ORIGINAL ARTICLE

Navigational Bronchoscopy or Transthoracic Needle Biopsy for Lung Nodules

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ABSTRACT

BACKGROUND

Each year, millions of pulmonary nodules are identified incidentally or through lung cancer screening, and many involve biopsy to distinguish cancer from benign processes. Both navigational bronchoscopy and computed tomography–guided transthoracic needle biopsy are commonly used in patients undergoing biopsies of peripheral pulmonary nodules, but the relative diagnostic accuracy of these two approaches is unclear.

METHODS

In this multicenter, randomized, parallel-group, noninferiority trial, we assigned patients with an intermediate-risk or high-risk peripheral pulmonary nodule measuring 10 to 30 mm in diameter to undergo navigational bronchoscopy or transthoracic needle biopsy at seven centers across the United States. The primary outcome was diagnostic accuracy, which was defined as the percentage of patients with biopsies that showed a specific diagnosis (cancer or a specific benign condition) that was confirmed to be accurate through 12 months of clinical follow-up (nonferiority margin, 10 percentage points). Secondary outcomes included procedural complications such as the occurrence of pneumothorax.

RESULTS

Among the 234 patients included in the primary-outcome analysis (5 of whom were lost to follow-up), biopsy resulted in a specific diagnosis that was confirmed to be accurate through month 12 in 94 of 119 patients (79.0%) in the navigational bronchoscopy group and in 81 of 110 patients (73.6%) in the transthoracic needle biopsy group (absolute difference, 5.4 percentage points; 95% confidence interval, −6.5 to 17.2; P=0.003 for noninferiority; P=0.17 for superiority). Pneumothorax occurred in 4 of 121 patients (3.3%) in the navigational bronchoscopy group and in 32 of 113 patients (28.3%) in the transthoracic needle biopsy group and led to the placement of a chest tube, hospital admission, or both in 1 patient (0.8%) and 13 patients (11.5%), respectively.

CONCLUSIONS

The diagnostic accuracy of navigational bronchoscopy was noninferior to that of transthoracic needle biopsy among patients with peripheral pulmonary nodules measuring 10 to 30 mm. (Funded by Medtronic and others; VERITAS ClinicalTrials.gov number, NCT04250194.)

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*A list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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Millions of pulmonary nodules are identified annually, and many involve biopsy to distinguish cancer from benign processes.[1-3] Transthoracic needle biopsy and navigational bronchoscopy are techniques for biopsy of peripheral pulmonary nodules. Transthoracic needle biopsy is guided by intraprocedural three-dimensional computed tomographic (CT) images. This technique provides an accurate diagnosis in up to 90% of cases but involves the passage of a needle through the chest wall and pleura, which has been reported to cause pneumothorax in up to 25% of cases.[4-8] During navigational bronchoscopy, biopsy of nodules is performed with the use of catheters that are guided through peripheral airways on the basis of CT images obtained before the procedure, without involvement of the pleurae. This method has been found to cause pneumothorax in 2% of cases.[9] However, navigational bronchoscopy has historically relied on the use of intraprocedural two-dimensional fluoroscopy, and diagnostic accuracy has been reported to be as low as 38%, with a pooled estimate of accuracy of 70% in previous meta-analyses.[9-12] In the past several years, intraprocedural three-dimensional imaging (digital tomosynthesis and cone-beam CT) has been integrated with navigational bronchoscopy platforms, and this combination has resulted in diagnostic accuracy that is similar to that of transthoracic needle biopsy in some studies.[13-16]

Estimates of diagnostic accuracy for both navigational bronchoscopy and transthoracic needle biopsy have been derived from single-group studies that had a high risk of selection, referral, and publication biases.[4,11] Randomized trials comparing navigational bronchoscopy with transthoracic needle biopsy are lacking.

To compare the effect of navigational bronchoscopy with that of transthoracic needle biopsy on diagnostic accuracy in patients undergoing biopsy of a peripheral pulmonary nodule, we conducted the VERITAS (Navigation Endoscopy to Reach Indeterminate Lung Nodules versus Transthoracic Needle Aspiration) trial. We hypothesized that the diagnostic accuracy of navigational bronchoscopy would be noninferior to that of transthoracic needle biopsy.

Methods

Trial Design and Oversight

VERITAS was an investigator-initiated, multicenter, open-label, randomized, parallel-group, noninferiority trial in which navigational bronchoscopy was compared with transthoracic needle biopsy in patients undergoing biopsy of an indeterminate pulmonary nodule. The trial was approved by the institutional review board at the clinical coordinating center of Vanderbilt University Medical Center and at each participating trial site, and it was registered at ClinicalTrials.gov before initiation. Details of the trial design were described previously, before the conclusion of enrollment,[17] and the protocol (including the statistical analysis plan) is available with the full text of this article at NEJM.org.

The last author had full authority over the trial design; the data collection, management, analysis, and interpretation; the writing of an earlier version of the manuscript; and the decision to submit the manuscript for publication. Central investigators designed the trial and wrote the first draft of the manuscript; all the authors agreed to submit the manuscript for publication. Trial oversight was performed by the coordinating center of the clinical trials office at Vanderbilt Ingram Cancer Center. Medtronic, a funder of the trial, had no role in the trial design; the data collection, management, analysis, or interpretation; trial oversight; the writing of the manuscript; or the decision to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Sites and Patient Population

The trial was conducted at seven sites across the United States. Adults who were referred for bronchoscopic or transthoracic needle biopsy of a single peripheral, indeterminate pulmonary nodule measuring 10 to 30 mm in diameter and had a calculated pretest probability of cancer of at least 10% were eligible for participation.[17-19] Patients were excluded if the nodule was accessible without navigation (e.g., if they had a central endobronchial lesion), if the patient had a separate condition for which linear endobronchial ultrasound-guided needle aspiration was indicated

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(e.g., mediastinal or hilar lymphadenopathy), if empirical treatment with stereotactic body radiation therapy was planned regardless of their biopsy results, or if a biopsy was not feasible by means of either navigational bronchoscopy or transthoracic needle biopsy. Details of the trial sites and inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

ENROLLMENT, RANDOMIZATION, AND BLINDING

Consecutive adults who were referred for lung-nodule biopsy were screened by a local site investigator. After written informed consent was provided, chest imaging was reviewed centrally by an interventional pulmonologist and an interventional radiologist to confirm that the nodule was technically amenable to both navigational bronchoscopy and transthoracic needle biopsy. Fully eligible patients were randomly assigned in a 1:1 ratio to undergo navigational bronchoscopy or transthoracic needle biopsy. Randomization was stratified according to nodule location (outer or middle third of the lung), pretest probability of cancer (≤50% or >50%[18,19]), and trial site with the use of permuted blocks of varying sizes. Randomization was performed with the use of a Web-based randomization tool.[20,21]

Clinicians and research personnel were aware of the trial-group assignments after randomization, given the nature of the intervention. However, outcome assessors were unaware of the trial-group assignments.

TRIAL INTERVENTION

Patients assigned to undergo navigational bronchoscopy underwent electromagnetic navigational bronchoscopy with integrated digital tomosynthesis (Illumisite fluoroscopic navigation platform, Medtronic).[13] The procedures were planned on the basis of a CT scan obtained within 3 months before the procedure. Bronchoscopy was performed, with the patient under general anesthesia, by an interventional pulmonologist with access to radial endobronchial ultrasound imaging for confirmation of localization of the nodule and rapid onsite cytologic assessment for assessment of the adequacy of the biopsy specimen. The use of digital tomosynthesis was encouraged when the initial radial ultrasound image suggested that the biopsy catheter was not pointed at the center of the nodule. The types of biopsy tools used and the number of biopsies performed with each tool were at the discretion of the proceduralist. Fluoroscopy was used to assess for pneumothorax immediately after the procedure.

Patients assigned to undergo transthoracic needle biopsy underwent CT-guided transthoracic needle biopsy under local anesthesia with moderate sedation or under general anesthesia, in accordance with local institutional protocols and clinician and patient preferences. Biopsies were performed by interventional radiologists with the use of dedicated interventional CT scanners. The number of biopsies, the size and type of biopsy needle, whether rapid on-site cytologic examination was performed, and the method of assessment for pneumothorax after the procedure were at the discretion of the proceduralists.

Patients who were found to have cancer on biopsy were referred for oncologic treatment. Patients in whom cancer was not identified underwent guideline-recommended follow-up by treating clinicians who managed all care after the biopsy, including any decision to pursue additional invasive diagnostic procedures and cadence of follow-up imaging.

DATA COLLECTION

Demographic and radiologic data were collected by local research personnel. For each patient, central investigators recorded technical feasibility for both procedures and the location of the nodule within the outer or middle third of the lung.[22] Procedural data, pathological findings, and complications were recorded on the basis of review of medical records and a telephone call with the patient 7 days after the procedure.

Biopsy specimens were reviewed by local pathologists for the presence of cancer. Specimens that were found to be nonmalignant on local review underwent central review by a thoracic pathologist who was unaware of the trial-group assignments. A central committee of three experts in pulmonary nodules, all of whom were also unaware of the trial-group assignments, reviewed data regarding all the biopsies that had been interpreted locally as nonmalignant to adjudicate whether the biopsy was diagnostic or

nondiagnostic. These data included the local and central pathological interpretations and preprocedural clinical records. A specific benign diagnosis required consensus among the three experts; cases in which consensus could not be reached were adjudicated as nondiagnostic.

Research personnel reviewed medical records for subsequent invasive procedures and CT scans. Records were monitored until there was a change in the presumed diagnosis of a nonmalignant lung nodule, until regression or resolution of the nodule was seen on subsequent scans, or for at least 12 months if the nodule remained stable on repeat CT scans.

OUTCOMES

The primary outcome was diagnostic accuracy, which was defined as the percentage of patients with biopsies that showed a specific diagnosis (cancer or a specific benign condition) that was confirmed to be accurate through 12 months of clinical follow-up (see Fig. S1 in the Supplementary Appendix).[17,23] In patients whose procedure was cancelled because same-day imaging performed before the start of the procedure showed nodule regression, their assigned intervention was considered to be diagnostic, but confirmation on follow-up diagnostic CT was required to be considered accurate. In patients whose procedure was cancelled on the day of the procedure for any other reason except safety (e.g., the patient presented with a new unstable arrhythmia), the intervention was considered to be nondiagnostic, as were any procedures that were started but not completed.

The secondary outcomes included diagnostic yield (defined as the percentage of patients with biopsies that were considered to be diagnostic without consideration of clinical follow-up), a confident clinical diagnosis (defined as a diagnosis that was based not only on the nodule biopsy but also on additional sampling procedures, such as lymph-node biopsies, that were performed at the time of the nodule biopsy), procedural complications (including safety outcomes such as the occurrence of pneumothorax), duration of the procedure, procedural and radiologic features associated with diagnostic yield, need for subsequent nodule biopsy or staging procedure, and radiation exposure. These outcomes are described in detail in the Supplementary Appendix.

STATISTICAL ANALYSIS

Demographic characteristics and nodule features were summarized for each trial group with the use of medians and quartiles for continuous variables and frequencies and percentages for categorical variables. Noninferiority of navigational bronchoscopy was tested with the use of a z-test, with a noninferiority margin of 10 percentage points. Details of the rationale for the noninferiority margin are provided in the Supplementary Appendix. The diagnostic accuracy of transthoracic needle biopsy was assessed at 90%, with a one-sided type I error rate of 5%. Therefore, a sample size of 112 patients per group would give the trial 80% power to determine noninferiority. Under the assumption of 15% attrition, the total sample size was calculated to be 258 patients (129 per group). No interim analysis was performed because both biopsy techniques are used in routine clinical care, and adjudication of the primary outcome required 12 months.

All the patients who had undergone randomization were included in the analyses, with the following exceptions: patients who had undergone additional imaging between randomization and the trial intervention that showed results that made them ineligible (e.g., repeat imaging that showed nodule growth to >30 mm or new nodal disease for which biopsy was indicated), patients who did not report for their scheduled trial intervention, patients whose procedure was cancelled owing to clinical instability before the initiation of the trial intervention, and patients with missing data on the primary outcome.

We examined whether prespecified baseline variables modified the effect of trial-group assignment on the primary outcome using a logistic-regression model with the trial-group assignment, the proposed effect modifier, and the interaction between the trial-group assignment and the proposed effect modifier as independent variables. Prespecified potential effect modifiers included nodule location (outer third vs. middle third of the lung), calculated probability of cancer (≤50% vs. >50%), nodule size (≤15 mm vs.

>15 mm in diameter), and presence or absence of the bronchus sign. The bronchus sign is a finding seen on CT that is characterized by a peripheral bronchus that terminates in or extends through a lung nodule.

Three sensitivity analyses of the primary efficacy outcome were performed. One analysis included all the patients who had undergone randomization, regardless of whether they underwent the randomly assigned intervention; patients who did not undergo a trial intervention were classified as not having met the criteria for the primary outcome. In a second analysis, the outcomes of patients who were lost to follow-up before month 12 and had a specific benign diagnosis on the basis of the biopsy were considered to be either all true negative for cancer or all false negative for cancer. A third analysis included only patients who underwent biopsy of the target nodule; patients whose biopsy was cancelled owing to nodule regression seen on imaging performed on the day of the intervention (before the start of the procedure) and those whose proceduralist declined to perform the procedure were excluded from the analysis.

Between-group differences in the secondary outcomes are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in the intervention effects between the two groups. All the analyses were performed with the use of R software, version 4.4.

RESULTS

PATIENTS

From September 16, 2020, through June 14, 2023, a total of 519 patients were assessed for eligibility. Among these patients, 231 were excluded or declined participation and 288 (55.5%) provided written informed consent (Fig. 1 and Fig. S2). The most common reason for exclusion was having a separate clinical indication for bronchoscopy. Among the patients who provided written informed consent, 30 were ineligible for randomization: 20 did not meet the criteria for undergoing a trial intervention after central review of imaging, 5 had new imaging results that met an exclusion criterion, and 5 withdrew consent. A total of 129 patients were randomly assigned to undergo navigational bronchoscopy and 129 patients to undergo transthoracic needle biopsy. After randomization, 6 patients in the navigational bronchoscopy group and 10 patients in the transthoracic needle biopsy group did not report for their scheduled trial intervention; 2 patients in the navigational bronchoscopy group and 1 patient in the transthoracic needle biopsy group presented with conditions that were clinically unstable and resulted in cancellation of their procedures; and 5 patients in the transthoracic needle biopsy group were excluded on the basis of results of positron-emission tomography and CT that were obtained before the biopsy. In total, 121 of the 129 patients (93.8%) assigned to undergo navigational bronchoscopy and 113 of the 129 patients (87.6%) assigned to undergo transthoracic needle biopsy were included in the primary-outcome analysis. Two of the 121 patients (1.7%) in the navigational bronchoscopy group and 3 of the 113 patients (2.7%) in the transthoracic needle biopsy group were lost to follow-up before collection of data for the primary outcome.

The demographic and clinical characteristics of the patients at baseline, along with nodule features, are shown in Table 1. The median diameter of the nodules was 15 mm (interquartile range, 12 to 19). Most of the patients (82.5%) had solid nodules, and most had nodules that were located in the outer third of the lung (87.6%).

PRIMARY OUTCOME

With respect to diagnostic accuracy, the primary outcome, biopsy indicated a specific diagnosis that was confirmed to be accurate through 12 months of clinical follow-up in 94 of 119 patients (79.0%) in the navigational bronchoscopy group and in 81 of 110 patients (73.6%) in the transthoracic needle biopsy group (absolute difference, 5.4 percentage points; 95% confidence interval [CI], −6.5 to 17.2; P=0.003 for noninferiority; P=0.17 for superiority) (Table 2). Through 12 months of clinical follow-up, 3 patients in the transthoracic needle biopsy group in whom a specific benign condition was diagnosed after biopsy and 1 patient in that group in whom regression was seen on imaging

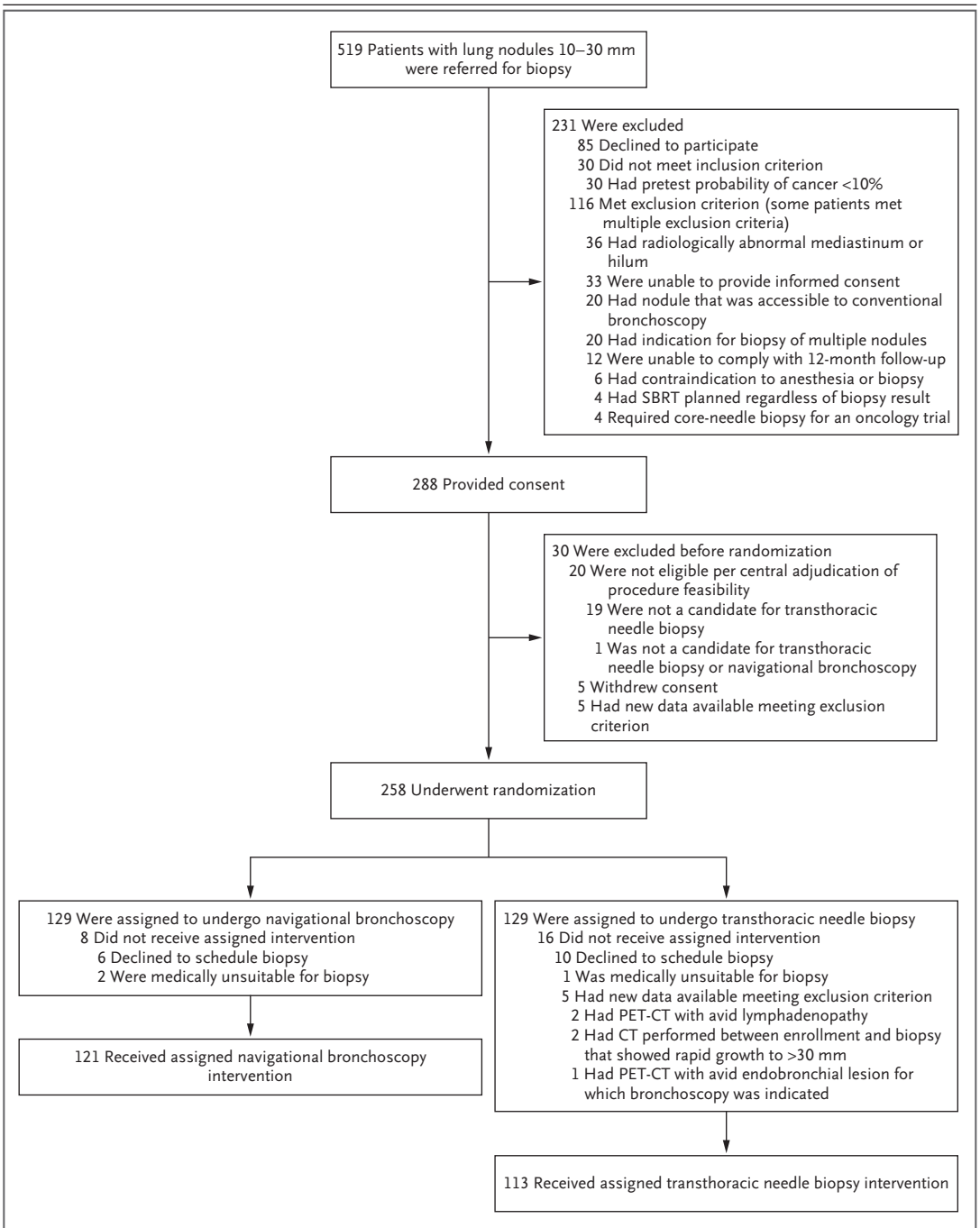

Figure 1. Screening and Randomization.

PET-CT denotes positron-emission tomography with computed tomography, and SBRT stereotactic body radiation therapy.

performed on the day of the intervention (before the start of the procedure) had nodules that were reclassified as malignant on the basis of subsequent findings; the incidence of false negative results was 3.6%. No patients in the navigational bronchoscopy group in whom a specific

Table 1. Characteristics of the Patients and Nodules.*

Characteristic	Navigational Bronchoscopy (N=121)	Transthoracic Needle Biopsy (N=113)
Patients		
Median age (IQR) — yr	66.0 (62.0–72.0)	68.0 (61.0–74.0)
Female sex — no. (%)	57 (47.1)	56 (49.6)
Race or ethnic group — no. (%)†		
White	110 (90.9)	105 (92.9)
Black	9 (7.4)	5 (4.4)
Asian	2 (1.7)	1 (0.9)
Native American or Native Alaskan	0	2 (1.8)
Hispanic ethnic group — no. (%)†	0	3 (2.7)
Coexisting conditions — no. (%)		
Current or previous cancer‡	46 (38.0)	55 (48.7)
Chronic obstructive pulmonary disease	49 (40.5)	48 (42.5)
Coronary artery disease	25 (20.7)	16 (14.2)
Median body-mass index (IQR)§	27.6 (23.9–31.5)	27.9 (24.0–31.2)
Tobacco smoking history		
Current smoker — no. (%)	39 (32.2)	24 (21.2)
Former smoker — no. (%)	55 (45.5)	66 (58.4)
Median pack-years (IQR)	43.0 (20.0–55.0)	35.0 (20.0–47.0)
Nodules		
Median diameter (IQR) — mm¶	15 (12–20)	14 (12–18)
Lung zone — no. (%)		
Outer third of lung	107 (88.4)	98 (86.7)
Middle third of lung	14 (11.6)	15 (13.3)
Density — no. (%)		
Solid	99 (81.8)	94 (83.2)
Part-solid	20 (16.5)	19 (16.8)
Pure ground-glass opacity	2 (1.7)	0
Radiologic features — no. (%)		
Spiculated	54 (44.6)	64 (56.6)
Lobular	36 (29.8)	28 (24.8)
Smooth	18 (14.9)	11 (9.7)
Cavitary or cystic component	9 (7.4)	4 (3.5)
Abutting pleura	14 (11.6)	19 (16.8)
Bronchus sign present‖	41 (33.9)	38 (33.6)
Median distance, nodule edge to nearest bronchus (IQR) — mm	10.0 (0.0–19.0)	12.0 (0.0–20.0)
Median distance, nodule edge to pleura (IQR) — mm	7.0 (0.0–17.2)	7.0 (0.0–20.0)
Median pretest probability of cancer (IQR)		
According to enrolling clinician	75.0 (50.0–90.0)	75.0 (50.0–90.0)
According to quantitative prediction model **	32.0 (20.0–55.8)	30.0 (16.0–51.6)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race and ethnic group were reported by the patient.
‡ Details are provided in Table S2.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ The diameter was calculated as the mean length of the short- and long-axis in the axial plane.
‖ The bronchus sign is present when a peripheral bronchus is found to terminate in or extend through a lung nodule on CT.
** The Brock model[18] was used if no positron-emission tomography (PET) data were available at the time of enrollment. The Herder model[19] was used if PET data were available at the time of enrollment.

benign condition was diagnosed had nodules that were reclassified as malignant. The overall prevalence of cancer through month 12 was 72.1% (74.8% in the navigational bronchoscopy group and 69.1% in the transthoracic needle biopsy group).

The results of sensitivity analyses of the primary outcome were similar to those of the primary-outcome analysis (see the Supplementary Appendix). No characteristics of the nodules nor the trial site appeared to modify the effect of the method of biopsy on diagnostic accuracy (Fig. 2 and Fig. S3).

SECONDARY OUTCOMES

The results of the secondary outcomes are provided in Table 2 and in the Supplementary Appendix. The median duration of the procedure was 36 minutes (interquartile range, 28 to 48) for navigational bronchoscopy and 25 minutes (interquartile range, 13 to 36) for transthoracic needle biopsy (median difference, 11; 95% CI, 8 to 18). An invasive diagnostic procedure was pursued after the biopsy that was performed during the trial in 13.2% of the patients in the navigational bronchoscopy group and in 13.3% of those in the transthoracic needle biopsy group (Table 2 and Table S9). Details of the procedural and radiologic features associated with diagnostic yield are provided in Tables S7 and S8.

SAFETY OUTCOMES

A procedural complication occurred in 6 of 121 patients (5.0%) in the navigational bronchoscopy group and in 33 of 113 patients (29.2%) in the transthoracic needle biopsy group (absolute risk difference, 24.2 percentage points; 95% CI, 15.0 to 35.6) (Table 3). Pneumothorax was the most common complication, occurring in 4 patients (3.3%) in the navigational bronchoscopy group and in 32 (28.3%) of those in the transthoracic needle biopsy group (absolute risk difference, 25.0 percentage points; 95% CI, 15.3 to 34.8). Pneumothorax resulting in the placement of a chest tube, hospital admission, or both occurred in 1 patient (0.8%) in the navigational bronchoscopy group and in 13 (11.5%) of those in the transthoracic needle biopsy group (absolute risk difference, 10.7 percentage points; 95% CI, 3.7 to 17.6). No hemorrhages resulting in medical intervention occurred, and there were no deaths during the 12-month follow-up period of the primary analysis.

DISCUSSION

The diagnostic accuracy of navigational bronchoscopy was noninferior to that of transthoracic needle biopsy among patients undergoing biopsy of a peripheral pulmonary nodule. Complications were less common during navigational bronchoscopy.

Early diagnosis of lung cancer, which often involves biopsy, offers the best chance for cure. Methodologically rigorous estimates of the accuracy and safety of available methods of biopsy are needed to inform the care of patients with indeterminate pulmonary nodules. The results of this trial suggest that navigational bronchoscopy, which elicited diagnostic accuracy similar to that of transthoracic needle biopsy but with fewer complications, should be the procedure of choice for biopsy of indeterminate lung nodules that appear to be technically amenable to both approaches.

The diagnostic performance of navigational bronchoscopy in this trial was similar to that seen in previous studies that used the same technique, in which diagnostic accuracy ranging from 77 to 83% was reported.[13-16] In this trial, transthoracic needle biopsy performed worse than previously reported. However, the typically higher estimates of diagnostic accuracy with transthoracic needle biopsy derive from noncomparative, and often retrospective, studies with a high risk of bias that used a variety of outcome definitions.[4,11,23] In addition, the median nodule size in this trial was relatively small, at 15 mm; the diagnostic performance of transthoracic needle biopsy has been reported to be notably lower when targeting smaller nodules.[5,24,25]

This trial has several strengths. First, patients were screened for eligibility when they were referred for navigational bronchoscopy or transthoracic needle biopsy, which mitigated the risk of referral bias. Second, patients were recruited at academic and community centers across different geographic regions, and therefore, the trial involved a representative sample of physicians and patients, which strengthens the generalizability of these results (see Table S1). Third, an independent panel adjudicated the technical feasibility of both biopsy methods to ensure that both were suitable options and to limit selection bias. Fourth, the pathologists and pulmonary nodule experts who adjudicated the primary

outcome were unaware of the trial-group assignments, thus minimizing observer bias, and there was minimal loss to follow-up with respect to the primary outcome. Fifth, a conservative approach was used to define the primary outcome, and the resulting final definition conformed to current recommendations.[23] Lastly, multiple prespecified sensitivity analyses of the primary outcome were performed; all the analyses corroborated the results of the main analysis, which showed the noninferiority of navigational bronchoscopy to transthoracic needle biopsy.

This trial also has several limitations. First, although both academic centers and community centers were included, navigational bronchoscopy was performed by experienced pulmonologists, so these results may not generalize to centers with less expertise. Second, it was not practicable to conceal the trial-group assignments from proceduralists or patients, although outcome

Table 2. Primary and Secondary Outcomes.

Outcome	Navigational Bronchoscopy (N=121)	Transthoracic Needle Biopsy (N=113)	Difference (95% CI)*
Primary outcome: diagnostic accuracy — no./total no. (%)†			
Accurate	94/119 (79.0)	81/110 (73.6)	5.4 (–6.5 to 17.2)‡
Inaccurate	25/119 (21.0)	29/110 (26.4)	—
False negative	0	4/110 (3.6)	—
Initially nondiagnostic	25/119 (21.0)	25/110 (22.7)	—
Lost to follow-up	2/121 (1.7)	3/113 (2.7)	—
Secondary outcome: diagnostic yield — no. (%)§			
Diagnostic¶	96 (79.3)	88 (77.9)	1.5 (–9.9 to 12.8)
Malignant‖	78 (64.5)	61 (54.0)	—
Specific benign	16 (13.2)	17 (15.0)	—
Granulomatous	6 (5.0)	10 (8.8)	—
Organizing pneumonia	1 (0.8)	5 (4.4)	—
Acute neutrophilic inflammation	3 (2.5)	1 (0.9)	—
Other specific benign**	6 (5.0)	1 (0.9)	—
Same-day regression††	2 (1.7)	10 (8.8)	—
Nondiagnostic	25 (20.7)	25 (22.1)	—
Nonspecific inflammation	10 (8.3)	8 (7.1)	—
Normal lung or airway	9 (7.4)	3 (2.7)	—
Atypia	4 (3.3)	2 (1.8)	—
No biopsy specimens obtained‡‡	2 (1.7)	6 (5.3)	—
Proceduralist declined to perform procedure§§	0	6 (5.3)	—
Additional secondary outcomes			
Underwent procedure — no. (%)¶¶	119 (98.3)	97 (85.8)	12.5 (4.8 to 20.2)
Median duration of procedure (IQR) — min	36 (28 to 48)	25 (13 to 36)	11 (8 to 18)
Median radiation exposure (IQR)‖‖	9800 (7190 to 18,850)	659 (253 to 1276)	NA
Intraprocedural rapid onsite cytologic assessment — no./total no. (%)	114/119 (95.8)	7/97 (7.2)	88.6 (81.4 to 95.8)
Subsequent invasive diagnostic procedure — no. (%)	16 (13.2)	15 (13.3)	0.1 (–8.8 to 8.7)

Table 2. (Continued.)

Outcome	Navigational Bronchoscopy (N=121)	Transthoracic Needle Biopsy (N=113)	Difference (95% CI)*
Subsequent invasive staging procedure — no. (%)	0	3 (2.7)	3.0 (–4.0 to 6.7)

* The difference is reported in percentage points. NA denotes not applicable.
† Diagnostic accuracy was defined as the percentage of patients with biopsies that showed a specific diagnosis (cancer or a specific benign condition) that was confirmed to be accurate through 12 months of clinical follow-up.
‡ P=0.003 for noninferiority; P=0.17 for superiority.
§ Diagnostic yield was defined as the percentage of patients with biopsies that were considered to be diagnostic without consideration of clinical follow-up.
¶ Biopsies were considered to be diagnostic if they showed malignant or specific benign pathological findings. Complete definitions and additional information are provided in the Supplementary Appendix.
‖ Details of malignant diagnoses are provided in Table S2.
** Other specific benign diagnoses were hamartoma (in 4 patients in the navigational bronchoscopy group), necroinflammatory (in 1 patient in the navigational bronchoscopy group), silicotic nodule (in 1 patient in the navigational bronchoscopy group), and fibroelastotic scar (in 1 patient in the transthoracic needle biopsy group).
†† Same-day regression was defined as substantial regression seen on same-day cross-sectional imaging performed before the start of the procedure; this finding indicated a high probability of a benign process without biopsy. Such imaging was required to be related to the biopsy method (e.g., scout CT that was intended to inform transthoracic needle placement or chest CT that was used for navigational bronchoscopy planning in patients who had not recently undergone CT).
‡‡ The procedure was started, but no biopsy specimens were ultimately obtained (e.g., owing to a complication).
§§ The proceduralist declined to proceed despite the fact that the patient had a nodule that had been peer-adjudicated as technically feasible and the patient was medically suitable for biopsy.
¶¶ Patients whose procedures were cancelled because same-day imaging showed regression and those whose proceduralist declined to perform the procedure on the day of the procedure are not included.
‖‖ The fluoroscopes that were used to perform two-dimensional fluoroscopy for navigational bronchoscopy and the CT scanners that were used for transthoracic needle biopsy reported the radiation dose in different units: dose-length product (in mGy·cm^2) for navigational bronchoscopy and dose-area product (in mGy·cm) for transthoracic needle biopsy. The units could not be converted; therefore, a direct comparison of the two trial groups with respect to median radiation exposure could not be made.

adjudication was blinded. Third, patients with nodules that were considered not to be accessible by transthoracic needle biopsy, navigational bronchoscopy, or both methods, as well as those with nodules in the inner third of the lung, were excluded. However, these exclusions accounted for only 20 of 288 (6.9%) provisionally eligible patients; these results suggest that our findings generalize to the majority of nodules referred for biopsy. Fourth, rapid onsite cytologic evaluation was used more commonly during navigational bronchoscopy than during transthoracic needle biopsy; whether this finding affects the diagnostic accuracy of these approaches is uncertain and should be the focus of future trials. Fifth, although cases of pneumothorax overall and of pneumothorax that resulted in hospital admission or the placement of a chest tube (or both) were each more common in the transthoracic needle biopsy group, these outcomes could have been influenced by the universal use of cross-sectional imaging in the transthoracic needle biopsy group and by differences in practice patterns regarding hospitalization on the basis of clinical specialty. Sixth, the results of the subgroup analysis of the primary outcome performed according to trial site showed that trial site did not modify the effect of the biopsy method on diagnostic accuracy, although small samples at some sites limited this analysis. Seventh, cost effectiveness was not assessed and should be the topic of future trials. Lastly, for patients in whom same-day preprocedural imaging showed substantial regression of the nodule, the assigned intervention was considered to be diagnostic in the primary analysis; a sensitivity analysis excluding these patients did not change the results. Diagnostic regression that was seen on the day of the biopsy was more common with transthoracic needle biopsy — a finding that potentially biased results in favor of this method and thus strengthens the finding that naviga-

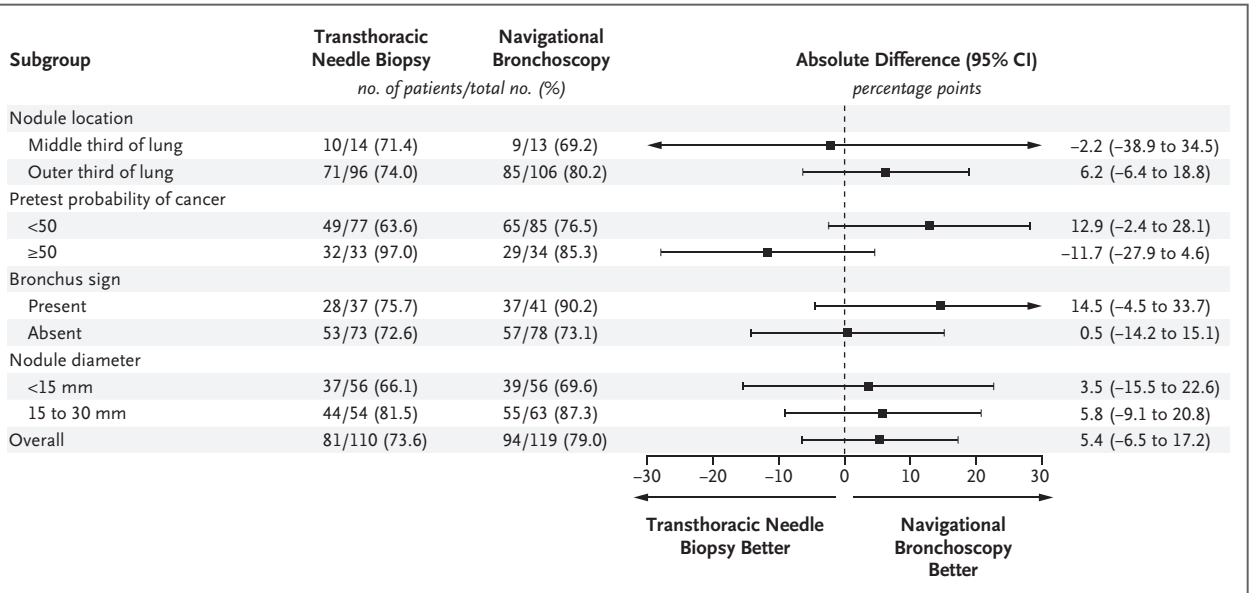

Figure 2. Subgroup Analyses of the Primary Outcome.

Shown are the unadjusted mean differences in diagnostic accuracy, the primary outcome, between patients who underwent navigational bronchoscopy and those who underwent transthoracic needle biopsy. Diagnostic accuracy was defined as the percentage of patients with biopsies that showed a specific diagnosis (cancer or a specific benign condition) that was confirmed to be accurate through 12 months of clinical follow-up. The bronchus sign is present when a peripheral bronchus is found to terminate in or extend through a lung nodule on CT. The horizontal bars represent the 95% confidence intervals around the mean difference. The number of patients in each group for whom a measure of diagnostic accuracy was available is shown. The pretest probability of cancer was calculated by a validated cancer risk assessment model.

Table 3. Safety Outcomes.

Outcome	Navigational Bronchoscopy (N=121)	Transthoracic Needle Biopsy (N=113)	Difference (95% CI)*	P Value
Any complication — no. (%)	6 (5.0)	33 (29.2)	24.2 (15.0 to 35.6)	<0.001
Pneumothorax				
Any grade — no. (%)	4 (3.3)	32 (28.3)	25.0 (15.3 to 34.8)	<0.001
Grade 1 or 2†	3 (2.5)	19 (16.8)	14.3 (6.0 to 22.6)	<0.001
Grade 3 or 4‡	1 (0.8)	13 (11.5)	10.7 (3.7 to 17.6)	<0.001
Median duration of chest tube in place (IQR) — days	1.0 (1.0 to 1.0)	1.0 (1.0 to 2.0)	0	0.65
Respiratory failure resulting in hospital admission — no. (%)	1 (0.8)	1 (0.9)	0.1 (–2.5 to 2.4)	0.96
Hemorrhage resulting in medical intervention — no. (%)	0	0	0	—
Acute coronary syndrome — no. (%)	1 (0.8)	0	0.8 (–1.6 to 3.3)	0.33

* The difference is reported in percentage points.
† Grade 1 or 2 indicates that pneumothorax was managed with observation or aspiration.
‡ Grade 3 or 4 indicates that pneumothorax led to hospital admission with or without the placement of a chest tube.

tional bronchoscopy was noninferior to transthoracic needle biopsy.

The results of this trial showed that the diagnostic accuracy of navigational bronchoscopy was noninferior to that of transthoracic needle biopsy and led to fewer complications.

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