ORIGINAL ARTICLE

NAVIGATE 24-Month Results: Electromagnetic Navigation Bronchoscopy for Pulmonary Lesions at 37 Centers in Europe and the United States

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***Disclosure:** The authors declare the following competing interests: Drs. Arenberg, Bansal, Bezzi, Bhadra, Bowling, Christensen, Flandes, Gildea, Hogarth, Khandhar, Krimsky, Lamprecht, Lau, LeMense, Mahajan, Mattingley, Murgu, Murillo, Nead, Pritchett, Singh, and Towe report receiving site payments for study participation from Medtronic. Drs. Folch, Flandes, Gildea, Khandhar, Krimsky, and Murgu report serving on the advisory board or steering committee for Medtronic. Drs. Hood, Lin, Mattingley, and Ms. Wolvers are full-time employees and stockholders of Medtronic. Drs. Bhadra, Bowling, Folch, Hogarth, Khandhar, Krimsky, Lau, LeMense, Mahajan, and Pritchett report receiving consultant fees from Medtronic. Dr. Hogarth reports receiving honoraria from Medtronic. Dr. Bansal reports serving on the speaker's bureau with Medtronic.*

Presented as a podium presentation at the IASLC 2020 World Conference on Lung Cancer, January 29, 2021. Folch E et al. MA02.05 NAVIGATE 24-Month Results: Electromagnetic Navigation Bronchoscopy for Pulmonary Lesions at 37 Centers in Europe and the United States. *J Thorac Oncol*. 2021;16(3):S134-S135.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2021.12.008

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Received 12 March 2021; revised 23 November 2021; accepted 10 December 2021
Available online - 29 December 2021

ABSTRACT

Introduction: Electromagnetic navigation bronchoscopy (ENB) is a minimally invasive, image-guided approach to access lung lesions for biopsy or localization for treatment. However, no studies have reported prospective 24-month follow-up from a large, multinational, generalizable cohort. This study evaluated ENB safety, diagnostic yield, and usage patterns in an unrestricted, real-world observational design.

Methods: The NAVIGATE single-arm, pragmatic cohort study (NCT02410837) enrolled subjects at 37 academic and community sites in seven countries with prospective 24-month follow-up. Subjects underwent ENB using the superDimension navigation system versions 6.3 to 7.1. The prespecified primary end point was procedure-related pneumothorax requiring intervention or hospitalization.

Results: A total of 1388 subjects were enrolled for lung lesion biopsy (1329; 95.7%), fiducial marker placement (272; 19.6%), dye marking (23; 1.7%), or lymph node biopsy (36; 2.6%). Concurrent endobronchial ultrasound-guided staging occurred in 456 subjects. General anesthesia (78.2% overall, 56.6% Europe, 81.4% United States), radial endobronchial ultrasound (50.6%, 4.0%, 57.4%), fluoroscopy (85.0%, 41.7%, 91.0%), and rapid on-site evaluation use (61.7%, 17.3%, 68.5%) differed between regions. Pneumothorax and bronchopulmonary hemorrhage occurred in 4.7% and 2.7% of subjects, respectively (3.2% [primary end point] and 1.7% requiring intervention or hospitalization). Respiratory failure occurred in 0.6%. The diagnostic yield was 67.8% (range: 61.9%–70.7%; 55.2% Europe, 69.8% United States). Sensitivity for malignancy was 62.6%. Lung cancer clinical stage was I to II in 64.7% (55.3% Europe, 65.8% United States).

Conclusions: Despite a heterogeneous cohort and regional differences in procedural techniques, ENB demonstrates low complications and a 67.8% diagnostic yield while allowing biopsy, staging, fiducial placement, and dye marking in a single procedure.

Keywords: Interventional pulmonology; Image-guided biopsy; Lung cancer diagnosis; Lung cancer; Electromagnetic navigation bronchoscopy

Introduction

Although lung cancer is the leading cause of cancer-related death in the United States, 5-year survival is substantially higher for cancers diagnosed at localized stages (59%) compared with late-stage diagnoses (6%).[1] Lung cancer screening may further reduce mortality rates[2,3]; however, optimal patient management would ideally minimize the number of invasive procedures conducted for benign disease. In an era of increased scrutiny over resource utilization, technologies with the ability to perform multiple procedures in the same setting and accelerate treatment are also critical to improve the efficiency and effectiveness of lung nodule evaluation. Clinical practice guidelines recommend diagnosis and staging of the mediastinum in a single setting to improve coordination of care and reduce time, cost, and risk.[4]

Image-guided techniques have advanced the field of bronchoscopy in the past 20 years.[5] Minimally invasive options such as radial endobronchial ultrasound (rEBUS) and electromagnetic navigation bronchoscopy (ENB) improve the diagnostic accuracy of bronchoscopy for early stage lung cancer and reduce the need for more invasive surgical procedures.[6] ENB also allows for lung biopsy, tissue collection for molecular testing, mediastinal staging, and fiducial or dye marking to facilitate treatment in the same procedure. Despite those advantages and a reduced complication risk compared with percutaneous lung biopsy,[7] the lower diagnostic yield of ENB is a limitation.

New imaging techniques and robotic navigation platforms have recently emerged with the goal of improving the localization accuracy of ENB and other forms of advanced bronchoscopy.[8–14] As these technologies mature, there is a need to identify which outcomes are generalizable across diverse settings. This requires a solid foundation of evidence in a real-world population against which to compare new devices. Although the safety and effectiveness of ENB-guided

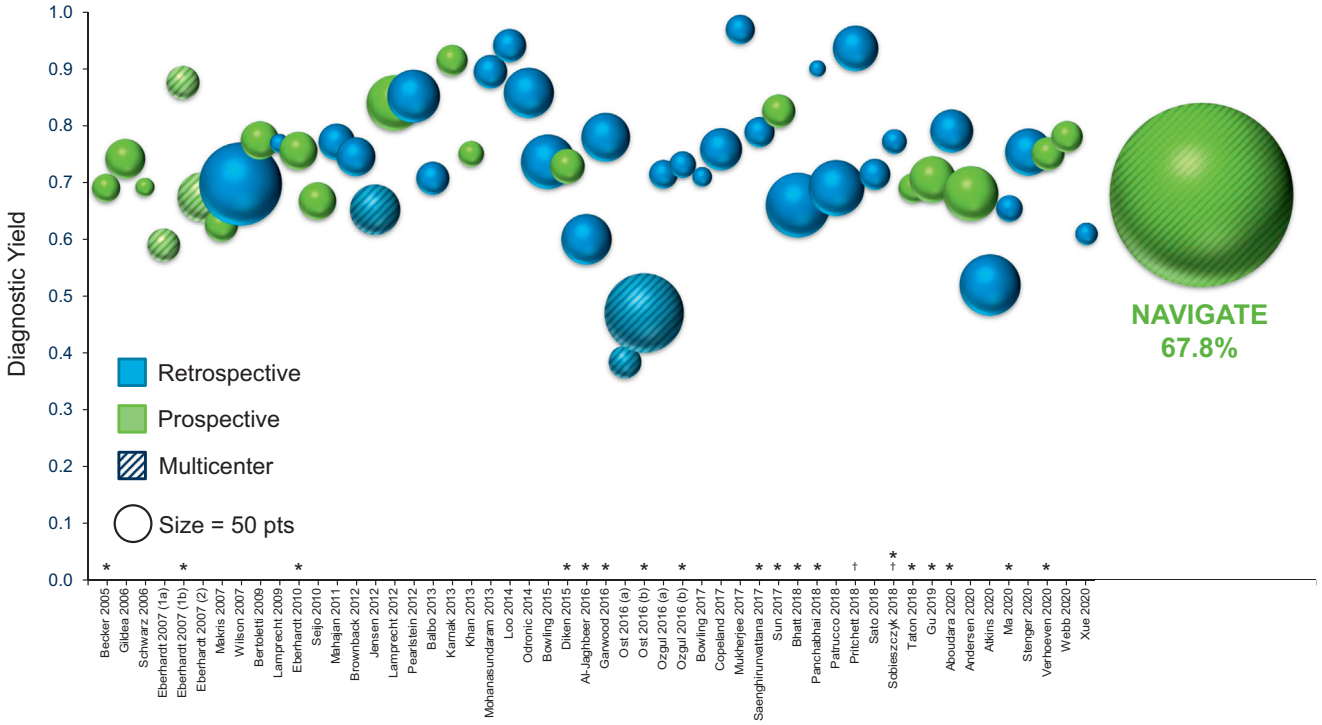

Figure 1. Diagnostic yield in published ENB studies. Diagnostic yield is defined as true positives plus true negatives on the basis of clinical and radiographic follow-up as reported in the original article, except for Ost 2016 and Aboudara 2020 which defined diagnostic yield as a malignant or specific benign on the ENB procedure day. *Radial endobronchial ultrasound used. †Cone-beam computed tomography used. ENB, electromagnetic navigation bronchoscopy; pts, patients.

biopsy have been evaluated in more than 40 clinical studies,[15] most have been small (<100 patients), single center, and retrospective (Fig. 1).

NAVIGATE is the largest multicenter ENB study to date and the only study with prospective 24-month follow-up in a multinational cohort.[16–18] The objective of this report is to describe the final global data with a focus on safety, diagnostic yield, and usage patterns across Europe and the United States.

Materials and Methods

NAVIGATE (NCT02410837) is a prospective, multicenter, single-arm, pragmatic cohort study of ENB using the superDimension navigation system, versions 6.3 to 7.1 (Medtronic, Minneapolis, Minnesota). Consecutive adult subjects presenting with lung lesions requiring evaluation and judged by physicians as suitable for an ENB procedure were enrolled. The pragmatic, observational design intentionally placed no restrictions on patient or lesion selection, procedural technique, complementary tools or imaging, concurrent fiducial marker or pleural dye placement, molecular testing, or lymph node staging (method or timing). Follow-up through 24 months was prespecified at all sites. All follow-up procedures (e.g., surgical tissue biopsy, repeat ENB, computed tomography [CT]-guided transthoracic needle biopsy or aspiration [TTNA], serial CT imaging, and lung health visits) were prospectively captured. Independent source data verification was conducted in 33.3% of data, and all safety end points and procedure-related adverse events were adjudicated by an independent medical monitor.

The primary end point was the incidence of procedure-related pneumothorax grade 2 or higher (requiring intervention or hospitalization), according to the validated Common Terminology Criteria for Adverse Events.[18] The primary end point was chosen as a safety end point applicable to ENB-guided lung lesion biopsy, fiducial placement, or dye marking. Pneumothorax grade 2 or higher could also include subjects kept overnight in the hospital for observation only, without requiring a chest tube. Secondary end points were the overall incidence of ENB-related pneumothorax, ENB-related bronchopulmonary hemorrhage grade 2 or higher, ENB-related respiratory failure grade 4 or higher, subject health status and quality of life evaluated by the three-level version EQ-5D questionnaire,[19] subject satisfaction at 1 month, and subject productivity and activity at 1 month. Other secondary end points were captured on the basis of the purpose of the individual procedure performed and included diagnostic yield, sensitivity,

specificity, positive predictive value, negative predictive value (NPV), the repeat biopsy rate, adequacy of samples for molecular testing and mutation type, diagnosis, stage at diagnosis, accurate fiducial placement as evaluated by follow-up imaging, the success rate of pleural dye marking revealed by surgical resection, and the success rate of obtaining a lymph node biopsy.[18] ENB-aided diagnostic yield, sensitivity, specificity, positive predictive value, and NPV were evaluated with respect to malignancy in subjects undergoing ENB-guided lung lesion biopsy. Diagnostic yield at 24 months was calculated as the rate of true positives (for malignancy) plus true negatives (TNs) (for malignancy) out of all attempted lung lesion biopsies. All ENB-aided results other than a malignant diagnosis (including histologic confirmation of benign disease) were considered negative for malignancy and then followed for 24 months to establish true versus false negative (FN) status. For the calculation of diagnostic yield in biopsy subjects who died or exited the study before 24 months, the last established diagnosis on the basis of follow-up data was carried forward. Negative cases with insufficient information to evaluate diagnostic yield were included in a sensitivity analysis, assuming all were FN or TN, to provide low and high estimates. Additional details have been published.[16–18]

No formal sample size estimates or statistical power calculations were conducted for this single-arm, observational study. Analyses were performed using SAS Version 9.4 (SAS Inc., Cary, NC). Data are summarized by descriptive statistics, including frequency distributions and cross-tabulations for discrete variables and median and interquartile range for continuous variables. Univariate and multivariate logistic

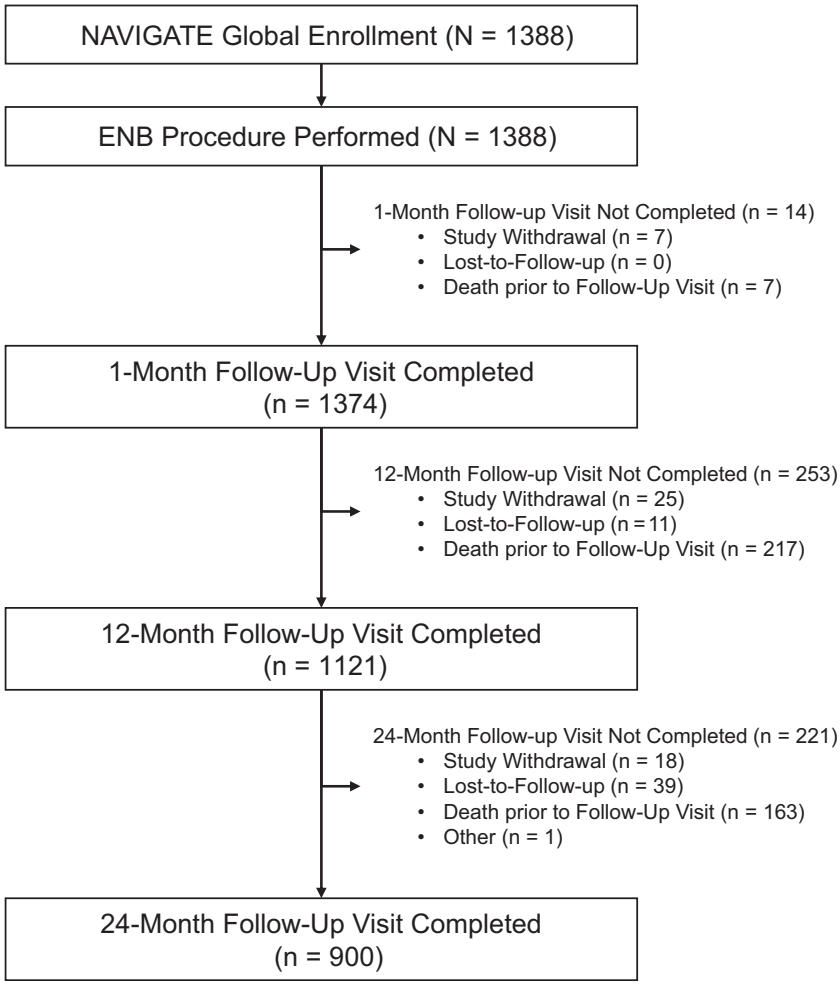

Figure 2. Follow-up rates for all enrolled subjects (N = 1388). For the calculation of diagnostic yield in biopsy subjects who died or exited the study before 24 months, the last established diagnosis on the basis of follow-up data was carried forward. Accounting for all available follow-up at all study time points (including subjects with verification or contradiction of the ENB-aided diagnoses before study exit or death), follow-up information for the diagnostic yield calculation was available in 90.7% of subjects with navigation completed and tissue obtained. ENB, electromagnetic navigation bronchoscopy.

regression models were conducted to determine predictors of 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.

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

Table 1. Demographics, Procedural, and Lesion Characteristics

Baseline Variables	Global	EU Only	U.S. Only
Subject demographics	1388 subjects	175 subjects	1213 subjects
Age at consent (y)	69.0 (61.0-76.0)	69.0 (61.0-77.0)	69.0 (60.0-76.0)
Subject age $\geq$ 65 y	64.4 (894/1388)	63.4 (111/175)	64.6 (783/1213)
Female/male	50.3/49.7	46.9/53.1	50.8/49.2
Tobacco history (current or former)	79.8 (1107/1388)	81.1 (142/175)	79.6 (965/1213)
COPD	43.3 (601/1388)	34.3 (60/175)	44.6 (541/1213)
Personal history of cancer	48.1 (667/1388)	43.4 (76/175)	48.7 (591/1213)
Family history of cancer	58.8 (816/1388)	38.3 (67/175)	61.7 (749/1213)
Procedural characteristics	1388 procedures	175 procedures	1213 procedures
General anesthesia	78.2 (1086/1388)	56.6 (99/175)	81.4 (987/1213)
Radial EBUS used during ENB	50.6 (703/1388)	4.0 (7/175)	57.4 (696/1213)
Cone-beam CT used during ENB	5.5 (77/1388)	9.7 (17/175)	4.9 (60/1213)
Fluoroscopy used during ENB[a]	85.0 (1299/1529)	41.7 (78/187)	91.0 (1221/1342)
Lesion visible on fluoroscopy[a]	59.1 (768/1299)	50.0 (39/78)	59.7 (729/1221)
Rapid on-site evaluation used[a]	61.7 (777/1260)	17.3 (29/168)	68.5 (748/1092)
Procedure planning time (min)	5.0 (5.0-10.0)	10.0 (10.0-15.0)	5.0 (4.0-9.0)
Total procedure time (min)[b]	50.0 (34.0-69.0)	40.0 (31.0-50.0)	52.0 (35.0-71.0)
ENB-specific procedure time (min)[b]	26.0 (16.0-41.0)	29.0 (21.0-40.0)	25.0 (15.0-41.0)
Operator's previous ENB experience[c]			
0-4 ENB cases per mo	16.8 (233/1388)	77.7 (136/175)	8.0 (97/1213)
5-10 ENB cases per mo	43.3 (601/1388)	21.1 (37/175)	46.5 (564/1213)
>10 ENB cases per mo	39.8 (553/1388)	0.6 (1/175)	45.5 (552/1213)
Lung lesion characteristics in biopsy cases	1529 lesions in 1329 subjects	187 lesions in 174 subjects	1342 lesions in 1155 subjects
Lesion size (mm), median	20.0 (14.0-29.0)	18.0 (13.0-28.0)	20.0 (14.0-29.0)
Lesion size < 20 mm	49.7 (759/1528)	53.5 (100/187)	49.1 (659/1341)
$\leq$4 mm	0.2 (3/1528)	0.0 (0/187)	0.2 (3/1341)
>4 mm to $\leq$8 mm	3.8 (58/1528)	5.3 (10/187)	3.6 (48/1341)
>8 mm to <20 mm	45.7 (698/1528)	48.1 (90/187)	45.3 (608/1341)
Lesion size $\geq$ 20 mm to <30 mm	25.7 (392/1528)	24.1 (45/187)	25.9 (347/1341)
Lesion size $\geq$ 30 mm to <40 mm	12.4 (189/1528)	11.8 (22/187)	12.5 (167/1341)
Lesion size $\geq$ 40 mm	12.3 (188/1528)	10.7 (20/187)	12.5 (168/1341)
Upper lobe lesion location	58.7 (897/1529)	62.6 (117/187)	58.1 (780/1342)
Peripheral third of the lung[d]	67.8 (1036/1529)	72.7 (136/187)	67.1 (900/1342)
Lesion distance to pleura (mm)	9.0 (0.0-20.0)	11.0 (0.0-25.0)	9.0 (1.0-20.0)
Pure to mostly ground glass[e]	6.2 (95/1523)	5.9 (11/187)	6.3 (84/1336)
Spiculated lesion border	60.4 (923/1527)	64.2 (120/187)	59.9 (803/1340)
Bronchus sign present on CT	50.8 (777/1529)	66.8 (125/187)	48.6 (652/1342)
Multiple lesions sampled	12.8 (170/1329)	6.9 (12/174)	13.7 (158/1155)
Pretest probability of malignancy > 65% (physician estimate)	61.4 (730/1188)	74.3 (139/187)	59.0 (591/1001)
Pretest probability of malignancy > 65% (calculated)[f]	52.0 (535/1029)	52.9 (64/121)	51.9 (471/908)

Note: Data are presented as % (n/N) or median (Q1-Q3).
[a]Only captured in subjects undergoing ENB for lung lesion biopsy.
[b]Total procedure time = bronchoscope in to bronchoscope out. ENB-specific procedure time = first entry of the locatable guide and EWC to last exit of the EWC.
[c]Operator experience data missing in one EU subject.
[d]As defined in Folch et al.[18]
[e]Suzuki class 1 or 2.
[f]Mayo clinic model.
COPD, chronic obstructive pulmonary disease; CT, computed tomography; EBUS, endobronchial ultrasound; ENB, electromagnetic navigation bronchoscopy; EU, European Union; EWC, extended working channel; Q, quartile; U.S., United States.

Role of the Funding Source

The study sponsor contributed to the study design, data collection and analysis, and manuscript writing.

Results

Subjects Included in the Analysis

From April 2015 to August 2017, a total of 1388 subjects were enrolled at 37 sites in the European Union (EU; eight sites total, including two in Austria, one in Denmark, one in France, two in Italy, one in Spain, and one in the United Kingdom) and the United States (29 sites). Sites represented academic (15 sites), private practice (12 sites), and mixed academic/private (10 sites) models.

ENB was used to guide lung lesion biopsy (95.7%, 1329 of 1388), fiducial marker placement (19.6%, n = 14 EU, 258 U.S.), pleural dye marking (1.7% (n = 23, all U.S.), or lymph node biopsy (2.6%, n = 6 EU, 30 U.S.). ENB was conducted for multiple purposes during the same procedure in 31.2% of subjects. Linear EBUS-guided staging was performed in the same procedure in 456 subjects (n = 9 EU, 447 U.S.). Outcomes of fiducial marker placement and dye marking have been published.[20,21]

Follow-up rates are in Figure 2. Total 24-month mortality was 29% (403 of 1388), accounting for most subjects with incomplete follow-up. Furthermore, 16 subjects who died completed the 24-month follow-up and 387 did not. Two-year mortality in subjects with confirmed lung malignancy (true positives plus FNs) was 35.5% (305 of 858). Including data obtained at the 1-month and 12-month visits (last observation carried forward), follow-up for the calculation of diagnostic yield was available in 90.7% of subjects with navigation completed and tissue obtained.

Subject, Procedural, and Lesion Characteristics

Subject demographics and medical history were similar between Europe and the United States (Table 1). General anesthesia, rEBUS, fluoroscopy, and rapid on-site evaluation (ROSE) were used less frequently in Europe, whereas cone-beam CT use was higher. The ENB-specific procedure time was similar across regions. Operator experience before enrolling in NAVIGATE was higher in the United States than Europe.

Biopsy tools used were aspirating needle in 56.6% (752 of 1329 overall; 81.6% EU, 52.8% U.S.), biopsy forceps in 83.6% (1111 of 1329; 96.6% EU, 81.6% U.S.), cytology brush in 49.0% (651 of 1329; 50.6% EU, 48.7% U.S.), needle-tipped cytology brush in 18.1% (241 of 1329; 9.8% EU, 19.4% U.S.), the superDimension triple needle cytology brush in 22.8% (303 of 1329; 12.1% EU, 24.4% U.S.), and the GenCut core biopsy system in 16.1% (214 of 1329; 2.3% EU, 18.2% U.S.). Three or more biopsy tools were used in 71.9% (955 of 1329). Additional details on biopsy tool usage patterns in NAVIGATE have been reported.[22]

Lesion characteristics were generally similar across geographies (Table 1, Supplementary Data 2) although the median lesion size was slightly smaller in Europe. A total of 96% of lesions were greater than 8 mm, 49.7% were less than 20 mm, and 24.7% were greater than or equal to 30 mm. A bronchus sign was present in 50.8%. The provider-estimated pretest probability of malignancy was higher in Europe, whereas the calculated probability[18] was similar across regions.

Primary End Point and ENB-Related Adverse Events

On the study primary end point, procedure-related pneumothorax Common Terminology Criteria for Adverse Events grade greater than or equal to 2 occurred in 3.2% (44 of 1388) of subjects (5.1% EU, 2.9% U.S.). Any-grade pneumothorax occurred in 4.7% (7.4% EU, 4.3% U.S.). Bronchopulmonary hemorrhage grade 2 or higher occurred in 1.7% (2.3% EU, 1.6% U.S.) and any-grade bronchopulmonary hemorrhage in 2.7% (4.0% EU, 2.5% U.S.). Respiratory failure (grade $\geq$ 4) occurred in 0.6% (8 subjects, all U.S.), including one death related to complications of general anesthesia 9 days post-ENB in a subject with multiple comorbidities.[17] There were no other procedure-related deaths. Pneumothorax rates were higher in cases without concurrent fluoroscopic and rEBUS imaging compared with cases with concurrent imaging (7.9% versus 4.4% and 6.4% versus 3.0%, respectively) and under moderate sedation (7.3%) versus general anesthesia (4.0%) (Supplementary Data 3–5). The lesion-to-pleura distance was also lower in subjects with pneumothorax (9.5 $\pm$ 13.0 mm) than in subjects without pneumothorax (13.5 $\pm$ 14.6 mm). Multivariate predictors of pneumothorax and composite complications have been published.[23]

Diagnostic Outcomes

Among the 1329 subjects undergoing ENB-guided biopsy, 94.8% (1260 of 1329) had navigation completed and tissue obtained. Malignancy was diagnosed in 42.6% (537 of 1260), and 57.4% (723 of 1260) were negative for malignancy on the basis of the ENB-aided procedure (Table 2).

These initial outcomes were then evaluated over 24 months by the decision pathway in Figure 3. There were no false positives. Of the 723 cases initially considered negative for malignancy, 285 were TN, 321 were FN, and 117 remained indeterminate at 24 months (Fig. 3). The global diagnostic yield was 67.8% (822 of 1212). The

Table 2. Results of the ENB-Aided Biopsy Procedure

Outcomes	Global (1260 Subjects)	EU Only (168 Subjects)	U.S. Only (1092 Subjects)
Positive for malignancy[a]	42.6 (537)	32.7 (55)	44.1 (482)
Lung cancer	37.1 (468)	28.0 (47)	38.6 (421)
NSCLC	33.9 (427)	26.8 (45)	35.0 (382)
Adenocarcinoma	22.1 (279)	21.4 (36)	22.3 (243)
Squamous carcinoma	10.6 (133)	5.4 (9)	11.4 (124)
Other NSCLC	1.3 (16)	0.0 (0)	1.5 (16)
Small cell carcinoma	2.1 (26)	0.6 (1)	2.3 (25)
Neuroendocrine carcinoma	1.3 (17)	0.6 (1)	1.5 (16)
Metastatic carcinoma	3.9 (49)	1.2 (2)	4.3 (47)
Lymphoma	0.2 (2)	0.0 (0)	0.2 (2)
Malignant cells (unable to characterize)	1.0 (12)	3.0 (5)	0.6 (7)
Atypical cells[b]	0.2 (3)	0.6 (1)	0.2 (2)
Other	0.2 (3)	0.0 (0)	0.3 (3)
Negative for malignancy[a]	57.4 (723)	67.3 (113)	55.9 (610)
Benign nonspecific	23.3 (294)	19.0 (32)	24.0 (262)
Benign inflammation	15.7 (198)	14.9 (25)	15.8 (173)
Benign other	7.7 (97)	4.2 (7)	8.2 (90)
Inconclusive	16.0 (201)	32.7 (55)	13.4 (146)
Normal lung tissue	9.4 (119)	10.7 (18)	9.2 (101)
Hamartoma	0.1 (1)	0.0 (0)	0.1 (1)
Granuloma	1.6 (20)	1.2 (2)	1.6 (18)
Infection	3.3 (41)	2.4 (4)	3.4 (37)
Bacterial	1.9 (24)	0.6 (1)	2.1 (23)
Fungal	1.1 (14)	1.8 (3)	1.0 (11)
Viral	0.2 (3)	0.0 (0)	0.3 (3)
Organizing pneumonia	0.6 (7)	0.0 (0)	0.6 (7)
Interstitial lung disease	0.6 (7)	0.0 (0)	0.6 (7)
Lymphocytes	0.8 (10)	0.0 (0)	0.9 (10)
Atypical cells[b]	1.6 (20)	0.6 (1)	1.7 (19)
Other	1.2 (15)	1.2 (2)	1.2 (13)

Note: Data are presented as % (n).
[a]Subjects with multiple lesions may be represented more than once in all subcategories.
[b]Atypical cells categorized as malignant were considered malignant by the providing physician at the time of the ENB procedure. Atypical cells categorized as indeterminate were considered nonmalignant by the providing physician at the time of the ENB procedure, pending further diagnostic testing.
ENB, electromagnetic navigation bronchoscopy; EU, European Union; U.S., United States.

diagnostic yield denominator was the total number of biopsy subjects (1329) minus the 117 indeterminate cases. In a sensitivity analysis, the diagnostic yield ranged from 61.9% to 70.7% assuming all 117 indeterminate cases were FN or TN, respectively. Diagnostic yield was 69.8% (range: 63.3%–72.6%) in the United States and 55.2% (range: 52.3%–57.5%) in the EU. In the global, U.S., and EU cohorts, sensitivity for malignancy (TP/TP + FN) was 62.6% (range: 55.1%–62.6%), 65.6% (range: 57.2%–65.6%), and 44.7% (range: 41.7%–44.7%) whereas NPV (TN/FN + TN) was 47.0% (range: 39.4%–55.6%), 49.6% (range: 40.8%–58.5%), and 34.6% (range: 31.9%–39.8%), respectively. The sensitivity for malignancy in the global cohort was 70.4% (range: 62.3%–70.4%) in lesions greater than or equal to 20 mm and 51.8% (range: 45.2%–51.8%) in lesions less than 20 mm. Specificity for malignancy and positive predictive value were 100%. Results on the basis of pretest probability of malignancy are detailed in Supplementary Data 6. Molecular testing was attempted in 34.9% (110 of 315) of lesions considered adenocarcinoma or NSCLC not otherwise specified. Among the 102 subjects (110 lesions) with molecular evaluation attempted, tissue was adequate to complete testing in 81.4% (83 of 102).

Repeat biopsy after the index ENB procedure (e.g., repeat ENB, surgical biopsy, TTNA, standard bronchoscopy, or EBUS-guided bronchoscopy) was conducted in 26.5% (334 of 1260). The median days to the first repeat diagnostic procedure in negative cases was 43.0 days (36.0 EU, 45.5 U.S.). Among subjects with an ENB-aided malignant diagnosis, 25.9% (139 of 537) underwent surgical resection and the median time from the ENB index procedure to surgery was 39.0 days (53.0 EU, 37.5 U.S.) (Supplementary Data 7).

The 12-month interim diagnostic yield was 56.4% in Europe and 73.0% in the United States.[16] With an additional year of follow-up, 28 of 1260 (2.2% overall,

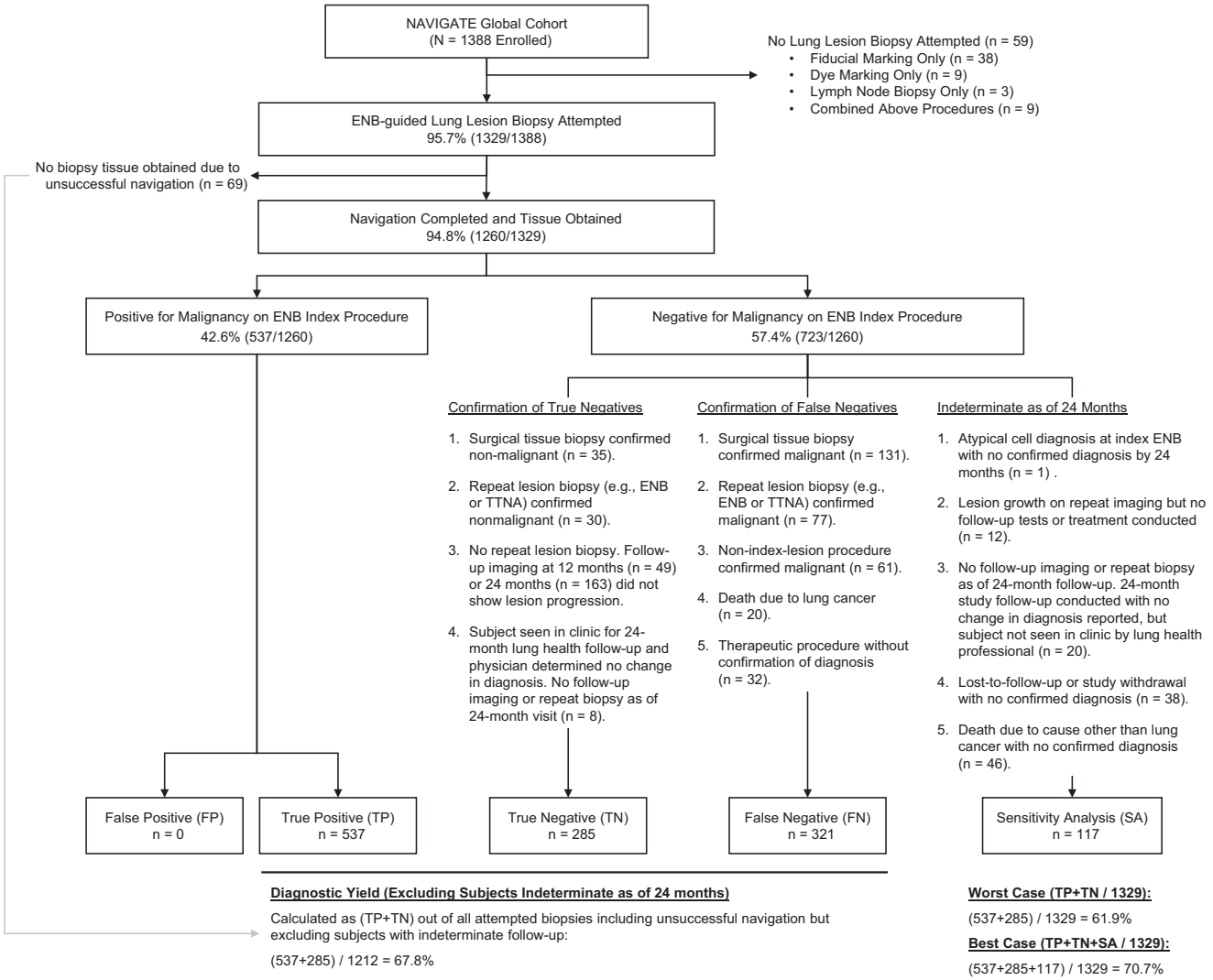

Figure 3. Global diagnostic results in ENB-aided biopsy subjects (n = 1329). Algorithm for determining diagnostic outcomes in subjects undergoing ENB-guided lung lesion biopsy. "Negative for Malignancy" refers to ENB-guided biopsy results that were diagnostic of a nonmalignant condition or indeterminate. ENB, electromagnetic navigation bronchoscopy; FN, false negative; FP, false positive; TN, true negative; TP, true positive; TTNA, transthoracic needle biopsy or aspiration.

1.2% EU, 2.4% U.S.) considered negative at 12 months were considered malignant at 24 months. Among those 28 subjects, 61% (17 of 28) became FN owing to reasons other than confirmed malignancy in the study lesion. These reasons were as follows: diagnosis of malignancy in another lesion (7 of 28; 25%); treatment without a confirmed diagnosis (4 of 28; 14%); and death owing to lung cancer without a confirmed diagnosis (6 of 28; 21%). Nevertheless, 12-month and 24-month diagnoses were consistent in 91.8% of lung biopsy subjects (1220 of 1329).

Predictors of Diagnostic Yield

Multivariate predictors of increased diagnostic yield were biopsy of multiple lesions, shorter procedure time, previous ENB experience of 5 to 10 cases per month (versus 0–4 per mo), bronchus sign presence, lymph node biopsy during the ENB procedure, and ROSE use (Table 3). A personal history of cancer and average lesion size less than 20 mm were statistically significant multivariate predictors of lower diagnostic yield. Diagnostic yield was 73% versus 62% in lesions greater than or equal to 20 mm and less than 20 mm, 73% versus 62% in lesions with and without a bronchus sign, and 75% versus 67% in lesions with and without ROSE use, respectively. Bronchus sign presence was the only significant factor in the European cohort. Notable candidate variables found to be not significantly associated with diagnostic yield included the presence of chronic obstructive pulmonary disease, rEBUS use (67.9% with versus 67.7% without), and the physician-estimated pretest probability of malignancy.

Table 3. Significant ($p < 0.05$) Univariate and Multivariate Predictors of Diagnostic Yield

Predictors	Global (1260 Subjects)	EU Only (168 Subjects)	U.S. Only (1092 Subjects)
Significant univariate predictors of higher diagnostic yield			
Multiple lesions biopsied	1.70 (1.14-2.53)	—	1.55 (1.02-2.36)
Previous ENB Use > 10 cases/mo[a]	1.63 (1.16-2.30)	—	—
Previous ENB Use 5-10 cases/mo[a]	1.58 (1.13-2.21)	—	—
Bronchus sign present	1.62 (1.27-2.07)	2.14 (1.10-4.17)	1.69 (1.30-2.21)
Lymph nodes biopsied	1.61 (1.24-2.09)	—	1.41 (1.07-1.85)
Fluoroscopy used	1.56 (1.14-2.14)	—	—
ROSE used	1.48 (1.14-1.92)	—	—
Upper lobe location	1.48 (1.16-1.88)	—	1.51 (1.16-1.97)
Total procedure time, 30-60 min[b,c]	—	—	1.57 (1.18-2.10)
Significant univariate predictors of lower diagnostic yield			
Hispanic or Latino ethnicity	0.63 (0.41-0.98)	—	—
Lesion size < 20 mm	0.60 (0.47-0.76)	—	0.58 (0.45-0.76)
Personal history of cancer	0.56 (0.44-0.72)	—	0.54 (0.42-0.71)
Significant multivariate predictors of higher diagnostic yield			
Multiple lesions biopsied	2.36 (1.48-3.77)	—	2.02 (1.30-3.16)
Total procedure time < 30 min[b]	2.27 (1.42-3.65)	—	2.07 (1.30-3.28)
Total procedure time 30-60 min[b]	1.85 (1.34-2.55)	—	1.86 (1.36-2.56)
Previous ENB use 5-10 cases/mo[a,d]	1.68 (1.14-2.48)	—	—
Bronchus sign present	1.50 (1.13-2.00)	2.14 (1.10-4.17)	1.59 (1.18-2.13)
Lymph nodes biopsied	1.55 (1.11-2.16)	—	1.51 (1.10-2.07)
ROSE used	1.47 (1.09-2.00)	—	—
Upper lobe location	—	—	1.46 (1.10-1.93)
Significant multivariate predictors of lower diagnostic yield			
Personal history of cancer	0.58 (0.44-0.76)	—	0.56 (0.43-0.75)
Average lesion size < 20 mm	0.72 (0.54-0.95)	—	0.72 (0.54-0.96)
General anesthesia use	—	—	0.66 (0.46-0.96)

Note: Data are presented as OR (95% CI). Full list of candidate predictors: Age, sex, race, ethnicity, tobacco use, presence of COPD, personal history of cancer, family history of cancer, general anesthesia use, radial EBUS use, fluoroscopy use, cone-beam CT use, rapid on-site evaluation, procedure time, fiducial marker placement during ENB, lymph node biopsy, lesion size, lesion location, lung zone (peripheral, middle, proximal), distance from lesion to pleura, ground glass opacity, spiculated lesion border, bronchus sign, multiple lesions, number of biopsy tools used, operator experience before NAVIGATE, and physician-estimated probability of malignancy.

[a]Versus the reference category operator experience of zero to four cases per month, before beginning enrollment in NAVIGATE.

[b]Versus the reference category procedure time greater than 60 minutes.

[c]Total procedure time less than 30 minutes versus total procedure time greater than 60 minutes is not statistically significant in the U.S. cohort univariate analysis (OR = 1.40, 95% CI: 0.94-2.10), but the overall effect of total procedure time is statistically significant ($p = 0.008$).

[d]Previous ENB use greater than 10 cases per month versus previous ENB use zero to four cases per month is not statistically significant in the multivariate analysis (OR = 1.47, 95% CI: 0.98-2.21), but the overall effect of previous ENB use is statistically significant ($p < 0.001$).

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; EBUS, endobronchial ultrasound; ENB, electromagnetic navigationbronchoscopy; EU, European Union; U.S., United States.

Discussion

As with all procedures in medical practice, the choice of a diagnostic biopsy technique requires a tradeoff between risks and benefits. Although ENB has traditionally had a lower diagnostic success rate than percutaneous biopsy, it has a lower complication risk and also allows for the biopsy of multiple nodules and mediastinal staging in the same procedure. NAVIGATE was designed as an observational study to provide real-world data on the safety and effectiveness of ENB across a heterogeneous cohort. As such, the primary safety end point (pneumothorax) and the secondary effectiveness end points (e.g., diagnostic yield, sensitivity for malignancy, success rates of fiducial placement or dye marking) evaluated the risk-to-benefit tradeoff in community and academic practices across seven countries. The NAVIGATE results reveal the utility of ENB as a minimally invasive platform to support a safe, multimodal approach to lung cancer and facilitate the diagnostic decision-making process. As this article is the first presentation of the global primary and secondary end point results, it reports both the safety and the 24-month diagnostic utility of the ENB procedure. When analyzed closely, several important themes emerge.

Safety in a Heterogeneous Cohort

Despite a diverse patient population and regional technique differences, a low complication risk was observed. The current article is the first presentation of the global primary end point, with a 3.2% rate of pneumothorax requiring intervention or hospitalization. Higher pneumothorax and bronchopulmonary hemorrhage rates have been reported after percutaneous biopsy and are associated with more frequent

hospitalization and longer length of stay.[7] A previously published NAVIGATE analysis described the predictors of lower complication rates, including general anesthesia, rEBUS, and fluoroscopy use.[23] In the current analysis, complication rates were higher in Europe where those technologies are less frequently available. New technologies with real-time location correction[8,9,11–14] may reduce complications with less reliance on secondary confirmatory imaging. NAVIGATE also established the need for a validated bronchopulmonary hemorrhage severity scale more suitable to bronchoscopic interventions.[24] Furthermore, the 24-month survival rate of 64.5% in NAVIGATE patients diagnosed with having lung cancer is consistent with the disease burden and the expected survival in this population.[1]

The Diagnostic Decision Algorithm

Minimally invasive bronchoscopic biopsy of any kind is not necessarily an end point, but rather a step in the diagnostic process to inform the probability of malignancy and the next step forward. Furthermore, when evaluating a suspicious lung lesion, any diagnostic result other than malignancy requires diligent follow-up to confirm or refute the negative outcome. For example, even an ENB-aided histologic confirmation of infection, such as *Aspergillus*, can sometimes grow adjacent to malignancy. NAVIGATE used prospective 24-month follow-up with a predefined algorithm for the hierarchy of certainty to determine true negative versus FN diagnoses. These decisions are rarely straightforward, and the interpretation of pathologic results may not be binary (cancer versus not cancer). Although not a prespecified objective of the study, NAVIGATE sheds light on how the navigation platform is used in the diagnostic process.

Although previous single-center studies by expert users have observed higher diagnostic yields,[25–28] the 67.8% diagnostic yield in NAVIGATE elucidates how the technology performs in the general community.[29] The lack of real-time image guidance and the occurrence of CT-to-body divergence may also prevent the diagnostic yield from routinely approaching that of CT-guided TTNA.[30] Compared with historical rates, technologies with real-time guidance and intraprocedural location correction have revealed higher diagnostic yields than the ENB system versions used in NAVIGATE.[8,11,31] Nonetheless, ENB remains a useful tool to aid in lung cancer diagnosis and management by providing a minimally invasive method to safely inform the probability of malignancy while allowing biopsy, staging, tissue collection for molecular testing, and fiducial or dye marking in the same procedure.

ENB Usage Patterns

NAVIGATE suggests that ENB is used more broadly than previously expected in patients with higher pretest probability of malignancy, in late-stage disease, to localize tumors for treatment, and in the same setting as mediastinal staging. For example, 61% of NAVIGATE subjects had a pretest probability of malignancy greater than 65%. Although these patients would typically be considered for surgery,[32] patients and surgeons increasingly require a confirmed diagnosis and stage before resection, preferably during the same minimally invasive procedure as suggested by guidelines.[4] Among all NAVIGATE patients undergoing a surgical lung resection, 40.5% (139 of 343) received an ENB-aided malignant diagnosis before surgery with a 39-day median time to resection, suggesting obtaining a diagnosis did not significantly delay treatment.

Linear EBUS-guided staging was performed concurrently with ENB in 456 NAVIGATE subjects. The order of lung lesion biopsy and lymph node staging was not prescribed or captured in NAVIGATE, although any patient who obtained a diagnosis by linear EBUS that precluded the need for ENB would not have been enrolled.[16] Although guidelines recommend that patients with suspected mediastinal involvement undergo nodal sampling first, increased awareness of the causes and sequelae of iatrogenic atelectasis has prompted some operators to instead sample lung nodules first.[33,34]

Studies of rEBUS-guided biopsy have suggested a comparable diagnostic accuracy to ENB (72.4% rEBUS versus 76.4% ENB in one meta-analysis) with similar safety profiles, yet at a lower cost.[35] Notably, rEBUS is not a directional tool but rather is a confirmatory imaging technology that requires a bronchus sign to access the lesion. In NAVIGATE, concurrent use of rEBUS during the ENB procedure did not affect diagnostic yield, but it was associated with lower pneumothorax rates. rEBUS was used in only 4% of NAVIGATE procedures in Europe, compared with 57% in the United States.

ENB-guided fiducial or dye marking was also conducted in more than 20% of subjects, with success rates of 99% and 91%, respectively, in previously published analyses.[20,21] NAVIGATE also revealed that ENB was used in late-stage disease, possibly in support of tissue acquisition for molecular or mutation analysis,[16] or for contralateral disease in the setting of multiple lesions.

Regional Practice Variations

Several regional differences in practice patterns were observed that likely affected outcomes. Previous ENB experience, biopsy of multiple lesions, and the use of general anesthesia, ROSE, fluoroscopy, and rEBUS

differed between regions and may have affected the diagnostic yield and the risk of pneumothorax. Future bronchoscopic studies from different countries will need to consider variations in operator experience, access to technology, and reimbursement. NAVIGATE also describes the relationship between previous ENB experience and outcomes. Previous ENB experience of zero to four cases per month (77% of EU investigators, 8% of U.S. investigators) was associated with a significantly lower diagnostic yield (58.9%) compared with those with 5 to 10 cases per month before NAVIGATE (diagnostic yield 69.3%). There seemed to be no additional benefit of previous ENB experience greater than 10 cases per month (diagnostic yield 70%). Thus, NAVIGATE suggests that the learning curve threshold for ENB is somewhere between five and 10 cases.

The Importance of Follow-Up

As mentioned previously, any diagnostic result other than cancer must be regarded with suspicion and followed carefully. With a NPV of 47% in the global cohort, NAVIGATE emphasizes the importance of careful follow-up. This is also true for TTNA with a reported NPV of 51%.[36] NAVIGATE provides insight into the length of follow-up required to evaluate diagnostic accuracy in a clinical study setting. Most FNs were identified in the first year and 92% of diagnoses were consistent between the 12- and 24-month visits. Nevertheless, 28 cases initially considered TN for malignancy at 12 months were considered FN in the second year (representing 10% of all TNs at the 12-month time point). Therefore, ongoing vigilance and 24-month follow-up remain necessary to definitely evaluate accuracy in clinical investigations, although 12-month follow-up may provide an early indication of device efficacy.

Limitations

Although the pragmatic design is a strength, NAVIGATE is a single-arm, nonrandomized, observational study. Second, diagnostic outcomes, although arguably of greater clinical relevance, were evaluated as secondary end points in the study to allow a primary safety evaluation of all ENB procedure types (including fiducial placement and dye marking). Finally, future randomized studies are needed to more fully evaluate the currently available advanced bronchoscopy systems.

Conclusions

NAVIGATE is the largest multicenter ENB study to date and the only multinational study to present usage patterns and ENB-aided diagnostic yield with prospective, independently verified 24-month follow-up. There are several lessons to be learned from NAVIGATE. ENB has low complication rates even in a heterogeneous population, with a 3.2% rate of pneumothorax requiring intervention or hospitalization. Nevertheless, the diagnostic yield and safety of early generations of the technology are at least partially dependent on procedural methods, ancillary imaging, and user experience. All nonmalignant outcomes require close clinical follow-up. Newer technologies with real-time location correction may improve both safety and efficacy.[8,11] Nevertheless, ENB is a useful diagnostic aid to guide follow-up while facilitating concurrent staging and localization for treatment.

CRediT Authorship Contribution Statement

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Haiying Lin: Software, Formal analysis.

Erik E. Folch, Kristin L. Hood, Sandeep J. Khandhar, Haiying Lin, Jennifer S. Mattingley, Jennifer J. Wolvers: Analysis design, Interpretation.

Douglas A. Arenberg, Sandeep Bansal, Michela Bezzi, Krish Bhadra, Mark R. Bowling, Merete Christensen, Javier Flandes, Thomas R. Gildea, Kyle Hogarth, William S. Krimsky, Bernd Lamprecht, Kelvin Lau, Amit K. Mahajan, Jennifer S. Mattingley, Septimiu D. Murgu, Boris A. Murillo, Michael A. Nead, Michael A. Pritchett, Jaspal Singh, Christopher W. Towe: Data collection.

Jennifer J. Wolvers: Data curation.

Erik E. Folch, Kristin L. Hood, Sandeep J. Khandhar: Writing—original draft.

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Kristin L. Hood: Visualization.

Acknowledgments

This study was sponsored and funded by Medtronic. Medical writing support was provided by Dr. Hood (Medtronic). The authors thank the investigators and staff of all participating clinical sites (Supplementary Data 1).

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.12.008.

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