

Safety and risk factors for bleeding complications of radial probe endobronchial ultrasound-guided transbronchial biopsy

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Abstract

Background: Radial probe endobronchial ultrasound (radial EBUS) is widely used to diagnose pulmonary lesions; however, the diagnostic value of radial EBUS-guided transbronchial biopsy (TBB) varies, and its complications (especially the risk of bleeding) are not properly understood.

Objectives: In this study, we evaluated the diagnostic performance and rate of complication of this procedure, and investigated the risk factors associated with the procedure-related bleeding events.

Design: A retrospective cohort study.

Methods: This was a retrospective study that included consecutive patients who underwent radial EBUS-guided TBB. Radial EBUS was performed under moderate sedation in inpatients or outpatients. The severity of bleeding was graded using the standardized definitions of bleeding.

Results: Of 133 patients (median age, 69 years; men 57.1%) included, 41 were outpatients (30.8%). The diagnostic accuracy, sensitivity, and specificity for malignancy were 76.1% (89/117), 71.1% (69/97), and 100% (20/20), respectively. The diagnostic accuracy ranged from 66.9% to 79.0%, depending on the classification of undiagnosed cases as either false negatives or true negatives. Twenty-seven patients (20.3%) developed complications (pneumothorax, 3; pneumonia, 5; complicated pleural effusion, 2; bleeding event grade 2 or higher, 21). Of the 41 outpatients, two developed complications (pneumothorax without intervention, 1; grade 2 bleeding event, 1). Of the 21 patients (15.8%) with procedure-related bleeding events, 18 had grade 2, and three had grade 3 bleeding complications. In multivariate analysis, a large size of ≥ 30 mm (adjusted odds ratio (OR), 5.09; $p=0.03$) and central lesion (adjusted OR, 3.67; $p=0.03$) were significantly associated with the risk of grade 2 or higher bleeding events.

Conclusion: Our results suggest that radial EBUS-guided TBB is an accurate and safe method for diagnosing pulmonary lesions. Clinically significant procedure-related bleeding was rare. The central location and larger size (≥ 30 mm) of pulmonary lesions were risk factors for grade 2 or higher bleeding events.

Keywords: bleeding, bronchoscopy, radial probe endobronchial ultrasound, transbronchial biopsy

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Introduction

Increasing use of low-dose computed tomography (LDCT) for lung cancer screening has facilitated the detection of pulmonary lesions. The

National Lung Screening Trial demonstrated that LDCT screening resulted in 20% lower lung cancer mortality than chest radiography screening in high-risk populations.¹ The Dutch-Belgian lung

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cancer screening trial study comparing LDCT with no screening also showed a reduction in lung cancer mortality.² Thus, the United States Preventive Services Task Force recommends annual lung cancer screening with LDCT in adults aged 55–80 years who have a 20-pack-year smoking history and currently smoke or quit within the past 15 years.³ In South Korea, national lung cancer screening using LDCT has been implemented since August 2019 for high-risk smokers between 55 and 74 years old who smoked more than 30 pack-years.⁴

With the increase in the detection rate of pulmonary lesions, it is essential to have reliable and minimally invasive diagnostic modalities to obtain histopathological specimens from pulmonary lesions. CT-guided transthoracic needle biopsy is a well-established traditional technique for diagnosing pulmonary lesions with a high diagnostic accuracy of approximately 85% to 97%.^{5–7} However, CT-guided transthoracic needle biopsy has a relatively high risk of complications such as pneumothorax or hemoptysis.^{8,9} In addition, it may not be feasible in patients with pulmonary lesions closer to major blood vessels, the heart, bronchi, or severe emphysematous parenchyma. The American College of Chest Physicians guidelines recommend the use of bronchoscopy with modalities such as electromagnetic navigation or radial probe endobronchial ultrasound (radial EBUS) for pulmonary lesions closer to the bronchus and with a visible bronchus sign or for individuals at high risk of pneumothorax.^{10,11}

Radial EBUS-guided transbronchial biopsy (TBB) is one of the most widely used advanced bronchoscopic techniques for diagnosing pulmonary lesions. Its diagnostic accuracy varies from 65% to 80%.^{12,13} In addition, few studies have focused on procedure-related complications. There is inadequate knowledge of the possible risk factors for bleeding associated with this procedure. Thus, this study aimed to evaluate the diagnostic performance and complication rate of radial EBUS-guided TBB and investigate risk factors associated with procedure-related bleeding events.

Methods

Study design and participants

We retrospectively reviewed all patients who underwent radial EBUS-guided TBB for the

diagnosis of pulmonary lesions at Seoul National University Hospital from December 2019 to July 2022. Among patients who underwent radial EBUS, those whose target lesion was invisible by radial EBUS, and those who underwent radial EBUS-guided transbronchial cryobiopsy were excluded. For patients who underwent repeated radial EBUS-guided TBB on separate days, data on the initial procedure were collected for analysis. When multiple pulmonary lesions were sampled in a patient, data on the largest lesion was collected for analysis.

Procedures

All patients underwent chest CT before bronchoscopy. All bronchoscopic procedures were performed by one of two experienced pulmonologists using radial probe EBUS (UM-S20-17S; Olympus, Tokyo, Japan) and a flexible bronchoscope with outer diameter 4.0 mm (BF-P260F), 4.9 mm (BF-260), or 5.9 mm (BF-1T260; Olympus, Tokyo, Japan) without fluoroscopy. This procedure was conducted on outpatients and inpatients under moderate sedation with intravenous midazolam and fentanyl, administered by an experienced nurse and titrated by the attending pulmonologist. The flexible bronchoscope was advanced orally without intubation by tracheal tube. When endobronchial lesions were not observed during the bronchial inspection with the flexible bronchoscope, radial probe EBUS was introduced. After confirming the target lesion by radial probe EBUS, TBB was performed using biopsy forceps with or without a guide sheath (SG-200C) at the pulmonologist's discretion. A biopsy forceps with an outer diameter of 1.5 mm (FB-233D) was used with a guide sheath, whereas a biopsy forceps with an outer diameter of 1.9 mm (FB-231D) was used without a guide sheath. The use of virtual bronchoscopy and additional procedures, including bronchial brushing, bronchial washing, bronchoalveolar lavage (BAL), concurrent mediastinal staging with convex probe EBUS, or rapid on-site evaluation (ROSE) were determined by the attending pulmonologist.

Measurement of variables and outcomes

The following clinical data were collected: age, sex, smoking status, comorbidities, laboratory or pulmonary function test results, radiologic characteristics of the target pulmonary lesion including size and the presence of bronchus sign,

procedure characteristics including use of virtual bronchoscopy and a guide sheath, concurrent administration of drugs, including antiplatelet or anticoagulant agents and immunosuppressants before the procedure, and use of prophylactic antibiotics before or immediately after the procedure without evidence of active infection. The size of the pulmonary lesion was measured as the longest diameter, and the distance from the pleura was measured as the shortest distance on an axial CT scan.¹⁴ A peripheral lung lesion is defined as a lesion located in the outer one-third of the lung and difficult to reach by traditional bronchoscopy, whereas the inner two-thirds of the lung is defined as a central lung lesion.¹⁵ The CT bronchus sign was defined according to the previous study: CT bronchial sign 0 refers to the absence of a bronchus sign, CT bronchial sign 1 refers to an airway that sits adjacent to the lesion, and CT bronchial sign 2 refers to an airway directly leading to the lesion.¹⁶

The final diagnosis was classified as malignancy, benign, or undiagnosed according to the pathological evidence obtained from radial EBUS or subsequent diagnostic attempts including radial or convex probe EBUS, CT-guided transthoracic needle biopsy, or surgery. The pathologically non-diagnostic lesions were classified as benign only if the lesion decreased or disappeared during chest CT follow-up for up to one year. Otherwise, they were classified as undiagnosed.

The following procedure-related complications were reviewed: bleeding, pneumonia, pneumothorax, and complicated pleural effusion. The severity of bleeding was graded from 1 to 4 by the Delphi consensus statement.¹⁷ Grade 1 is defined as bleeding that ceased spontaneously when suction or wedging of the bronchoscope lasted < 1 min. Bleeding requiring suctioning > 1 min or the need for rewedging of the bronchoscope or the use of cold saline, vasoactive substances, or thrombogenic agents is grade 2. Grade 3 is defined as bleeding requiring endotracheal intubation or balloon/bronchial blocker for <20 min or requiring premature interruption of the procedure. If persistent intubation over 20 min or new admission to the ICU or additional intervention such as packed red blood cell transfusion or embolization was required, it is defined as grade 4. Pneumothorax was classified according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).¹⁸ Grade 1 is defined as

asymptomatic, with intervention not indicated, grade 2 is defined as symptomatic, requiring intervention such as tube placement, grade 3 is defined as operative intervention or hospitalization indicated, and grade 4 is defined as life-threatening consequences occurring.

Statistical analysis

Categorical variables were presented as numbers (percentages), and continuous variables as medians (interquartile range (IQR)). To estimate the diagnostic performance of radial probe EBUS-guided TBB, the accuracy, sensitivity, specificity, and positive and negative predictive values were calculated and reported according to the Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines.¹⁹ We conducted several sensitivity analyses in which undiagnosed cases were classified as false negatives in the low estimate and as true negatives in the high estimate, or where patients who did not undergo TBB were included. We also determined the diagnostic performance for central and peripheral lesions separately. To find predictors of diagnostic accuracy for malignancy, we performed multivariate logistic regression. We also performed multivariate logistic regression to investigate the risk factors associated with grade 2 or higher procedure-related bleeding events. Variables with $p < 0.20$ in univariate analyses were included in the multivariate analyses. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org>) and Stata software version 17.0 (StataCorp., College Station, TX, USA).

Results

Baseline and procedural characteristics

Of 161 patients who underwent bronchoscopy with radial EBUS, 26 who did not undergo TBB were excluded from the study: 22 due to invisible target lesions on radial EBUS and 4 due to technical difficulties. Two patients with pulmonary lesions biopsied by radial EBUS-guided transbronchial cryobiopsy were also excluded. Finally, 133 patients were analyzed.

The baseline characteristics of the 133 patients (median age, 69 years; men 57.1%) are shown in

Table 1. Baseline characteristics of participants.

Characteristic	Total (N = 133)	Bleeding grade 2 or higher (N = 21)	No bleeding or grade 1 (N = 112)
Age, years	69 (60–76)	64 (57–72)	69 (62–76)
Male sex	76 (57.1)	9 (42.9)	67 (59.8)
Type of admission			
Inpatient	92 (69.2)	20 (95.2)	72 (64.3)
Outpatient	41 (30.8)	1 (4.8)	40 (35.7)
Smoking status			
Never	65 (48.9)	13 (61.9)	52 (46.4)
Former	45 (33.8)	7 (33.3)	38 (33.9)
Current	23 (17.3)	1 (4.8)	22 (19.6)
Smoking, pack-years (n = 129)	0 (0–30)	0 (0–19)	1 (0–30)
Comorbidity			
Chronic obstructive pulmonary disease	9 (6.8)	0 (0.0)	9 (8.0)
Asthma	2 (1.5)	0 (0.0)	2 (1.8)
Interstitial lung disease	1 (0.8)	0 (0.0)	1 (0.9)
Diabetes mellitus	20 (15.0)	4 (19.0)	16 (14.3)
Coronary heart disease	9 (6.8)	0 (0.0)	9 (8.0)
Congestive heart failure	2 (1.5)	0 (0.0)	2 (1.8)
Stroke	4 (3.0)	0 (0.0)	4 (3.6)
Chronic kidney disease	5 (3.8)	0 (0.0)	5 (4.5)
Chronic liver disease	4 (3.0)	2 (9.5)	2 (1.8)
Transplantation	2 (1.5)	0 (0.0)	2 (1.8)
Use of drugs before procedure			
Antiplatelet agent	2 (1.5)	0 (0.0)	2 (1.8)
Anticoagulant agent	0	0	0
Immunosuppressant	2 (1.5)	0 (0.0)	2 (1.8)
Pulmonary function test			
FVC, % (n = 122)	97 (87–109)	98 (89–111)	97 (87–108)
FEV ₁ , % (n = 122)	102 (86–113)	100 (91–109)	102 (86–114)
FEV ₁ /FVC (n = 122)	73 (67–78)	73.0 (67–80)	73 (68–77)
D _{LCO} , % (n = 105)	90 (77–102)	89 (78–100)	91 (77–102)

(Continued)

Table 1. (Continued)

Characteristic	Total (N= 133)	Bleeding grade 2 or higher (N= 21)	No bleeding or grade 1 (N= 112)
Laboratory data			
Platelet, 10 ³ /μL	247.5 [200.0–301.0]	265.0 [219.0–317.0]	242.5 [193.0–297.5]
PT INR	1.0 [0.9–1.0]	1.0 [0.9–1.0]	1.0 [0.9–1.0]
aPTT, s	30.9 [28.9–32.9]	30.7 [28.7–33.8]	30.9 [28.9–32.9]
Data are presented as <i>n</i> (%) and median (interquartile range) unless otherwise noted. BUN, blood urea nitrogen; CRP, C-reactive protein; D _{LCO} , diffusing capacity of the lung for carbon monoxide; FEV ₁ , forced expiratory volume in one second; FVC, forced vital capacity; PT, prothrombin time; PT INR, prothrombin time international normalized ratio; WBC, white blood cell.			

Table 2. Characteristics of pulmonary lesions.

Characteristic	Total (N= 133)	Bleeding grade 2 or higher (N= 21)	No bleeding or grade 1 (N= 112)
Size (longest diameter on CT), mm	35.0 [26.0–49.0]	40.0 [30.0–50.0]	35.0 [25.0–49.0]
Location			
RUL	34 (25.6)	5 (23.8)	29 (25.9)
RML	11 (8.3)	1 (4.8)	10 (8.9)
RLL	33 (24.8)	6 (28.6)	27 (24.1)
LUL upper division	22 (16.5)	4 (19.0)	18 (16.1)
LUL lingular division	11 (8.3)	1 (4.8)	10 (8.9)
LLL	22 (16.5)	4 (19.0)	18 (16.1)
Lung zone			
Central, two-thirds	36 (27.1)	9 (42.9)	27 (24.1)
Peripheral, one-third	97 (72.9)	12 (57.1)	85 (75.9)
Distance from the pleura, mm	8.5 [0.0–18.0]	9.0 [0.0–19.0]	8.5 [0.0–17.5]
Lesion appearance on CT			
Solid nodule	76 (57.1)	10 (47.6)	66 (58.9)
Part-solid nodule	13 (9.8)	2 (9.5)	11 (9.8)
Cavitary lesion	8 (6.0)	1 (4.8)	7 (6.2)
Consolidative lesion	36 (27.1)	8 (38.1)	28 (25.0)
Low-density area on CT	18 (13.5)	4 (19.0)	14 (12.5)
CT bronchus sign			
0	3 (2.3)	2 (9.5)	1 (0.9)
1	3 (2.3)	1 (4.8)	2 (1.8)
2	127 (95.5)	18 (85.7)	109 (97.3)
Data are presented as <i>n</i> (%) and median (interquartile range) unless otherwise noted. LLL, left lower lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe.			

Table 3. Procedural characteristics.

Characteristic	Total (N= 133)	Bleeding grade 2 or higher (N= 21)	No bleeding or grade 1 (N= 112)
Use of virtual bronchoscopy	18 (13.5)	0 (0.0)	18 (16.1)
Use of a guide sheath	69 (51.9)	9 (42.9)	60 (53.6)
Probe location			
Within, concentric	74 (55.6)	9 (42.9)	47 (42.0)
Within, eccentric	44 (33.1)	2 (9.5)	20 (17.9)
Adjacent	15 (11.3)	10 (47.6)	45 (40.2)
Number of biopsies	6 (3–7)	6 (5–6)	6 (3–7)
Bronchial brushing	116 (87.2)	17 (81.0)	99 (88.4)
Bronchial washing or BAL	125 (94.0)	19 (90.5)	106 (94.6)
ROSE	98 (73.7)	14 (66.7)	84 (75.0)
Concurrent EBUS-TBNA for mediastinal staging	17 (12.8)	3 (14.3)	14 (12.5)
Procedure time, min	22 (15–31)	30 (20–45)	22 (14–29)
Dose of sedatives			
Midazolam, mg	5 (4–7)	7 (5–8)	5 (4–5)
Fentanyl, µg	50 (50–50)	50 (50–100)	50 (50–50)
Administration of prophylactic antibiotics	20 (15.0)	4 (19.0)	16 (14.3)

Data are presented as *n* (%) and median (interquartile range) unless otherwise noted.
BAL, bronchoalveolar lavage; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; ROSE, rapid on-site evaluation.

Table 1. Outpatients accounted for one-third. Two patients underwent the procedure without discontinuing the antiplatelet within 5 days prior to the procedure. The median longest diameter of the pulmonary lesion was 35 mm (IQR, 26.0–49.0 mm). The pulmonary lesions were mainly located in the upper lobe (right upper lobe and left upper division, 56 [42.1%]) and the lower lobe (right lower lobe and left lower lobe, 55 (41.4%)) and in the peripheral outer one-third of the lungs (97, 72.9%). Solid nodules, part-solid nodules, cavitory lesions, and consolidative lesions were observed in 76 (57.1%), 13 (9.8%), 8 (6.0%), and 36 (27.1%) patients, respectively. Eighteen (13.5%) pulmonary lesions had low-density areas on the CT. Most target lesions had bronchus signs on CT (Table 2). Procedural characteristics are summarized in Table 3. Radial EBUS-guided TBB was performed using a virtual bronchoscopy

in 18 (13.5%) patients, and guide sheath in 69 (51.9%) patients. The median procedure time was 22 min (IQR, 15–31 min), and a median of 6 (IQR, 3–7) biopsies were performed.

Diagnostic performance

The final diagnosis is listed in Supplemental Table 1. Of the 133 pulmonary lesions, 97 (72.9%) were diagnosed as malignant, 20 (15.0%) as benign, and 16 (12.0%) as undiagnosed. Lung adenocarcinoma (78, 58.6%) was the most common diagnosis. The diagnostic performance of radial EBUS-guided TBB in the pulmonary lesion is summarized in Supplemental Table 2. The diagnostic accuracy, sensitivity, and specificity for malignancy were 76.1% (89/117), 71.1% (69/97), and 100% (20/20), respectively, when the undiagnosed cases were excluded. The accuracy varied

Table 4. Post-procedural complications.^a

Characteristic	Value (N= 133)
All complications	27 (20.3)
Bleeding ^b	21 (15.8)
Grade 2	18 (13.5)
Grade 3	3 (2.3)
Grade 4	0
Pneumonia	5 (3.8)
Pneumothorax ^c	3 (2.3)
Grade 1	1 (0.8)
Grade 2	2 (1.5)
Grade 3	0
Complicated pleural effusion	2 (1.5)

Data are presented as *n* (%).

^aTwo patients had more than one complication.

^bSeverity of bleeding was graded by the Delphi consensus statement.

^cSeverity of pneumothorax was graded by the Common Terminology Criteria for Adverse Events (CTCAE v5.0). Two patients who required percutaneous catheter placement for pneumothorax were classified as grade 2.

from 66.9% to 79.0%, assuming that all undiagnosed cases were false negatives and true negatives, respectively. The diagnostic accuracy for central lesions was similar to that for peripheral lesions (Supplemental Table 3). When the 26 patients who did not undergo TBB were included, the diagnostic accuracy for malignancy was 67.2%. The accuracy varied from 57.9% to 71.7%, assuming that twenty-two undiagnosed cases were false negatives and true negatives, respectively (Supplemental Table 4). In multivariate analysis, pulmonary lesions with low-density areas on CT showed a significantly lower diagnostic accuracy for malignancy (adjusted odds ratio (OR), 0.14; 95% confidence interval (CI), 0.04–0.55; $p=0.01$; Supplemental Table 5).

Post-procedural complications

Procedure-related complications occurred in 27 (20.3%) of the 133 patients (Table 4). Pneumonia occurred in five (3.8%), complicated pleural effusion occurred in two (1.5%), and no cases of hemothorax were observed. Pneumothorax

developed in three (2.3%) patients; two required percutaneous catheter placements. Of 21 patients (15.8%) with procedure-related bleeding events, 18 had Delphi grade 2 bleeding events, and only 3 had Delphi grade 3 bleeding events. Epinephrine was used in 19 patients, and a balloon blocker was used in one of them for bleeding control. There was no bleeding event in the two patients who did not discontinue the antiplatelet agent within 5 days prior to the procedure. Two patients discontinued the procedure due to complications. Among the 41 patients who underwent radial EBUS-guided TBB on an outpatient basis, only two developed minor complications (pneumothorax without intervention, 1; grade 2 bleeding event, 1).

Risk factors for procedure-related bleeding

The risk factors associated with grade 2 or higher bleeding events are shown in Table 5. In multivariate analyses, a larger size (≥ 30 mm) was a significant risk factor for grade 2 or higher bleeding events (adjusted OR, 5.09; 95% CI, 1.15–22.56; $p=0.03$). The centrally located pulmonary lesion was also significantly associated with the risk of bleeding events (adjusted OR, 3.67; 95% CI, 1.14–11.83; $p=0.03$). The use of a guide sheath and the number of biopsies (≥ 6 times) were not associated with the bleeding risk (All $p>0.05$).

Discussion

The diagnosis of pulmonary lesions is a challenge for clinicians. This study confirmed the utility of radial EBUS-guided TBB by showing its low rate of complications and acceptable diagnostic accuracy. In our study, only three (2.3%) patients had pneumothorax. Although 21 patients (15.8%) experienced procedure-related bleeding events, only three had grade 3 bleeding, considered clinically significant; most had grade 2 bleeding events. Central location and larger size (≥ 30 mm) were risk factors for grade 2 or higher bleeding events.

Several studies have evaluated the diagnostic performance of radial EBUS-guided TBB. The diagnostic accuracy of radial EBUS-guided TBB varies from 65% to 80%.^{20–22} Serial meta-analysis revealed that its pooled diagnostic yield was approximately 70%.^{23–25} Another recent meta-analysis reported that the diagnostic yield of radial EBUS-guided TBB without fluoroscopy was

Table 5. Risk factors for grade 2 or higher bleeding after radial EBUS-guided transbronchial biopsy.

Variable	Univariate analysis		Multivariate analysis	
	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Age	0.96 (0.91–1.00)	0.06	0.96 (0.91–1.00)	0.08
Male sex	0.50 (0.20–1.29)	0.15	0.62 (0.14–2.63)	0.52
Smoking status (vs never)				
Former	0.74 (0.27–2.02)	0.55	0.85 (0.19–3.84)	0.84
Current	0.18 (0.02–1.48)	0.11	0.21 (0.02–2.43)	0.21
Size (longest diameter on CT, ≥ 30 mm)	3.21 (0.89–11.56)	0.08	5.09 (1.15–22.56)	0.03
Location (vs upper lobe)				
Middle lobe ^a	0.52 (0.10–2.64)	0.43		
Lower lobe	1.16 (0.43–3.12)	0.77		
Lung zone (central, two-third)	2.36 (0.90–6.21)	0.08	3.67 (1.14–11.83)	0.03
Distance from the pleura (≥ 10 mm)	1.05 (0.41–2.67)	0.92		
Lesion appearance on CT				
Solid nodule	0.63 (0.25–1.61)	0.34		
Part-solid nodule	0.97 (0.20–4.71)	0.97		
Cavitary lesion	0.75 (0.09–6.43)	0.79		
Consolidative lesion	1.85 (0.69–4.91)	0.22		
Low-density area on CT	1.65 (0.48–5.61)	0.43		
Use of a guide sheath	0.65 (0.25–1.67)	0.37		
Probe location (vs concentric)				
Eccentric	1.52 (0.57–4.02)	0.40		
Adjacent	0.41 (0.05–3.43)	0.41		
Number of biopsies (≥ 6)	2.50 (0.90–6.91)	0.08	1.21 (0.37–4.01)	0.75
Bronchial brushing	0.56 (0.16–1.92)	0.35		
Bronchial washing/BAL	0.54 (0.10–2.87)	0.47		
ROSE	0.67 (0.24–1.82)	0.43		
Concurrent EBUS-TBNA for mediastinal staging	1.17 (0.30–4.48)	0.82		
Procedure time (≥ 20 min)	2.58 (0.88–7.53)	0.08	2.01 (0.58–7.03)	0.27
Laboratory data				
Platelet	1.00 (0.996–1.01)	0.42		
PT INR	1.12 (0.00–38.39)	0.47		
aPTT	1.05 (0.94–1.16)	0.42		

^aMiddle lobe includes right middle lobe and left lingular segment.

aPTT, activated partial thromboplastin time; BAL, bronchoalveolar lavage; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; PT, prothrombin time; PT INR, prothrombin time international normalized ratio; ROSE, rapid on-site evaluation.

70%.²⁶ In our study performing radial EBUS-guided TBB without fluoroscopy, the diagnostic accuracy was 76.1%. A recent randomized controlled trial demonstrated that the diagnostic yield of radial EBUS-guided TBB using a guide sheath without fluoroscopy is non-inferior to the procedure with fluoroscopy (non-fluoroscopy-guided-group, 84.0% vs fluoroscopy-guided-group, 84.6%).²⁷ Radial EBUS-guided TBB can be conducted effectively without fluoroscopy.

We found that the diagnostic accuracy was significantly reduced in pulmonary lesions with necrosis, which appeared as low-density areas on CT. Previous studies have shown that necrosis in pulmonary lesions increases the likelihood of diagnostic failure when performing CT-guided lung biopsy.^{28,29} However, few studies have investigated the relationship between necrotic lesions observed on CT and accuracy in advanced diagnostic bronchoscopy. This study suggests that necrosis in pulmonary nodules can adversely affect diagnostic accuracy. To improve diagnostic accuracy, it is important to target lesions without necrosis whenever possible. In addition, combining transbronchial cryobiopsy can help improve the diagnostic yield of pulmonary nodules up to 90%, while the incidence of grade 3 or higher bleeding ranges from 1.2% to 3.5%.^{30–32}

Although radial EBUS-guided TBB is considered less invasive, few studies have focused on procedure-related complications and their risk factors. Previous studies have reported post-procedural complications within a range of 4%–10%,^{13,33–35} with the most common complications being bleeding and pneumothorax. In particular, bleeding occurred from 4% to 9% according to previous investigations; however, there was substantial variability in the bleeding definitions used.^{35–38} No validated scale has been widely accepted for describing bleeding severity among patients undergoing flexible bronchoscopy with TBB.¹⁷ Standardized definitions of bleeding after TBB were established in 2020, known as the Delphi consensus statement.¹⁷ Uniform reporting of the severity of bleeding during bronchoscopic procedures could improve the quality of information obtained, and several studies reported the incidence of bleeding complications after transbronchial cryobiopsy using this scale.^{31,39–41} To the best of our knowledge, our study is the first to assess bleeding severity after radial EBUS-guided TBB without cryobiopsy using the Delphi

consensus statement. In this study, 13.5% had grade 2 bleeding events, which was not clinically significant. A grade 3 bleeding complication occurred in 2.3%; however, these events were not life-threatening.

We found that grade 2 or higher bleeding events were more likely to occur in cases where the pulmonary lesions were centrally located and larger in size. Previous research showed that the diagnostic yield of radial EBUS increases with increasing size of the pulmonary lesion.⁴² However, the relationship between the size of the pulmonary lesions and the risk of bleeding complications during the procedure is not well established. Previous research reported that the size of the pulmonary lesion was not associated with clinically significant bleeding during transbronchial cryobiopsy, with a threshold of 20 mm.⁴¹ However, a recent study reported that a larger size (≥ 30 mm) was a risk factor for bleeding complications during radial EBUS-guided TBB using a guide sheath (adjusted OR, 2.78; 95% CI, 1.17–6.62; $p=0.021$),⁴³ which was consistent with our findings. As the size of a pulmonary lesion increases, the likelihood of it being malignant also increases,⁴⁴ and angiogenesis is critical to tumor viability and growth.⁴⁵ Larger pulmonary lesions with a greater vascular volume and a higher number of vessels⁴⁶ might increase the risk of bleeding after TBB. In addition, we observed that the central location of the pulmonary lesion was associated with an increased risk of bleeding. The previous study on radial EBUS-guided TBB using a guide sheath found that the central location of the pulmonary lesion was associated with bleeding complications (OR, 5.30; 95% CI, 2.36–11.91; $p<0.001$), although the association was attenuated in multivariate analysis (adjusted OR 2.11; 95% CI, 0.81–5.49; $p=0.125$).⁴³ This association can be explained by the fact that the centrally located pulmonary lesion receives blood supply from a relatively large vessel compared to the peripheral one.

We performed radial EBUS under moderate sedation of outpatients or inpatients. One-third of the study participants were outpatients, and only two of them had minor complications. Our study might have had a selection bias, as patients with a higher complication risk could have been admitted for the procedure. However, our study suggests that radial EBUS-guided TBB can be conducted on an outpatient and under moderate sedation. In addition,

based on our findings, patients presenting with risk factors for bleeding, such as centrally located and larger pulmonary lesions, might preferably undergo radial EBUS-guided TBB in an inpatient setting. This approach allows for closer monitoring and timely management of any potential bleeding complications that may arise.

Our study had several limitations. First, this was a retrospective study conducted in a single center. Second, most patients had a positive bronchus sign, which may limit the generalizability of the findings (especially diagnostic performance) to those without the bronchus sign. Similarly, the median size of pulmonary lesions was relatively large, which may limit the generalizability of our findings to smaller lesions. Third, the proportion of patients with bleeding-predisposing underlying diseases such as advanced chronic kidney or liver diseases and other coagulopathy or concurrent administration of antiplatelet agents or anticoagulants was low; therefore, the association between these factors and the risk of bleeding could not be evaluated. Fourth, the number of patients with post-procedural infectious complications was small; therefore, further analysis related to infectious complications could not be performed.

Conclusion

Our results suggest that radial EBUS-guided TBB is an accurate and safe method for diagnosing pulmonary lesions. Clinically significant procedure-related bleeding was rare. The grade 2 or higher bleeding events were associated with the central location and larger size of pulmonary lesions.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Seoul National University Hospital (H-2212-083-1386) and conducted according to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable.

Author contributions

Eunhye Bae: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Writing – original draft; Writing – review & editing.

Hyeontaek Hwang: Resources.

Joong-Yub Kim: Resources.

Young Sik Park: Resources.

Jaeyoung Cho: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data are available upon request to the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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