CHEST

Diagnostic Yield and Synergistic Impact of Needle Aspiration and Forceps Biopsy With Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions

A Randomized Controlled Trial

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BACKGROUND: Electromagnetic navigation bronchoscopy (ENB) is an advanced imaging-guided technique used to diagnose peripheral pulmonary lesions. However, the optimal strategy for selecting biopsy devices remains unclear.

RESEARCH QUESTION: Does the combination of needle aspiration and forceps biopsy improve diagnostic yield compared with using a single device alone?

STUDY DESIGN AND METHODS: We conducted a randomized crossover study during ENB performed under moderate sedation. This trial recruited participants with peripheral pulmonary lesions requiring biopsy who were eligible for elective ENB. ENB-guided needle aspiration and forceps biopsy were sequentially performed in a randomized order. The primary outcome was diagnostic yield, defined as the percentage of patients for whom the biopsy provided a specific diagnosis able to inform patient management. The diagnostic yield achieved by each biopsy modality individually and in combination was evaluated.

RESULTS: Between December 1, 2021, and November 13, 2023, 142 participants were enrolled and underwent the study procedures. Complete follow-up data were obtained for 140 participants. Diagnostic yield was 44.4% (63 of 142) for forceps biopsy, 51.4% (73 of 142) for needle aspiration ($P = .221$ vs forceps), and 66.9% (95 of 142) for the combination ($P < .001$ vs forceps alone, $P < .001$ vs needle alone). Sensitivities for malignancy were 47.5% (57 of 120) for forceps biopsy and 58.3% (70 of 120) for needle aspiration ($P = .074$). The combination of the 2 modalities resulted in a significantly improved sensitivity of 71.7% (86 of 120) compared with either individual modality ($P < .001$ vs forceps alone and needle alone). Pneumothorax occurred in 3.5% (5 of 142) of patients, and 1.4% (2 of 142) developed pneumothorax requiring tube drainage.

INTERPRETATION: Our results show that when performing ENB under moderate sedation, the combination of needle aspiration and forceps biopsy significantly improves the diagnostic yield and sensitivity for malignancy compared with each modality alone, with a favorable safety profile. These results indicate that a multimodal approach using needles and forceps is a valid diagnostic strategy for ENB.

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KEY WORDS: diagnostic imaging; electromagnetic navigation bronchoscopy; lung neoplasms; pulmonary medicine

Take-Home Points

Study Question: Does the combination of needle aspiration and forceps biopsy improve the diagnostic yield compared with a single device alone when performing electromagnetic navigation bronchoscopy (ENB) under moderate sedation?

Results: From a randomized crossover study which enrolled 142 participants to undergo ENB-guided needle aspiration and forceps biopsy in a randomized order, the combination of needle aspiration and forceps biopsy significantly improved diagnostic yield and sensitivity compared with either forceps biopsy or needle aspiration alone. The overall rates of pneumothorax and pneumothorax requiring tube drainage were 3.5% and 1.4%, respectively.

Interpretation: Our results indicate that the combination of ENB-guided needle aspiration and forceps biopsy significantly improves the overall diagnostic yield and sensitivity compared with either approach alone for diagnosing pulmonary lesions, with a favorable safety profile.

The increasing use of chest CT scan for thoracic imaging in clinical practice and the widespread implementation of lung cancer screening with low-dose chest CT scan have significantly increased the detection of pulmonary lesions requiring diagnostic evaluation.[1-3] Invasive diagnostic testing for pulmonary lesions is challenging and involves a multidisciplinary approach with various biopsy techniques.[4] Current clinical practice guidelines recommend the least invasive approach with the highest expected yield.[5,6] For peripheral lesions inaccessible by conventional flexible bronchoscopy, CT scan-guided transthoracic needle biopsy (TTNB) has traditionally been considered the standard of care, with a high reported yield of approximately 90%. However, complications are common with TTNB, with pneumothorax reported in over 18% of cases and more than 6% requiring chest tube placement. In addition, some lesions are not technically amenable to this percutaneous approach.[7,8]

Over the last 2 decades, advanced image-guided technologies have been developed to improve the sampling of peripheral lesions with flexible bronchoscopy.[9] Electromagnetic navigational bronchoscopy (ENB) is an evolving technique that is widely used. ENB involves generating an electromagnetic field around the patient to track biopsy tools and their position vis-à-vis the lesion to improve the diagnostic yield of bronchoscopy.[10] The reported diagnostic yield of ENB ranges from 67% to 84% for peripheral pulmonary lesions, with a markedly lower complication rate (< 5% for pneumothorax) than TTNB.[11,12]

When performing ENB, forceps biopsy and needle aspiration are the most commonly used tissue sampling tools.[13,14] Previous results from nonrandomized studies on guided bronchoscopic biopsy suggest that the choice of biopsy tool can impact diagnostic performance.[15-18] Although previous studies on bronchoscopic biopsy suggested an enhanced diagnostic yield with the use of an aspiration needle, this tool appears to be underused in real-world practice.[16,19] Moreover, its true benefit in an ENB-specific setting is yet to be verified. In clinical practice, the selection of biopsy tools is influenced by multiple factors, including the expected efficacy and safety of bronchoscopic biopsies, local preferences, market availability, and reimbursement coverage. In particular, the tradeoffs involving procedural cost, time, and complexity of using an additional biopsy

ABBREVIATIONS: ENB = electromagnetic navigation bronchoscopy; R-EBUS = radial endobronchial ultrasonography; ROSE = rapid on-site evaluation; TTNB = transthoracic needle biopsy

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tool are important limiting factors in deciding on a multitool strategy without clearly established benefits and safety. Therefore, data from a controlled trial evaluating the synergistic effects of needle aspiration and forceps biopsy, along with comparisons of the diagnostic performances of each device, are warranted.

To this end, we conducted the Comparison and Synergistic Evaluation of Needle Aspiration and Forceps Biopsy for Diagnosing Pulmonary Lesions with Electromagnetic Navigation Bronchoscopy (CONFIDENT-ENB) trial, which followed a randomized crossover design. This study aimed to evaluate whether a combination of needle aspiration and forceps biopsy improves the diagnostic yield of ENB compared with forceps alone and to assess the comparative yield and discordance between the 2 devices in a minimal setting under moderate sedation, without adjunct guidance techniques or rapid on-site evaluation (ROSE).

Study Design and Methods

Study Design and Participants

We conducted a randomized crossover study to evaluate the impact of ENB-guided needle aspiration, forceps biopsy, and their combination on diagnostic yield by performing biopsies with both devices in a randomized sequence. Eligible participants were consecutively recruited from Seoul National University Bundang Hospital, a tertiary referral hospital in South Korea. The inclusion criteria were (1) aged ≥ 18 years; (2) individuals with a suspicious pulmonary lesion requiring definitive diagnosis, as determined by the attending pulmonologist or multidisciplinary tumor board; and (3) lesions predicted to be difficult to access with conventional bronchoscopy alone but amenable to elective ENB. The exclusion criteria were (1) inability or unwillingness to provide informed consent or comply with the follow-up schedule; (2) participation in an investigational drug or device research study within 90 days of enrollment, with possible interference with this study; (3) contraindications to moderate sedation or allergies to any of the sedatives planned for use or contraindications to the bronchoscopy procedure; (4) those with multiple lesions requiring ENB-guided sampling; (5) significant regression of the lesion on the same-day CT scan obtained for ENB planning; and (6) successful biopsy from a visible endobronchial tumor lesion in patients initially scheduled for ENB, precluding the need for electromagnetic navigation, or failure to perform ENB-guided biopsy due to technical risks or inability. At the institution where the study was conducted, CT scan-guided TTNB was also available as a biopsy modality. The decision to perform ENB as the biopsy method was primarily based on the lesion's accessibility via ENB, as judged by the attending pulmonologist. ENB was chosen because of its lower predicted complication rates than the transthoracic approach, particularly when the lesion was considered accessible with ENB. Written informed consent was obtained from all participants before undergoing ENB. This study adhered to the Declaration of Helsinki and all regulatory requirements. The study protocol was approved by the institutional review board of Seoul National University Bundang Hospital (No. B-2112-715-302) and was registered at ClinicalTrials.gov (identifier No. NCT05110131).

Randomization

Immediately before the ENB procedure, participants were randomly assigned to receive either ENB-guided needle aspiration followed by forceps biopsy (the needle-first group) or ENB-guided forceps biopsy followed by needle aspiration (the forceps-first group) in a 1:1 ratio. This randomization was aimed to balance the confounding effect of a device being a second biopsy modality, which can be penalized as tissue disruption caused by the first biopsy modality. The randomization sequence was generated by an independent statistician not involved in the clinical study using a computer-generated list created with SAS version 9.4 (SAS Institute). Participants were masked to their group allocation. However, the performing bronchoscopists could not be masked because of the nature of the intervention.

Procedures

All ENB procedures were performed by 1 of the 9 bronchoscopists experienced in ENB under moderate sedation using the Spin Thoracic Navigation System (SYS-4230 K; Veran Medical). A detailed procedure protocol has been published previously and is available in e-Appendix 1 (Supplementary Methods).[20] On the procedure day, participants underwent paired inspiration/expiration chest CT scans for software registration and virtual airway route reconstruction. These planning CT scans were independently reviewed by 2 thoracic radiologists to assess lesion size, type, lobe location, lung zone (inner one-third, middle one-third, or outer one-third of the hemithorax), CT scan bronchus sign, and other

parenchymal findings. Procedures were performed under moderate sedation, with IV administration of midazolam and fentanyl at the onset of the procedure, along with local anesthesia using topical 1% lidocaine.

Based on group allocation, ENB-guided biopsy was first attempted at least 3 times with a 22-G or 21-G aspirating needle (INS-0392 or INS-5410; Veran Medical) or forceps (INS-0372; Veran Medical), followed by the same procedure with the other device with at least 3 attempts. There were no protocol-specific restrictions on the maximum number of attempts, which was at the discretion of the performing bronchoscopist. All procedures were performed without complementary localization techniques (eg, radial endobronchial ultrasonography [R-EBUS], fluoroscopy, cone-beam CT scan). ROSE of the specimens was not performed in any of the procedures. This setting reflects the standard practice of ENB in South Korea, where the study was carried out. Randomizing the biopsy device sequence, controlling the minimum number of attempts, and restricting complementary techniques mitigated potential risks of order effects (eg, influence of the first biopsy on tissue condition, procedure time spent with the first biopsy, and bronchoscopist preference for a particular modality or complementary technique).

All participants underwent chest radiograph postprocedurally and the day after the procedure. With ENB-guided biopsy, histologic samples from needle aspiration and forceps biopsy, and cytology samples from needle aspiration, were obtained from each participant. All samples were interpreted by 2 pathologists (J. H. C. and Y. B. H.) masked to the sequences of the biopsy devices.

Outcomes

The primary outcome was the diagnostic yield of combined needle aspiration and forceps biopsy for diagnosing pulmonary lesions compared with that of forceps biopsy alone. Strict and conservative definitions for diagnostic yield were adopted for nonmalignant findings to avoid overestimation of performance. Diagnostic yield was defined as the proportion of participants whose biopsy yielded a definitive diagnosis. A biopsy was considered diagnostic if the specimen established a definitive malignancy (true positive) or a specific benign diagnosis that sufficiently represented the lesion and informed further management (true negative). Other findings, including nonspecific benign tissue (eg, acute/chronic inflammation) and nondiagnostic results (eg, atypical cells, normal lung parenchyma, insufficient tissue), were considered nondiagnostic according to conservative definitions of yield.[21-23] After the outcome reporting consensus,[21] the primary outcome was determined solely based on the ENB procedural encounter. For all nonmalignant findings on ENB, the final diagnosis was confirmed through clinical/radiologic follow-up for 12 months (or until confirmative diagnosis by an additional procedure or regression without cancer treatment) to confirm true- or false-negative results. Secondary outcomes included the diagnostic yield of the combined approach compared with needle aspiration alone, sensitivity for malignancy, and the strictly defined diagnostic accuracy based on 12-month follow-up results to determine true or false negatives. Participants with nonmalignant ENB results lacking confirmative follow-up for up to 12 months were excluded from the analyses for sensitivity and diagnostic accuracy. The proportion of successful lesion approach, sampling duration, number of attempts for needle and forceps biopsy, and adverse events related to the ENB procedure were also evaluated. Adverse events were classified according to the Common Terminology Criteria for Adverse Events scale, version 5.0.[24] Pneumothorax was assessed using chest radiograph postprocedurally and the day after the procedure. All participants were followed-up at 2 weeks postprocedure to evaluate the presence of delayed complications. Outcomes are reported according to the Standards for Reporting Diagnostic Accuracy Studies guidelines.[25]

Statistical Analysis

The sample size was calculated to detect a 15% difference in diagnostic accuracy between forceps alone (threshold at 67%) and the combination of needle and forceps (hypothesized 82%, calculation based on paired proportions, numbers based on previously conducted observational studies that suggested an improved diagnostic accuracy with the use of needle aspiration and combination of modalities).[11,12,16,26,27] With a 2-sided significance of 0.05 and 80% power and an estimated dropout rate of 5%, a sample size of 142 participants (71 in each allocation group, resulting in 142 biopsies for each device and combination) was targeted with calculations using Power Analysis & Sample Size 2021 (NCSS, LLC). Although the initial design of this trial focused on diagnostic accuracy over 12 months of follow-up, we have adjusted our primary outcome reporting to align with the recent consensus recommendations by the American Thoracic Society[21] to facilitate interpretation and comparison with future trials.

Demographic and radiologic characteristics were presented as means with SDs for continuous data and frequencies with proportions for categorical data. Comparisons between allocation groups were performed using Student t test for continuous variables and χ^2 test (or Fisher exact test) for categorical variables. Diagnostic yield and accuracy were compared using McNemar test for forceps vs combination, needle vs combination, and needle vs forceps, respectively. A paired analysis was used because the crossover design of the study allowed for the comparison of each sampling strategy for the same pulmonary lesion. Additionally, P values adjusted for multiple comparisons using the Bonferroni correction were calculated for the primary outcomes, assuming multiple comparisons were made (combination vs either). All analyses were 2-sided, with $P < .05$ considered statistically significant. Analysis was performed using R version 4.1.0 (R Foundation for Statistical Computing, https://www.r-project.org) and STATA version 16.0 (StataCorp).

Results

Between December 1, 2021, and November 13, 2023, 173 patients with pulmonary lesions were assessed for eligibility, and 142 participants were enrolled. Nine different bronchoscopists successfully completed ENB-guided needle aspiration and forceps biopsy, and complete data with up to 12-months follow-up were obtained for 140 participants (Fig 1). The baseline characteristics of the participants and biopsied lesions are summarized in Table 1. Characteristics were well balanced between the needle-first group (n = 71) and forceps-first group (n = 71). The mean age ± SD of the participants was 68.2 ± 9.0 years, with 84 male participants (59.2%). The mean lesion size ± SD was 20.8 ± 7.7 mm, with 119 (83.8%) solid lesions, 80 (56.3%) located in the upper lobes, 83 (58.5%) in the

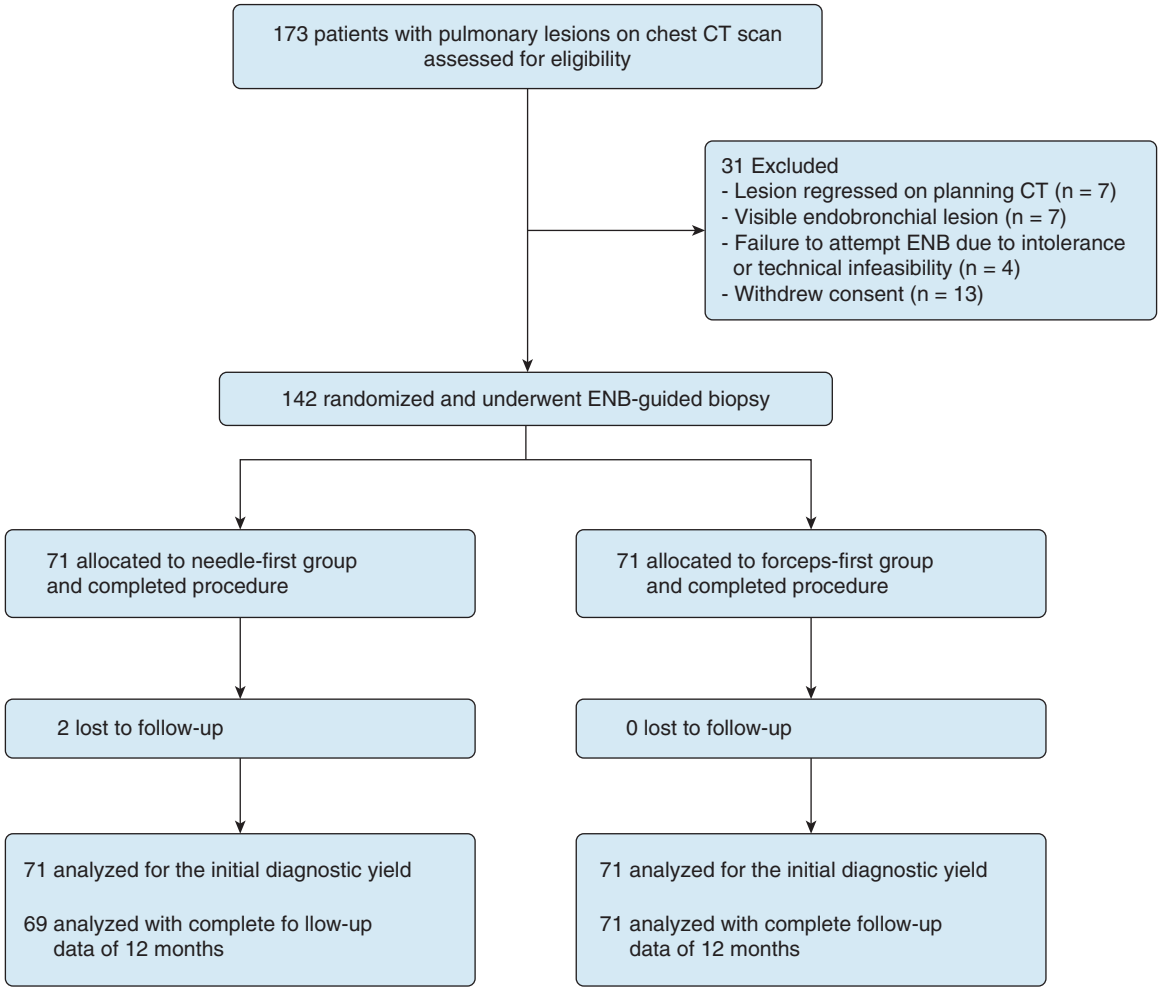

Figure 1 – *Flow diagram of the study population. ENB = electromagnetic navigation bronchoscopy.*

TABLE 1] Baseline Demographic and Radiologic Characteristics

Characteristics	Total (N = 142)	Needle-First Group (n = 71)	Forceps-First Group (n = 71)	*P* Value
Age, y	68.2 [9.0]	69.3 [9.5]	67.2 [8.5]	.168
Sex				> .999
Male	84 (59.2)	42 (59.2)	42 (59.2)	
Female	58 (40.8)	29 (40.8)	29 (40.8)	
Smoking status				.103
Does not smoke	61 (43.0)	30 (42.3)	31 (43.7)	
Previous tobacco use	61 (43.0)	35 (49.3)	26 (36.6)	
Active tobacco use	20 (14.1)	6 (8.5)	14 (19.7)	
Pack-y smoked	21.0 [24.9]	18.3 [20.4]	23.6 [28.6]	.206
BMI, kg/m^2	24.2 [3.2]	24.6 [3.4]	23.9 [3.0]	.223
Family history of lung cancer	19 (13.4)	14 (19.7)	5 (7.0)	.049
ECOG performance				.559
0	100 (70.4)	49 (69.0)	51 (71.8)	
1	37 (26.1)	19 (26.8)	18 (25.4)	
2	4 (2.8)	3 (4.2)	1 (1.4)	
3	1 (0.7)	0 (0)	1 (1.4)	
Lesion size, mm	20.8 [7.7]	20.2 [7.0]	21.5 [8.3]	.311
Lesion type				.280
Solid	119 (83.8)	63 (88.7)	56 (78.9)	
Subsolid	20 (14.1)	7 (9.9)	13 (18.3)	
Cavitary	3 (2.1)	1 (1.4)	2 (2.8)	
Lesion location				.089
Right upper lobe	36 (25.4)	16 (22.5)	20 (28.2)	
Right middle lobe	17 (12.0)	13 (18.3)	4 (5.6)	
Right lower lobe	36 (25.4)	14 (19.7)	22 (31.0)	
Left upper lobe	27 (19.0)	16 (22.5)	11 (15.5)	
Left lower lobe	26 (18.3)	12 (16.9)	14 (19.7)	
Centrality,				.233
Inner two-thirds	59 (41.5)	33 (46.5)	26 (36.6)	
Outer one-third	83 (58.5)	38 (53.5)	45 (63.4)	
Distance to pleura, mm	17.7 (13.6)	19.8 (14.3)	15.6 (12.7)	.065
CT scan bronchus sign	91 (64.1)	46 (64.8)	45 (63.4)	.861
Other parenchymal findings				
Emphysema	35 (24.6)	15 (21.1)	20 (28.2)	.436
Interstitial fibrosis	11 (7.7)	6 (8.5)	5 (7.0)	> .999
Bronchiectasis	12 (8.5)	7 (9.9)	5 (7.0)	.763
Mayo Clinic probability for malignancy	47.2 [24.7]	45.7 [23.7]	48.8 [25.8]	.459

Data are presented as mean [SD], No. (%), or as otherwise indicated. ECOG = Eastern Cooperative Oncology Group.

outer one-third of the hemithorax, and 91 (64.1%) with a positive CT scan bronchus sign. The mean procedural time ± SD for ENB was 37.1 ± 11.5 minutes. The total time of needle biopsy was longer than the total time of forceps biopsy (mean, 18.6 vs 11.7 minutes, respectively; $P < .001$) (e-Table 1).

The results from the ENB-guided biopsies are presented in Table 2. The primary outcome of diagnostic yield for the combined procedure was 66.9% (95 of 142). The combination of needle aspiration and forceps biopsy resulted in a significantly higher diagnostic yield than with forceps biopsy alone (44.4% [63 of 142]; $P < .001$

TABLE 2] Diagnostic Results and Yields of Electromagnetic Navigation Bronchoscopy-Guided Needle and Forceps Biopsy at the Index Procedure

Results	Needle (N = 142)	Forceps (N = 142)	Needle + Forceps (N = 142)
Diagnostic yield			
Definitive diagnosis[a]	73 (51.4)	63 (44.4)	95 (66.9)[b,c]
No definitive diagnosis	69 (48.6)	79 (55.6)	47 (33.1)
Malignancy	70 (49.3)	57 (40.1)	86 (60.6)
NSCLC, adenocarcinoma	41 (28.9)	37 (26.1)	52 (36.6)
NSCLC, squamous	13 (9.2)	11 (7.7)	15 (10.6)
NSCLC, PD or NOS	14 (9.9)	5 (3.5)	15 (10.6)
Carcinoid tumor	0 (0)	1 (0.7)	1 (0.7)
Sarcoma	1 (0.7)	1 (0.7)	1 (0.7)
Lymphoma	1 (0.7)	1 (0.7)	1 (0.7)
Metastatic carcinoma	0 (0)	1 (0.7)	1 (0.7)
Specific benign	3 (2.1)	6 (4.2)	9 (6.3)
Infection/abscess	3 (2.1)	1 (0.7)	4 (2.8)
TB	0 (0)	2 (1.4)	2 (1.4)
NTM	0 (0)	1 (0.7)	1 (0.7)
Dense anthracofibrosis	0 (0)	1 (0.7)	1 (0.7)
Eosinophilic pneumonia	0 (0)	1 (0.7)	1 (0.7)
Nonspecific benign	15 (10.6)	15 (10.6)	15 (10.6)
Nondiagnostic	54 (38.0)	64 (45.1)	32 (22.5)

Data are presented as No. (%). NOS = not otherwise specified; NSCLC = non-small cell lung cancer; NTM = nontuberculous mycobacteria; PD = poorly differentiated.

[a]Specimen established a definitive malignancy (true positive) or a specific benign diagnosis that sufficiently represented the lesion (true negative).

[b]$P < .05$ vs needle biopsy.

[c]$P < .05$ vs forceps biopsy.

vs combination). In addition, the combination resulted in a significantly higher diagnostic yield than needle aspiration alone (51.4% [73 of 142]; $P < .001$ vs combination). No significant difference was observed between the diagnostic yield of each single modality ($P = .221$ for needle vs forceps). In 41 participants (28.9%), both needle aspiration and forceps biopsy established a definitive diagnosis. Forceps biopsy failed to establish a diagnosis in 32 cases, of which a diagnosis was established with needle aspiration (non-small cell lung cancer: n = 29, infection/abscess: n = 3). Conversely, needle aspiration failed to establish a diagnosis in 22 cases, for which the diagnosis was determined by forceps biopsy (non-small cell lung cancer: n = 14, carcinoid tumor: n = 1, metastatic carcinoma: n = 1, mycobacterial diseases: n = 3, infection/abscess: n = 1, eosinophilic pneumonia: n = 1, dense anthracofibrosis: n = 1) (e-Fig 1). The diagnostic accuracy through 12-month follow-up was 45.0% (63 of 140) for forceps biopsy, 52.1% (73 of 140) for needle aspiration ($P = .221$ vs forceps), and 67.9% (95 of 140) for the combination ($P < .001$ vs forceps alone, $P < .001$ vs needle alone) (e-Table 2). The higher diagnostic yield and accuracy for the combination of needle and forceps compared with either device alone remained significant when P values were adjusted for multiple comparisons (raw P value $\times 2$).

Among the 140 participants with complete follow-up data and adjudication of final diagnosis, final diagnoses for initially nondiagnostic cases were achieved via sequential endobronchial ultrasonography-guided nodal biopsy in 2.1% (3 of 140), CT scan-guided transthoracic biopsy in 2.9% (4 of 140), surgical biopsy in 20.0% (28 of 140), nonindex site biopsy in 0.7% (1 of 140), and regression without cancer treatment or stability at 12-month follow-up in 6.4% (9 of 140) (e-Table 3). Overall, 120 of 140 pulmonary lesions (85.7%) were determined to be malignant. Subgroup analyses of the diagnostic yield of the ENB procedure according to the final diagnosis and lesion characteristics are presented in Table 3. The sensitivity of the combined ENB procedure for detecting malignancy was 71.7% (86 of 120). The combination of needle aspiration and forceps biopsy led to a significant increase in sensitivity compared with

TABLE 3] Diagnostic Yield by Subgroups

Diagnostic Yield	Needle	Forceps	Needle + Forceps
Final diagnosis with 12-mo follow-up			
Malignancy (sensitivity)	70/120 (58.3)	57/120 (47.5)	86/120 (71.7)[a,b]
Benign	3/20 (15.0)	6/20 (30.0)	9/20 (45.0)[a]
Lesion size, mm			
≤ 20	34/69 (49.3)	27/69 (39.1)	46/69 (66.7)[a,b]
> 20	39/73 (53.4)	36/73 (49.3)	49/73 (67.1)[a,b]
Lesion location			
Upper lobe[c]	39/80 (48.8)	41/80 (51.3)	54/80 (67.5)[a,b]
Lower lobe	34/62 (54.8)[b]	22/62 (35.5)[a]	41/62 (66.1)[a,b]
Lesion type			
Solid or cavitary	68/122 (55.7)[b]	52/122 (42.6)[a]	83/122 (68.0)[a,b]
Subsolid	5/20 (25.0)	11/20 (55.0)	12/20 (60.0)[a]
Bronchus sign			
Positive	57/91 (62.6)	50/91 (54.9)	72/91 (79.1)[a,b]
Negative	16/51 (31.4)	13/51 (25.5)	23/51 (45.1)[a,b]
Peripheral location			
Outer one-third	43/83 (51.8)	36/83 (43.4)	56/83 (67.5)[a,b]
Inner two-thirds	30/59 (50.8)	27/59 (45.8)	39/59 (66.1)[a,b]
Emphysematous lung			
Yes	21/35 (60.0)	17/35 (48.6)	24/35 (68.6)[b]
No	52/107 (48.6)	46/107 (43.0)	71/107 (66.4)[a,b]

Data are presented as No./total No. (%).
[a]$P < .05$ vs needle biopsy.
[b]$P < .05$ vs forceps biopsy.
[c]Upper lobe includes the right upper, right middle, and left upper lobes, and lingula.

forceps biopsy alone (47.5% [57 of 120]; $P < .001$ vs combination) and needle aspiration alone (58.3% [70 of 120]; $P < .001$ vs combination, $P = .074$ for needle vs forceps, e-Fig 2). The difference between the combination and either device remained significant after adjusting P values for multiple comparisons. The synergistic effect of combining needle aspiration and forceps biopsy on increased diagnostic yield was significant in all subgroups classified by lesion size, location, type, presence of bronchus sign, centrality, and presence of emphysema. The diagnostic yield and sensitivity of the combined approach, needle aspiration, and forceps biopsy did not significantly differ between the needle-first and forceps-first groups (Table 4). Additional diagnostic outcome measures, including specificity, positive predictive value, negative predictive value, and area under receiver operating characteristic curves for each modality and combination, are presented in e-Table 4.

TABLE 4] Diagnostic Yield and Sensitivity for Malignancy of the Needle-First and Forceps-First Groups

Parameter	Needle-First Group	Forceps-First Group	*P* Value
Diagnostic yield (combination)	49/71 (69.0)	46/71 (64.8)	.721
Diagnostic yield (needle)	37/71 (52.1)	36/71 (50.7)	> .999
Diagnostic yield (forceps)	32/71 (45.1)	31/71 (43.7)	> .999
Sensitivity (combination)	43/58 (74.1)	43/62 (69.4)	.705
Sensitivity (needle)	35/58 (60.3)	35/62 (56.5)	.805
Sensitivity (forceps)	28/58 (48.3)	29/62 (46.8)	> .999

Data are presented as No./total No. (%) or as otherwise indicated.

TABLE 5] Adverse Events

Parameter	ENB (N = 142)
Pneumothorax	5 (3.5)
Pneumothorax requiring tube drainage	2 (1.4)
Bleeding (CTCAE grade)	
None or grade 1	132 (93.0)
Grade 2	10 (7.0)
Grade 3-5	0 (0)
Respiratory failure	0 (0)
Procedure-related mortality	0 (0)

Data are presented as No. (%). CTCAE = Common Terminology Criteria for Adverse Events; ENB = electromagnetic navigation bronchoscopy.

No severe complication related to the ENB procedure including respiratory failure or death was reported during postprocedural evaluation or during subsequent follow-up (Table 5). Pneumothorax occurred in 3.5% (5 of 142) of participants, with 1.4% (2 of 142) requiring chest tube drainage. No significant bleeding events requiring transfusion or invasive interventions occurred.

Discussion

The findings from our prospective comparative trial showed that when performing ENB under moderate sedation for diagnosing pulmonary lesions, the combination of needle aspiration and forceps biopsy significantly improves the diagnostic yield and sensitivity for malignancy compared with each device alone. To our knowledge, this is the first prospective study evaluating the synergistic effect of a combined multimodal approach of needle aspiration and forceps biopsy with strict control of the following methodologic aspects: procedure sequence and process, exclusion of complementary techniques other than ENB (eg, R-EBUS, fluoroscopy), and a strict assessment of diagnostic yield per current recommendations. The use of sole ENB under moderate sedation, without additional guidance techniques or ROSE, is the standard practice in South Korea and many Asian institutions, where advanced bronchoscopic procedures are typically performed without general anesthesia, and the availability of various localization and confirmation tools is limited. Therefore, our findings would be generalizable to settings with similar medical systems and practice patterns. In addition, this study provides valuable insights into the individual contributions of biopsy tools and the implications of discordant results when both devices are used. Given the low complication rate, our results suggest that when ENB is performed under moderate sedation and without adjunct imaging guidance, a multimodal biopsy approach should be preferred.

Current guidelines for diagnosing pulmonary lesions recommend that the diagnostic approach should consider factors (eg, lesion characteristics, expected yield of the available procedure, potential risk of complications).[6,28] When performing ENB, the optimal selection of biopsy tools is critically important; however, evidence informing this decision is lacking. To date, forceps biopsy remains the primary modality for tissue sampling, followed by needle aspiration.[14,29,30] Needle aspiration can offer unique advantages in providing extended access beyond the airway, but has limitations in approaching lesions that require passage through sharp angles (eg, lesions in the upper lobes or superior segment of the lower lobes), and is reported to be underused in real-world practice.[16,19] Although previous studies on bronchoscopic sampling suggest that needle aspiration enhances diagnostic yield, its actual benefit in an ENB-specific setting remains unverified.[17,31] A randomized trial by Chao et al[31] reported that in R-EBUS-guided biopsy for peripheral pulmonary lesions, adding needle aspiration to transbronchial biopsy and bronchial washing significantly increased diagnostic yield. Similarly, data on the benefit of the multimodal approach, along with benchmark yield and accuracy achieved by each device, would be clinically significant for settings using ENB as the localization technique for peripheral lung lesion biopsy. The Clinical Evaluation of superDimension Navigation System for Electromagnetic Navigation Bronchoscopy (NAVIGATE) study, the largest single-arm prospective ENB study to date, reported that forceps biopsy was used in 83.6% of cases and needle aspiration in 56.6%.[13] In a post hoc analysis assessing the relative contribution of different biopsy tools in 416 participants with proven malignancy by ENB, the true-positive rate was increased by 9.3% by adding forceps biopsy and 5.8% by adding needle aspiration.[14] However, in the full-set analysis of 1,260 cases that underwent ENB-guided biopsy, the number of biopsy tools used did not significantly predict the diagnostic performance.[13] A meta-analysis on ENB studies that evaluated sensitivity as the primary outcome reported a pooled sensitivity of 67% for studies using 1 device and 72% for studies using 2 devices.[12] Nevertheless, most previous studies on ENB were limited by inherent limitations (eg, lack of controlled comparisons between needle aspiration and

forceps biopsy), hindering the determination of individual contributions of each device and evaluation of the incremental benefit of combination. These limitations arise from the observational design without predefined controls for device selection strategy, usage of complementary localization techniques, and definition criteria for diagnostic accuracy measures.[13,16]

In this study, although the yield for each device appears to be lower than those reported by previous studies on ENB, which reported diagnostic yield between 67% and 80%,[10,11,27] we must consider the strict definition criteria for diagnostic yield adopted in this study and the exclusion of complementary localization techniques. Considerable variation exists in the definition of diagnostic yield across published studies on diagnostic bronchoscopy.[22,23] A simulation analysis conducted by Vachani et al[32,33] revealed that estimates of diagnostic yield can differ by $>$ 20% when different definitions are adopted from the same data set and can be influenced by the prevalence of malignancy. The NAVIGATE study initially reported a diagnostic accuracy of 73% based on a liberal definition and 1-year follow-up. However, if a strict definition is applied, the yield decreased to 49%.[34] Our result of 66.9% diagnostic yield with the combination of needle and forceps compares favorably with other ENB studies that used similar definition criteria, which reported yield between 39% and 49%.[16,35] The overall sensitivity of 71.7% aligns with prior reports.[12] When interpreting our results, the predefined exclusion of complementary localization techniques (eg, fluoroscopy, R-EBUS) could potentially confound the yield. The high prevalence of malignancy in this cohort should also be considered because higher prevalence is known to enhance diagnostic yield.[33] Given that the current consensus on reporting outcomes of diagnostic bronchoscopy studies recommends using strict definitions for standardization,[21,22] our results provide benchmark yields for ENB-guided needle aspiration, forceps biopsy, and their combination in a minimally invasive setting under moderate sedation, without reliance on additional technologies. The data presented reflect common practice in our region, where ENB and the 2 most frequently used biopsy tools are used. Moreover, with the strict definition applied, the diagnostic yields at index procedure, which is recommended for reporting diagnostic outcomes to allow data publication without delays needed for follow-up completion, demonstrated excellent concordance with the conservative diagnostic accuracy.[21,23]

Notably, in our study, 38.0% of participants (54 of 142) were nondiagnostic with a single device but were successfully diagnosed with the combination of needle and forceps. It is also noteworthy that the synergistic impact of the combined approach was significant across all subgroups, including lesions $<$ 20 mm and those with a negative bronchus sign, which are established factors associated with lower expected diagnostic yield with ENB.[11,35] Despite the use of both devices, the overall complication rate remained low (3.5% pneumothorax rate, 1.4% requiring chest tube drainage), with no cases of respiratory failure or mortality. This suggests that the combined approach can enhance the diagnostic yield for pulmonary lesions without increasing safety concerns. When performing guided bronchoscopic biopsy, various factors (eg, expected efficacy, real-world usage patterns, compatibility with platforms, market availability, additional costs) can influence the choice of biopsy tool, posing challenges to adopting a multitool strategy without clear benefits. Demonstrating benefits with robust methodology is essential for understanding the true value of multimodal biopsy strategies, including novel tools.[36] In addition to our main findings, future cost-effectiveness analyses are needed to determine whether the improvements in diagnostic performance justify the additional costs associated with using extra devices, especially in different health care settings.

Our study has several limitations. First, participants were recruited from a single center in Korea, which may limit generalizability. Our study cohort reflects the patient population in Korea and represents the minimal setting (moderate sedation without additional techniques and no reliance on ROSE) for performing ENB; therefore, the findings may not be directly applicable to other populations undergoing ENB with general anesthesia, adjunct imaging, or confirmation techniques. Second, the use of multiple biopsy tools precluded a specific analysis of complication rates associated with individual tools. This limitation was intentional because the study was designed to prioritize evaluating the synergistic effect and discordance between needle aspiration and forceps biopsy used in ENB. Third, although our primary hypothesis demonstrated statistical significance, our study was not powered to assess potential differences in diagnostic yields between single modalities. Although needle aspiration demonstrated a 7.0% higher diagnostic yield and 10.8% higher sensitivity than forceps biopsy, these differences did not reach statistical significance in this cohort. Regarding direct comparisons, although our

crossover design enabled relevant comparisons of each technique and the combined approach within identical lesions, it was important to find that the sequence of the 2 techniques did not influence the diagnostic yield of each technique.

Interpretation

In conclusion, our study demonstrated that the combination of ENB-guided needle aspiration and forceps biopsy significantly improves the overall diagnostic yield and sensitivity compared with either approach alone for diagnosing pulmonary lesions, with a favorable safety profile. Our results indicate that a combined multimodal approach using both needle aspiration and forceps biopsy is a safe and valid strategy for ENB procedures.

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

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