure could be conducted for more than one purpose in the same anesthetic event, including lung lesion biopsy, fiducial marker placement, pleural dye marking, or lymph node biopsy. Not drawn to scale. Not shown in graph: fiducial placement plus lymph node biopsy (n = 15); fiducial placement plus lymph node biopsy plus dye marking (n = 1). Revised and used with permission under a Creative Commons license (http://creativecommons.org/licenses/by/4.0/).[4] ENB, electromagnetic navigation bronchoscopy.

```
┌─────────────────────────────────────────────┐
│   NAVIGATE United States Cohort (n=1,215)     │
└─────────────────────────────────────────────┘
                      │
                      ▼
┌─────────────────────────────────────────────┐
│      ENB Procedure Performed (n=1,215)        │
└─────────────────────────────────────────────┘
```

1-Month Follow-up Visit Not Completed (n=13)
- Study Withdrawal (n=6)
- Lost-to-Follow-up (n=0)
- Death prior to Follow-Up Visit (n=7)

1-Month Follow-Up Visit Completed
(n=1,202; 98.9%)

12-Month Follow-up Visit Not Completed (n=239)
- Study Withdrawal (n=27)
- Lost-to-Follow-up (n=10)
- Death prior to Follow-Up Visit (n=202)

12-Month Follow-Up Visit Completed
(n=976; 80.3%)

Figure 2. Subjects included in the analysis. NAVIGATE United States cohort 12-month analysis. ENB, electromagnetic navigation bronchoscopy.

Bronchopulmonary hemorrhage occurred in 2.5% overall and 1.5% CTCAE grade 2 or greater. Grade 4 or greater respiratory failure occurred in 0.7%.

There were 233 deaths within 12 months. There was one anesthesia-related death due to grade 5 hypoxic respiratory failure 9 days post-ENB in a subject with multiple comorbidities.[4] No deaths were related to the ENB device or associated tools.

Diagnostic Outcomes

Among the 1157 lung lesion biopsy cases, navigation was successful and tissue was obtained in 94.4% (1092 of 1157) (Fig. 4). Navigation was unsuccessful in 65 patients (Supplemental Data 4). ENB-aided biopsy procedures diagnosed malignancy in 44.3% (484 of 1092) and were negative (see definition in Methods) in 55.7% (608 of 1092) (Fig. 4). Malignancies included 35.1% with NSCLC and 4.3% with metastatic carcinoma. Negative cases were evaluated according to clinical and radiologic follow-up using a predetermined hierarchy of certainty. As of 12 months, 284 initially negative outcomes were considered true-negative and 220 were false-negative. The physician-estimated pretest probability of malignancy was 81.8% in true-positives, 70.4% in false-negatives, and 47.8% in true-negatives.

The 12-month diagnostic yield was 72.9% (Table 2), calculated as true-positives (for malignancy) plus true-negatives (for malignancy) (numerator = 484 + 284) (Fig. 4) of all attempted biopsy cases excluding the deferred cases (denominator = 1157 – 104). The denominator included subjects with unsuccessful navigation. Twelve-month diagnostic yield ranged from 66.4% to 75.4% assuming all deferred cases were false-negatives and true-negatives, respectively. Sensitivity for malignancy and NPV were 68.8% (range: 59.9%–68.8%) and 56.3% (range: 46.7%–63.8%), respectively (Table 2). All positive and negative results will be re-evaluated at 24 months.

Multivariate predictors of diagnostic yield are shown in Figure 5. A personal history of cancer was a significant multivariate predictor of lower diagnostic yield. Use of less than three biopsy tools, lymph node sampling during the ENB procedure, presence of a

Table 1. Demographics, Lesion Properties, Procedural Characteristics

Demographics	N = 1215 Subjects
Subject Age ≥65 years	64.6% (785/1215)
Male	50.8% (617/1215)
Non-Caucasian race	14.8% (180/1215)[a]
Hispanic or Latino ethnicity	2.1% (26/1215)
Tobacco history (current or former)	79.6% (966/1214)
Chronic obstructive pulmonary disease	44.6% (541/1214)
Personal history of cancer	48.7% (591/1214)
Family history of cancer	61.7% (749/1214)

Lesion properties	N = 1344 lesions in 1157 subjects undergoing lung lesion biopsy
Average lesion size < 20 mm	49.1% (660/1343)
Upper lobe lesion location	58.0% (780/1344)
Lesion in peripheral third of the lung	66.9% (899/1344)
Median distance from lesion to pleura (mm)	9.0 (1-20)
Ground glass lesions (Suzuki class 1 or 2)	6.3% (84/1338)
Spiculated lesion border	59.9% (804/1342)
Bronchus sign present on CT	48.5% (652/1344)
Multiple lesions sampled	13.7% (158/1157)
Pre-test probability of malignancy ≥65%[b]	59.0% (591/1002)[c]

Procedure characteristics	N = 1215 ENB procedures in 1215 subjects
General anesthesia	81.4% (989/1215)
Radial EBUS used during ENB	57.4% (698/1215)
Cone-beam CT used during ENB	4.9% (60/1215)
Fluoroscopy used during ENB	91.0% (1223/1344 lesions)
ROSE used	68.5% (748/1092 subjects)
Median total procedure time (bronchoscope in/out)	52.0 min (35-71)
Median ENB-specific procedure time (LG/EWC in/out)	25.0 min (14-40)
≥3 Biopsy tools used to sample lung lesions	72.7% (794/1092)
Operator experience prior to NAVIGATE	
0-4 ENB cases per month	7.9% (96/1215)
5-10 ENB cases per month	46.6% (566/1215)
> 10 ENB cases per month	45.5% (553/1215)
ENB-guided fiducial placement conducted	21.2% (258/1215)

Data are presented as % (n/N), or median (Q1-Q3).
[a]Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander.
[b]Physician estimate.
[c]Data missing in 342 lesions in 303 subjects.
CT, computed tomography; ENB, electromagnetic navigation bronchoscopy; EBUS, endobronchial ultrasound; ROSE, rapid on-site evaluation; LG, locatable guide; EWC, extended working channel.

bronchus sign, biopsy of multiple lesions, and procedure time less than 60 minutes were significant multivariate predictors of higher diagnostic yield. Unadjusted for other factors, diagnostic yield was 70.6% in cases using rEBUS and 76.4% without rEBUS (univariate $p = 0.04$); however, the multivariate effect was not statistically significant. ROSE use (78.6%, versus 75.8% without ROSE), lesion size 20 mm or greater (77.6%, versus 67.3% for lesions less than 20 mm), and upper lobe location (76.5%, versus 67.9% for middle/lower) were not significant multivariate predictors of diagnostic yield. Lesion size 20 mm or greater and upper-lobe location were significant univariate factors (Supplemental Data 5).

In the 423 subjects diagnosed with primary lung cancer, the clinical stage as reported by the investigator after the ENB procedure (and any contemporaneous EBUS-guided staging) was 54.1% stage I, 11.1% stage II, 17.0% stage III, and 17.7% stage IV.

Molecular Analysis

Molecular testing was attempted in 30.7% of subjects with adenocarcinoma or NSCLC not otherwise specified (80 of 261), including 19.0% (27 of 142) in stage I, 29.6% (8 of 27) in stage II, 29.3% (12 of 41) in stage III, 64.7% (33 of 51) in stage IV, and 57.9% (33 of 57) in stage IIIB/IV combined. Providers' reasons for not testing stage IIIB/IV samples were "not necessary" in 17.5%, "not standard practice" in 14.0%, and "other" in 10.5%. Among the 80 subjects (87 lung lesions) with molecular evaluation attempted, tissue was adequate to complete testing in 86.2% (75 of 87). Results indicated mutations in EGFR, KRAS, and BRAF in 14.7% (11 of 75), 9.3% (7 of 75), and 1.3% (1 of 75), respectively, and ALK receptor tyrosine kinase (ALK) and ROS1 rearrangements in 4.0% (3 of 75) and 1.3% (1 of 75), respectively.

Discussion

NAVIGATE is the first large, multicenter study to evaluate ENB diagnostic yield and complication rates with prospective, long-term follow-up of negative cases in the context of real-world decision-making and diverse practice patterns. NAVIGATE highlights the complexities of lung nodule management and provides a new benchmark for the validation of future diagnostic modalities.

Diagnostic Yield in Perspective

The NAVIGATE 12-month diagnostic yield was 73%, which is consistent with published pooled ENB diagnostic yield estimates of 65% to 73%.[8,9] Accounting for

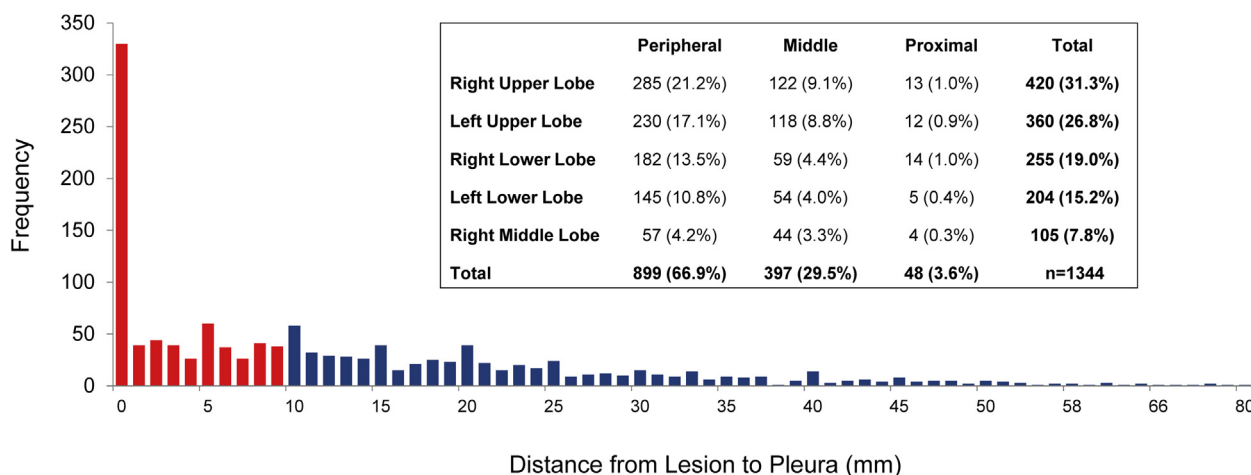|	Peripheral	Middle	Proximal	Total
Right Upper Lobe	285 (21.2%)	122 (9.1%)	13 (1.0%)	**420 (31.3%)**
Left Upper Lobe	230 (17.1%)	118 (8.8%)	12 (0.9%)	**360 (26.8%)**
Right Lower Lobe	182 (13.5%)	59 (4.4%)	14 (1.0%)	**255 (19.0%)**
Left Lower Lobe	145 (10.8%)	54 (4.0%)	5 (0.4%)	**204 (15.2%)**
Right Middle Lobe	57 (4.2%)	44 (3.3%)	4 (0.3%)	**105 (7.8%)**
Total	**899 (66.9%)**	**397 (29.5%)**	**48 (3.6%)**	**n=1344**

Figure 3. Lesion location. Graph shows distance from lung lesion to pleura in 1344 lesions (1157 subjects undergoing lung lesion biopsy). Lesions were less than 10 mm from the pleura (*red bars*) in 680 of 1329 (51.2%) and 10 mm or greater from the pleura (*blue*) in 649 of 1329 (48.8%). Lesions were on the pleural surface in 330 of 1329 (24.8%). Data missing in 15 subjects. Inset shows lesion distribution by lung lobe and location.

the low and high scenarios, NAVIGATE suggests that diagnostic yield in the 66% to 75% range is achievable in challenging lesions across academic and community settings. Of note, NAVIGATE cases with unsuccessful navigation were included in the diagnostic yield denominator. This is aligned with the purpose of ENB as a navigation tool and provides a more conservative estimate. Excluding unsuccessful navigation cases would have resulted in a diagnostic yield of 77.7% (low–high estimates: 70.3% – 79.9%).

TTNA diagnostic accuracy ranges from 75% to 97%, with a published meta-analysis rate of 92%.[10] However, few TTNA studies report the long-term follow-up of negative results. In one analysis, half of all negative TTNA specimens were false-negative (51% NPV for malignancy).[11] In contrast to NAVIGATE's consecutive enrollment, most TTNA studies also exclude patients at high risk for complications (i.e., chronic obstructive pulmonary disease [COPD]) or with lesions not reachable percutaneously. TTNA has been associated with pooled pneumothorax rates of 19% to 25%,[10,12] which could be even higher when accounting for immediate aspiration of periprocedural pneumothoraces.[13] The pneumothorax risk in NAVIGATE was low (4.3% overall and 2.9% requiring hospitalization or intervention) and was not increased in subjects with COPD or poor pulmonary function.[14] With 25% of lesions on the pleura and similar diagnostic yield regardless of the distance from the pleura (Supplemental Data 5*B*), NAVIGATE suggests that lesions traditionally evaluated with percutaneous biopsy can safely undergo ENB with mediastinal staging in the same anesthetic episode.

Negative Results in Clinical Practice

At 12 months, 284 NAVIGATE cases were considered true-negative. Initially negative results were re-evaluated at 12 months based on pre-specified criteria (Fig. 4) aligned with guidelines.[1,6] Whereas some were confirmed by surgical tissue biopsy, repeat ENB, or TTNA, most were followed with serial CT imaging. Those with lesion resolution or stability are assumed to be true-negative for malignancy as of 12 months. Assumptions made in everyday practice must be categorized within a clinical study to readily compare across data sets. Although true-negatives represent the largest area of uncertainty at 12 months, they provide insight into real-life scenarios in patient management that physicians face every day. To truly measure the accuracy of any diagnostic procedure for lung nodules would require surgical resection and biopsy following every negative result. However, that approach would expose patients to unnecessary risk. Guidelines recommend surgical biopsy when the pretest probability is greater than 65%.[1] NAVIGATE true-negative cases followed radiologically had an average pretest probability of only 47%. NAVIGATE suggests that many practitioners use a watch-and-wait approach for lesions with a low/moderate malignancy risk. As a minimally invasive option for both diagnosis and staging, ENB may draw a higher proportion of intermediate-risk nodules, in keeping with published guidelines.[1] The 12-month prevalence of malignancy in NAVIGATE is 67%, similar to 76.5% (range: 57%–92%) reported in one ENB meta-analysis.[9] Thus, although ENB has a NPV of only 56% it provides a low-risk option for concurrent diagnostic testing, EBUS-guided staging, and localization (by fiducial markers or
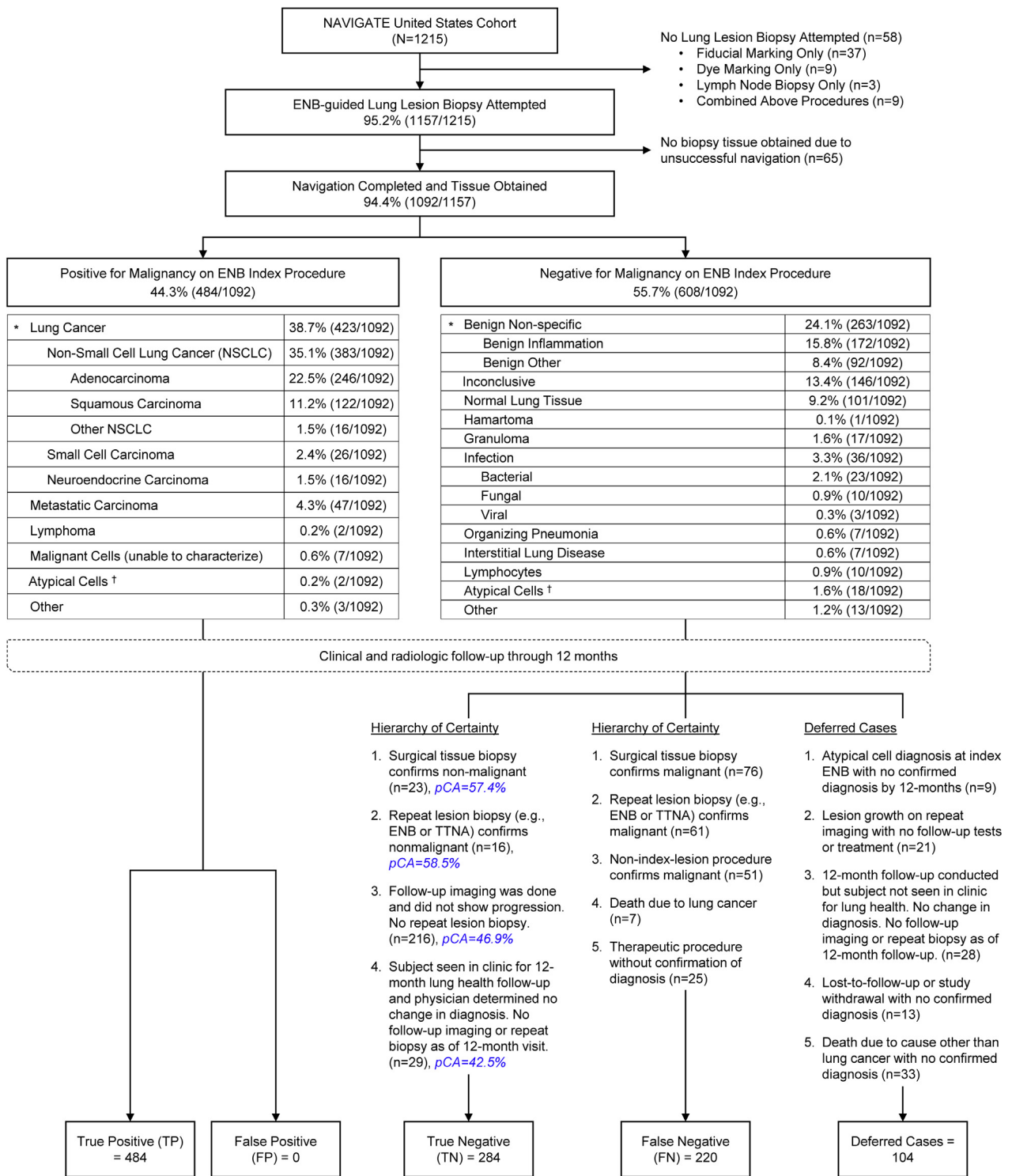
NAVIGATE United States Cohort
(N=1215)

No Lung Lesion Biopsy Attempted (n=58)
- Fiducial Marking Only (n=37)
- Dye Marking Only (n=9)
- Lymph Node Biopsy Only (n=3)
- Combined Above Procedures (n=9)

ENB-guided Lung Lesion Biopsy Attempted
95.2% (1157/1215)

No biopsy tissue obtained due to
unsuccessful navigation (n=65)

Navigation Completed and Tissue Obtained
94.4% (1092/1157)

Positive for Malignancy on ENB Index Procedure
44.3% (484/1092)

* Lung Cancer	38.7% (423/1092)
Non-Small Cell Lung Cancer (NSCLC)	35.1% (383/1092)
Adenocarcinoma	22.5% (246/1092)
Squamous Carcinoma	11.2% (122/1092)
Other NSCLC	1.5% (16/1092)
Small Cell Carcinoma	2.4% (26/1092)
Neuroendocrine Carcinoma	1.5% (16/1092)
Metastatic Carcinoma	4.3% (47/1092)
Lymphoma	0.2% (2/1092)
Malignant Cells (unable to characterize)	0.6% (7/1092)
Atypical Cells †	0.2% (2/1092)
Other	0.3% (3/1092)

Negative for Malignancy on ENB Index Procedure
55.7% (608/1092)

* Benign Non-specific	24.1% (263/1092)
Benign Inflammation	15.8% (172/1092)
Benign Other	8.4% (92/1092)
Inconclusive	13.4% (146/1092)
Normal Lung Tissue	9.2% (101/1092)
Hamartoma	0.1% (1/1092)
Granuloma	1.6% (17/1092)
Infection	3.3% (36/1092)
Bacterial	2.1% (23/1092)
Fungal	0.9% (10/1092)
Viral	0.3% (3/1092)
Organizing Pneumonia	0.6% (7/1092)
Interstitial Lung Disease	0.6% (7/1092)
Lymphocytes	0.9% (10/1092)
Atypical Cells †	1.6% (18/1092)
Other	1.2% (13/1092)

Clinical and radiologic follow-up through 12 months

Hierarchy of Certainty

1. Surgical tissue biopsy confirms non-malignant (n=23), *pCA=57.4%*

2. Repeat lesion biopsy (e.g., ENB or TTNA) confirms nonmalignant (n=16), *pCA=58.5%*

3. Follow-up imaging was done and did not show progression. No repeat lesion biopsy. (n=216), *pCA=46.9%*

4. Subject seen in clinic for 12-month lung health follow-up and physician determined no change in diagnosis. No follow-up imaging or repeat biopsy as of 12-month visit. (n=29), *pCA=42.5%*

Hierarchy of Certainty

1. Surgical tissue biopsy confirms malignant (n=76)

2. Repeat lesion biopsy (e.g., ENB or TTNA) confirms malignant (n=61)

3. Non-index-lesion procedure confirms malignant (n=51)

4. Death due to lung cancer (n=7)

5. Therapeutic procedure without confirmation of diagnosis (n=25)

Deferred Cases

1. Atypical cell diagnosis at index ENB with no confirmed diagnosis by 12-months (n=9)

2. Lesion growth on repeat imaging with no follow-up tests or treatment (n=21)

3. 12-month follow-up conducted but subject not seen in clinic for lung health. No change in diagnosis. No follow-up imaging or repeat biopsy as of 12-month follow-up. (n=28)

4. Lost-to-follow-up or study withdrawal with no confirmed diagnosis (n=13)

5. Death due to cause other than lung cancer with no confirmed diagnosis (n=33)

True Positive (TP) = 484

False Positive (FP) = 0

True Negative (TN) = 284

False Negative (FN) = 220

Deferred Cases = 104

Figure 4. Diagnostic results. Algorithm for determining 12-month diagnostic outcomes in subject undergoing ENB-guided lung lesion biopsy. Twelve-month follow-up was prospectively captured at all clinical sites, including all follow-up visits, diagnostic tests, imaging, and procedures. For the purposes of this analysis, "Negative for Malignancy" refers to ENB-guided biopsy results that were diagnostic of a non-malignant condition or indeterminate. *Patients with multiple lesions may be represented more than once in all subcategories. †Atypical cells categorized as malignant were diagnosed by the providing physician as malignant. Atypical cells categorized as indeterminate were considered nonmalignant by the providing physician, pending further diagnostic testing. pCA, pre-test probability of malignancy (physician estimate); ENB, electromagnetic navigation bronchoscopy; TTNA, transthoracic needle aspiration.

Table 2. Outcomes at 12 Months[a]

	Excluding Deferred Cases (n = 1053)	Low Estimate (n = 1157)	High Estimate (n = 1157)
12-month diagnostic yield ([TP + TN] / all attempted biopsies)	72.9% (768/1053)	66.4% (768/1157)	75.4% (872/1157)
Sensitivity for malignancy (TP / [TP + FN])	68.8% (484/704)	59.9% (484/808)	68.8% (484/704)
Specificity for malignancy (TN / [FP + TN])	100% (284/284)	100% (284/284)	100% (388/388)
Positive predictive value (TP / [TP + FP])	100% (484/484)	100% (484/484)	100% (484/484)
Negative predictive value (TN / [FN + TN])	56.3% (284/504)	46.7% (284/608)	63.8% (388/608)

12-month diagnostic yield includes cases with no tissue obtained due to unsuccessful navigation (n = 65) in the denominator.
[a]n = 1157 subjects with lung lesion biopsy attempted.
FN, false-negative for malignancy; FP, false-positive for malignancy; TN, true-negative for malignancy; TP, true-positive for malignancy.

pleural dye) of intermediate-risk nodules, which may be particularly advantageous in patients with poor pulmonary function.[14]

There were 101 (9.6%) pathology reports of normal lung tissue in NAVIGATE, including 42 categorized as false-negative and 40 as true-negative. The remaining 19 cases were deferred and included in the low/high estimate scenarios. Six of 40 normal lung tissue cases considered true-negatives were diagnosed by surgical tissue biopsy, repeat ENB, or TTNA; the rest were followed by serial CT without evidence of lesion progression (31 cases) or office visits in which the provider reported no change in diagnosis (3 cases). Although inaccurate ENB-guided localization could explain some normal lung tissue findings, nodule resolution between the initial CT and the ENB procedure may also have occurred. In prior studies, 7% to 10% of nodules decreased in size or resolved compared to initial CT findings.[15,16]

The Importance of Follow-Up

When conducting large studies, detailed longitudinal follow-up of indeterminate results is critical. It is acknowledged that not all true-negatives can currently be considered a final diagnosis.

NAVIGATE is the first large, multicenter study to follow negative results over time within the continuum of patient care. As in most prior ENB studies, the diagnostic yield calculation in NAVIGATE includes true-positives and true-negatives (Supplemental Data 2). A large multicenter ENB registry reported diagnostic yields of 38.5% for ENB alone and 47.1% for ENB + rEBUS.[17] However, follow-up was limited to 4 of 15 centers, and true-negatives based on radiographic follow-up were excluded from the diagnostic yield numerator. In the follow-up subset, the sensitivity of ENB for malignancy was estimated at 54% to 69%, similar to the NAVIGATE sensitivity estimates (60%–69%).[17]

All negative results will be evaluated over 24 months in accordance with accepted guidelines,[6] thus reflecting what practitioners face daily in their practice. The final follow-up of NAVIGATE will help delineate those negative results that should have a repeat biopsy based on the pretest probability of malignancy.

Multivariate Predictors of Diagnostic Yield

With consecutive enrollment, NAVIGATE includes a significant portion of traditionally difficult lesions: 49% were less than 20 mm, 58% were in the upper lobe, 51% without a reported bronchus sign, 67% in the peripheral third of the lung, 25% on the pleura, and 41% with a low/moderate pretest probability. Multivariate predictors of increased diagnostic yield were procedure time less than 60 minutes, use of fewer than three biopsy tools, lymph node sampling, biopsy of multiple lesions, and presence of a bronchus sign.

The effect of tool use and procedure time may be intuitively explained by more complex cases in those situations requiring more time and more tools to achieve desired results. Similarly, intuition would suggest that lymph node sampling and biopsy of multiple lesions during ENB may provide additive information to assist pathologists in making a diagnostic call. Further research is required to tease out these multifactorial effects.

The absence of a bronchus sign has been associated with lower diagnostic yield in prior ENB and rEBUS studies, with ENB diagnostic yields of 31% to 44% without a bronchus sign.[18-20] The diagnostic yield of 67% in non–bronchus-sign NAVIGATE cases may reflect improved software, user training, experience, and tool availability in more recent years.

Surprisingly, the NAVIGATE diagnostic yield was higher without rEBUS use (76.4%) than with rEBUS use (70.6%), although the multivariate effect was not statistically significant. In a randomized trial, diagnostic yield was significantly higher with ENB + rEBUS (87.5%) than with ENB alone (59.0%).[21] Balancing lesion complexity between groups in a randomized setting eliminates the effect of patient selection. rEBUS may be used selectively for the most challenging cases, or when accurate ENB localization is uncertain. AQuIRE
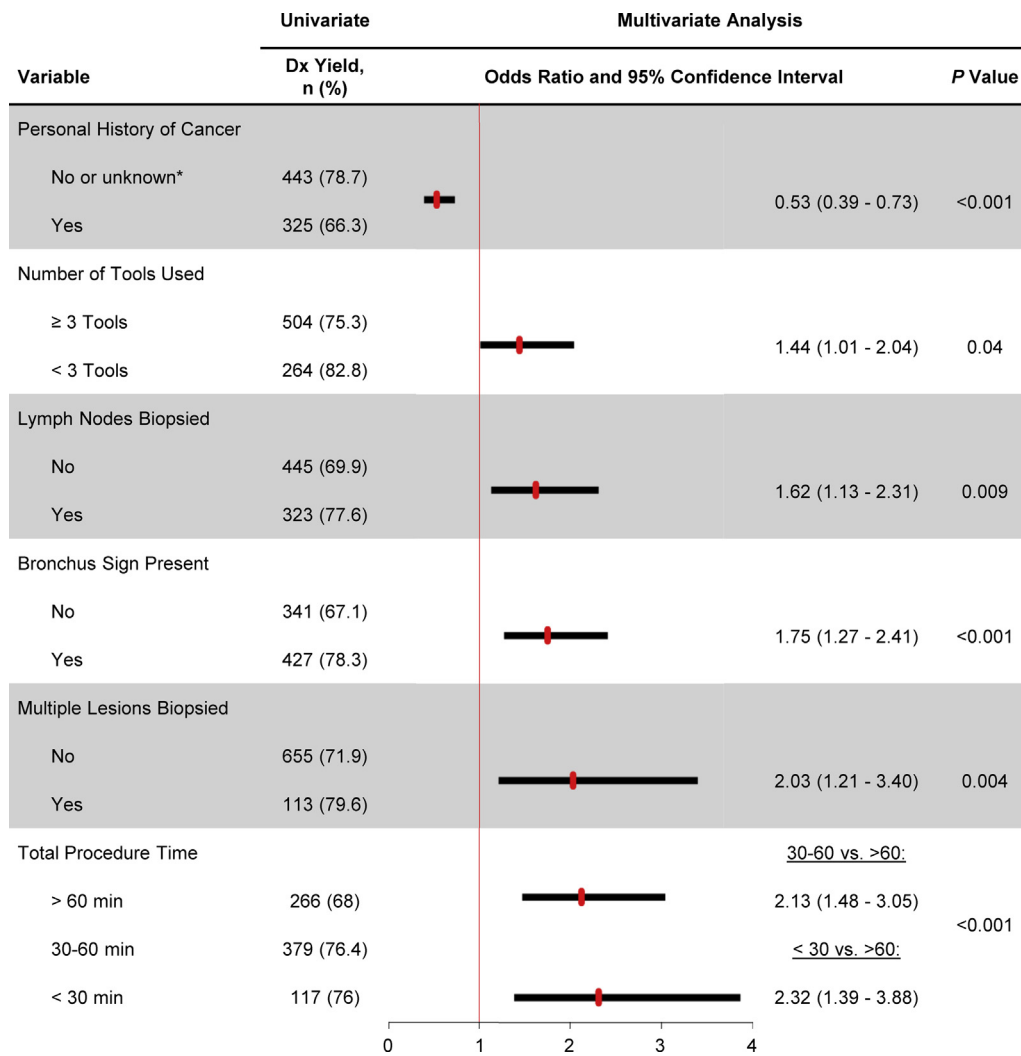
	Univariate	Multivariate Analysis	
Variable	**Dx Yield, n (%)**	**Odds Ratio and 95% Confidence Interval**	***P* Value**
Personal History of Cancer			
No or unknown*	443 (78.7)	0.53 (0.39 – 0.73)	<0.001
Yes	325 (66.3)		
Number of Tools Used			
≥ 3 Tools	504 (75.3)	1.44 (1.01 – 2.04)	0.04
< 3 Tools	264 (82.8)		
Lymph Nodes Biopsied			
No	445 (69.9)	1.62 (1.13 – 2.31)	0.009
Yes	323 (77.6)		
Bronchus Sign Present			
No	341 (67.1)	1.75 (1.27 – 2.41)	<0.001
Yes	427 (78.3)		
Multiple Lesions Biopsied			
No	655 (71.9)	2.03 (1.21 – 3.40)	0.004
Yes	113 (79.6)		
Total Procedure Time		30-60 vs. >60:	
> 60 min	266 (68)	2.13 (1.48 – 3.05)	<0.001
30-60 min	379 (76.4)	< 30 vs. >60:	
< 30 min	117 (76)	2.32 (1.39 – 3.88)	

Figure 5. Univariate (*left*) and multivariate logistic regression models (*right*) for 12-month diagnostic yield. Predictors of 12-month diagnostic yield in all subjects with ENB-guided biopsy attempted, excluding 104 deferred cases but including 65 cases with unsuccessful navigation (N = 1053) (Fig. 4). *Personal history of cancer unknown in 16 subjects. See Supplemental Data 5 for the full univariate analysis. The following factors were evaluated (significant univariate predictors are indicated with † and significant multivariate predictors are indicated with ‡): age, sex, race, ethnicity, smoking, COPD, personal history of cancer,[†,‡] family history of cancer, anesthesia type, radial EBUS used,[†] fluoroscopy, cone-beam CT, ROSE, 3 or more biopsy tools,[†,‡] total procedure time,[†,‡] fiducial placement, lymph node sampling,[†,‡] lesion size smaller than 20 mm,[†] upper lobe location,[†] peripheral location, distance to pleura, ground glass morphology, lesion border (spiculated or not), bronchus sign present,[†,‡] multiple lesions biopsied,[‡] operator experience (cases per month before NAVIGATE), and pre-test probability of malignancy. ENB, electromagnetic navigation bronchoscopy; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ROSE, rapid on-site evaluation; Dx, diagnostic.

found no significant benefit of rEBUS and the authors theorized that rEBUS and ENB were used in the most difficult cases.[17] In a nonrandomized study, diagnostic yield was 71.4% without rEBUS and 73.1% with rEBUS.[22] rEBUS may also give operators a false sense of security if, after visual confirmation by rEBUS, biopsy tool insertion causes deflection of the EWC. However, NAVIGATE only evaluated whether rEBUS was used during ENB and not whether rEBUS provided visual location confirmation. Thus, any conclusions with regard to rEBUS use are speculative.

Integrated Approach

NAVIGATE supports ENB as an integrated approach to aid in lung lesion biopsy, localization by pleural dye marking and fiducial placement (Fig. 1), and tissue collection for molecular testing.[4] Lymph node staging was attempted during the ENB index procedure in 463 subjects. Although 448 of those were guided by linear EBUS, bronchoscopy allows ENB-guided lung lesion biopsy and staging in the same anesthetic event, in contrast to transthoracic methods. Of the NAVIGATE subjects diagnosed with lung cancer, 65% were at stage

I-II at the time of the ENB index procedure. The ability to diagnose early and stage in a single procedure may improve survival and reduce treatment costs.[23,24] Furthermore, the overall procedure time in this study was less than an hour, including 25 minutes of ENB-specific navigation and biopsy time.

Tissue adequacy for molecular testing was 86% in NAVIGATE. A meta-analysis of EBUS-guided transbronchial needle aspiration reported a 95% adequacy rate.[25] The molecular testing failure rate of percutaneous transthoracic core-needle biopsies was reported at 32% for EGFR, compared to 11% for transbronchial biopsies.[26] Molecular testing was attempted in only 58% of NAVIGATE stage IIIB/stage IV cases. Although current guidelines recommend molecular testing for all late-stage NSCLC, the NAVIGATE results reflect guidelines and practice patterns during study enrollment (2015–2016).[27] With frequent guideline updates, the number of actionable genomic alterations has now more than doubled.[27] In a 15-center study of 814 stage IIIB/IV patients (2013–2015), only 58% underwent guideline-recommended EGFR and ALK testing.[28] Molecular testing in NAVIGATE may have been underestimated if conducted on a different sample or if tissue was sent to an external oncologist and not reported to the NAVIGATE clinical site. Lack of reimbursement may also reduce molecular testing rates, particularly at community centers. With continuing discussions regarding the value of broad-based genomic analysis and routine testing of early-stage cancers, these observations will need to be tested in future studies.[29]

Limitations

Although single-arm and nonrandomized, NAVIGATE was designed as a pragmatic, observational study to reflect everyday practice patterns and provide a generalizable assessment of ENB diagnostic yield and safety.[5] The study did not dictate — and thus was not designed to validate — physician judgment in patient selection or technique, including stage of disease, rEBUS or fluoroscopy use, or whether to conduct molecular testing. Thus, the study is not able to answer questions about the optimal ENB technique. Because the majority of operators conducted more than five ENB cases per month before participation in NAVIGATE, the current results may need to be confirmed in physicians conducting fewer than five cases per month (Supplemental Data 5C). The 12-month results have immediate applicability given the current challenges in lung nodule diagnosis and management; however, final 24-month follow-up will provide a full evaluation of negative results and the association between pretest probability and diagnostic accuracy based on patient and lesion risk factors.

Conclusions

The NAVIGATE results are the most robust and generalizable ENB data yet collected in the bronchoscopic literature and show that a diagnosis can be safely obtained in approximately three-quarters of evaluable patients with pulmonary lesions across community and academic settings and in challenging areas of the lung. Future technologies aim to increase diagnostic yield by providing real-time location confirmation and improved visualization. The NAVIGATE methodology sets new standards for the clinical burden of proof to evaluate the safety and efficacy of novel diagnostic platforms.

Acknowledgments

Appendix

Carlos Anciano, East Carolina University, Greenville, NC, USA

Alejandro Aragaki, University of Cincinnati Physicians Company, LLC, Cincinnati, OH, USA

Douglas Arenberg, University of Michigan, Ann Arbor, MI, USA

Omar Awais, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Ricardo Balestra, University of Cincinnati Physicians Company, LLC, Cincinnati, OH, USA

Sandeep Bansal, Penn Highlands Healthcare, DuBois, PA, USA

Emanuela Barisione, IRCCS Azienda Ospedaliera Universitaria San Martino, Genova, Italy

Rabih Bechara, Southeastern Regional Medical Center, Newnan, GA, USA

Sadia Benzaquen, University of Cincinnati Physicians Company, LLC, Cincinnati, OH, USA

Michela Bezzi, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

Krishnendu Bhadra, Pulmonary Medicine Center of Chattanooga, Chattanooga, TN, USA

Julio Bird, Gunderson Lutheran Medical Foundation, Inc., La Crosse, WI, USA

Alessandro Blanco, IRCCS Azienda Ospedaliera Universitaria San Martino, Genova, Italy

Mark Bowling, East Carolina University, Greenville, NC, USA

Robert Cerfolio, University of Alabama at Birmingham, Birmingham, AL, USA

Merete Christensen, Rigshospitalet, Copenhagen, Denmark

Joseph Cicenia, Cleveland Clinic, Cleveland, OH, USA

Antony Courey, University of Michigan, Ann Arbor, MI, USA

John Doty, Carolinas HealthCare System, Charlotte, NC, USA

Kevin Eggleston, CAMC Health Education and Research Institute, Inc., Charleston, WV, USA

Blesilda Ellis, Pulmonary Associates of Mobile, P.C., Mobile, AL, USA

Iker Fernandez, Hospital Fundación Jiménez Díaz, Madrid, Spain

Javier Flandes, Hospital Fundación Jiménez Díaz, Madrid, Spain

Erik Folch, Massachusetts General Hospital, Boston, MA, USA

Alexandre Furman, Pulmonary and Sleep of Tampa Bay, Brandon, FL, USA

George David Gass, East Texas Medical Center Regional Healthcare System, Tyler, TX, USA

Thomas Gildea, Cleveland Clinic, Cleveland, OH, USA

Anil Gogineni, Ocala Lung and Critical Care, Ocala, FL, USA

Musija Fikreta Grabcanovic, Salzburger Landesklinik (SALK), Salzburg, Austria

John David Hinze, Seton Medical Center, Austin, TX, USA

David Kyle Hogarth, The University of Chicago, Chicago, IL, USA

Raj Karunakara, Ocala Lung and Critical Care, Ocala, FL, USA

Jordan Kazakov, University Hospitals Case Medical Center, Cleveland, OH, USA

Sandeep Khandhar, Inova Fairfax Hospital, Falls Church, VA, USA

Sandhya Khurana, University of Rochester, Rochester, NY, USA

William Krimsky, Pulmonary and Critical Care Associates of Baltimore, P.A., Baltimore, MD, USA

Ganesh Krishna, Palo Alto Medical Foundation, Mountain View, CA, USA

Roman Krol, Virtua Medical Group, PA, Marlton, NJ, USA

Roland Kropfmüller, Kepler Universitätsklinikum, Linz, Austria

Bernd Lamprecht, Kepler Universitätsklinikum, Linz, Austria

Kelvin Lau, St. Bartholomew's Hospital, London, UK

Andrew Lee, Virtua Medical Group, PA, Marlton, NJ, USA

Gregory LeMense, Blount Memorial Hospital, Maryville, TN, USA

Philip Linden, University Hospitals Case Medical Center, Cleveland, OH, USA

Peter Lutz, Pulmonary Associates of Mobile, P.C., Mobile, AL, USA

Amit Mahajan, Inova Fairfax Hospital, Falls Church, VA, USA

Kamran Mahmood, Duke University, Durham, NC, USA

Fabien Maldonado, Vanderbilt University, Nashville, TN, USA

Rafael Martinez, Pulmonary and Sleep of Tampa Bay, Brandon, FL, USA

Jennifer Mattingley, Gunderson Lutheran Medical Foundation, Inc., La Crosse, WI, USA

Douglas Minnich, University of Alabama at Birmingham, Birmingham, AL, USA

Septimiu Murgu, The University of Chicago, Chicago, IL, USA

Boris Murillo, Providence Health Center, Waco, TX, USA

Katie Nason, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Michael Nead, University of Rochester, Rochester, NY, USA

Christopher Parks, Southeastern Regional Medical Center, Newnan, GA, USA

Kenneth Perret, Seton Medical Center, Austin, TX, USA

Peter Porsch, Salzburger Landesklinik (SALK), Salzburg, Austria

Michael Pritchett, Pinehurst Medical Clinic, Inc., Pinehurst, NC, USA

Otis Rickman, Vanderbilt University, Nashville, TN, USA

Maydee Rosario, Providence Health Center, Waco, TX, USA

Mario Salio, IRCCS Azienda Ospedaliera Universitaria San Martino, Genova, Italy

Saiyad Sarkar, Pulmonary and Critical Care Associates of Baltimore, P.A., Baltimore, MD, USA

Andrew Seevaratnam, Ocala Lung and Critical Care, Ocala, FL, USA

Sonali Sethi, Cleveland Clinic, Cleveland, OH, USA

Jaspal Singh, Carolinas HealthCare System, Charlotte, NC, USA

Michael Studnicka, Salzburger Landesklinik (SALK), Salzburg, Austria

Eric Sztejman, Virtua Medical Group, PA, Marlton, NJ, USA

Tamejiro Takubo, CAMC Health Education and Research Institute, Inc., Charleston, WV, USA

Catalina Teba, University Hospitals Case Medical Center, Cleveland, OH, USA

Christopher Towe, University Hospitals Case Medical Center, Cleveland, OH, USA

Marco Trigiani, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

JeanRichel Vergnon, University Hospitals of Saint Etienne France, St. Etienne, France

Niels-Erik Viby, Rigshospitalet, Copenhagen, Denmark

Momen Wahidi, Duke University, Durham, NC, USA

Ernest Waller, Blount Memorial Hospital, Maryville, TN, USA

Benjamin Wei, University of Alabama at Birmingham, Birmingham, AL, USA

Dragos Zanchi, Pulmonary and Sleep of Tampa Bay, Brandon, FL, USA

Michael Zgoda, Carolinas HealthCare System, Charlotte, NC, USA

Supplementary Data

References

1. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e93S-e120S.

2. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e142S-e165S.

3. Folch EE, Bowling MR, Gildea TR, et al. Design of a prospective, multicenter, global, cohort study of electromagnetic navigation bronchoscopy. *BMC Pulm Med*. 2016;16:60.

4. Khandhar SJ, Bowling MR, Flandes J, et al. Electromagnetic navigation bronchoscopy to access lung lesions in 1000 subjects: first results of the prospective, multicenter NAVIGATE study. *BMC Pulm Med*. 2017;17:59.

5. Ford I, Norrie J. Pragmatic trials. *N Engl J Med*. 2016;375:454-463.

6. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*. 2017;284:228-243.

7. Swensen SJ, Silverstein MD, Ilstrup DM, et al. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. *Arch Intern Med*. 1997;157:849-855.

8. Bowling MR, Anciano CJ. Updates in advanced diagnostic bronchoscopy: electromagnetic navigational bronchoscopy chasing the solitary pulmonary nodule. *Clin Pulm Med*. 2017;24:60-65.

9. Gex G, Pralong JA, Combescure C, et al. Diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules: a systematic review and meta-analysis. *Respiration*. 2014;87:165-176.

10. DiBardino DM, Yarmus LB, Semaan RW. Transthoracic needle biopsy of the lung. *J Thorac Dis*. 2015;7:304-316.

11. Fontaine-Delaruelle C, Souquet PJ, Gamondes D, et al. Negative predictive value of transthoracic core-needle biopsy: a multicenter study. *Chest*. 2015;148:472-480.

12. Heerink WJ, de Bock GH, de Jonge GJ, et al. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. *Eur Radiol*. 2017;27:138-148.

13. Yamagami T, Terayama K, Yoshimatsu R, et al. Role of manual aspiration in treating pneumothorax after computed tomography-guided lung biopsy. *Acta Radiol*. 2009;50:1126-1133.

14. Towe CW, Nead MA, Rickman OB, et al. Safety of electromagnetic navigation bronchoscopy in patients with COPD: results from the NAVIGATE study. *J Bronchology Interv Pulmonol*. 2019;26:33-40.

15. Semaan RW, Lee HJ, Feller-Kopman D, et al. Same-day computed tomographic chest imaging for pulmonary nodule targeting with electromagnetic navigation bronchoscopy may decrease unnecessary procedures. *Ann Am Thorac Soc*. 2016;13:2223-2228.

16. Zhao YR, Heuvelmans MA, Dorrius MD, et al. Features of resolving and nonresolving indeterminate pulmonary nodules at follow-up CT: the NELSON study. *Radiology*. 2014;270:872-879.

17. 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.

18. Ali MS, Sethi J, Taneja A, et al. Computed tomography bronchus sign and the diagnostic yield of guided bronchoscopy for peripheral pulmonary lesions. A systematic review and meta-analysis. *Ann Am Thorac Soc*. 2018;15:978-987.

19. Seijo LM, de Torres JP, Lozano MD, et al. Diagnostic yield of electromagnetic navigation bronchoscopy is highly dependent on the presence of a bronchus sign on CT imaging: results from a prospective study. *Chest*. 2010;138:1316-1321.

20. Balbo PE, Bodini BD, Patrucco F, et al. Electromagnetic navigation bronchoscopy and rapid on site evaluation added to fluoroscopy-guided assisted bronchoscopy and rapid on site evaluation: improved yield in pulmonary nodules. *Minerva Chir*. 2013;68:579-585.

21. Eberhardt R, Anantham D, Ernst A, et al. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. *Am J Respir Crit Care Med*. 2007;176:36-41.

22. Ozgul G, Cetinkaya E, Ozgul MA, et al. Efficacy and safety of electromagnetic navigation bronchoscopy with or without radial endobronchial ultrasound for peripheral lung lesions. *Endosc Ultrasound*. 2016;5:189-195.

23. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7-30.

24. Gildea TR, DaCosta Byfield S, Hogarth DK, et al. A retrospective analysis of delays in the diagnosis of lung cancer and associated costs. *Clinicoecon Outcomes Res*. 2017;9:261–269.

25. Labarca G, Folch E, Jantz M, et al. Adequacy of samples obtained by endobronchial ultrasound with transbronchial needle aspiration for molecular analysis in patients with non-small cell lung cancer. Systematic review and meta-analysis. *Ann Am Thorac Soc*. 2018;15:1205-1216.

26. Vanderlaan PA, Yamaguchi N, Folch E, et al. Success and failure rates of tumor genotyping techniques in routine pathological samples with non-small-cell lung cancer. *Lung Cancer*. 2014;84:39-44.

27. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer, Version 6.2018, NCCN Clinical Practice Guidelines in Oncology. https://www.nccn. org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 6, 2018.

28. Gutierrez ME, Choi K, Lanman RB, et al. Genomic profiling of advanced non-small cell lung cancer in community settings: gaps and opportunities. *Clin Lung Cancer*. 2017;18:651-659.

29. Presley CJ, Tang D, Soulos PR, et al. Association of broad-based genomic sequencing with survival among patients with advanced non-small cell lung cancer in the community oncology setting. *JAMA*. 2018;320: 469-477.