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Cone-Beam Computed Tomography-Guided Electromagnetic Navigation for Peripheral Lung Nodules

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Keywords
Cone-beam computed tomography · Electromagnetic navigation · Peripheral lung nodules

Abstract
Background: Electromagnetic navigation bronchoscopy (ENB) is a minimally invasive technology for the diagnosis of peripheral pulmonary nodules. However, ENB is limited by the lack of real-time confirmation of various biopsy devices. Cone-beam computed tomography (CBCT) could increase diagnostic yield by allowing real-time confirmation to overcome the inherent divergence of nodule location. ***Objectives:*** The aim of this study was to assess the diagnostic yield of ENB plus CBCT as compared with ENB alone for biopsy of peripheral lung nodules. ***Method:*** We conducted a retrospective study of patients undergoing ENB before and after the implementation of CBCT. Data from 62 consecutive patients with lung nodules located in the outer two-thirds of the lung who underwent ENB and combined ENB-CBCT were collected. Radial endobronchial ultrasound was used during all procedures as well. Diagnostic yield was defined as the presence of malignancy or benign histological findings that lead to a specific diagnosis. ***Results:*** Thirty-one patients had ENB-CBCT, and 31 patients had only ENB for peripheral lung lesions. The median size of the lesion for the ENB-CBCT group was 16 (interquartile range (IQR) 12.6–25.5) mm as compared to 21.5 (IQR 16–27) mm in the ENB group ($p = 0.2$). In the univariate analysis, the diagnostic yield of ENB-CBCT was 74.2% and ENB 51.6% ($p = 0.05$). Following multivariate regression analysis adjusting for the size of the lesion, distance from the pleura, and presence of bronchus sign, the odds ratio for the diagnostic yield was 3.4 (95% CI 1.03–11.26, $p = 0.04$) in the ENB-CBCT group as compared with ENB alone. The median time for the procedure was shorter in patients in the ENB-CBCT group (74 min) than in those in the ENB group (90 min) ($p = 0.02$). The rate of adverse events was similar in both groups (6.5%, $p = 0.7$). ***Conclusions:*** The use of CBCT might increase the diagnostic yield in ENB-guided peripheral lung nodule biopsies. Future randomized clinical trials are needed to confirm such findings.

Fayez Kheir and Sanket Thakore contributed equally to the work (co-first authorship).

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Introduction

Diagnostic sampling of suspicious peripheral lung nodules has become increasingly important, as early diagnosis of malignancy can provide an opportunity for potentially curative resection and improved survival. Traditionally, computed tomography (CT)-guided transthoracic needle aspiration (TTNA) was the most accepted modality to obtain tissue diagnosis of suspicious peripheral lung nodules, with a diagnostic yield reported in the literature ranging from 77 to 98% [1–4]. However, despite the high diagnostic yield, pneumothorax can occur in up to 35% of patients, with up to 15% requiring chest tube placement, increasing hospital stays and overall health-care costs [5, 6]. This is in contrast to the transbronchial approach, in which the risk of pneumothorax is only around 0.02–4.9% [7–10]. Furthermore, CT-guided TTNA might be associated with a higher incidence of local recurrence with pleural dissemination than transbronchial or open lung biopsy [11].

Transbronchial biopsy is a safe diagnostic tool recommended for patients with peripheral lung nodules, with the limitation of a lower diagnostic yield than CT-guided TTNA. The diagnostic yield of transbronchial biopsy guided by fluoroscopy is widely variable, ranging from 18 to 80%, and is strongly dependent on the lesion size [12, 13]. In order to increase the diagnostic yield of the transbronchial approach, techniques and devices such as the ultrathin bronchoscope, radial endobronchial ultrasonography with guided sheath, electromagnetic navigation bronchoscopy (ENB), and cone-beam computed tomography (CBCT) are becoming widely utilized [11].

ENB allows bronchoscopists to safely navigate to and sample peripheral lung lesions minimally invasively with an acceptable safety profile. Furthermore, the ability to provide concurrent lymph node staging with linear endobronchial ultrasound (EBUS) or assist in nodule localization via pleural dye or fiducial marking in a single procedure could potentially decrease health-care costs and improve patient satisfaction [10, 14]. However, due to CT-to-body divergence and atelectasis, increasing diagnostic yield has been an ongoing challenge.

Recently, CBCT has emerged as a promising adjunct to navigational bronchoscopy, allowing real-time "needle in lesion" confirmation, with a potential increase in diagnostic yield [15]. To our knowledge, there has not been a study comparing ENB to ENB along with CBCT confirmation. We aimed to describe our experience of comparing the diagnostic yield of ENB plus CBCT with that of ENB alone in patients with peripheral nodules suspicious for malignancy.

Methods

Study Design

We conducted a retrospective study of patients undergoing ENB before and after the introduction of CBCT to assess the diagnostic yield. Data from 62 consecutive patients with lung nodules <3 cm located in the outer two-thirds of the lung who underwent ENB-guided lung biopsy from December 1, 2018, to October 1, 2019, were collected.

Population

Sixty-two patients with peripheral lung nodules were included in the study and assigned to 2 groups to assess the diagnostic yield based on the type of procedure: ENB or ENB-CBCT. CBCT was introduced in May 2019, and for practical reasons, we included data from 5 months prior and 5 months after the introduction of CBCT. All the interventions were part of the standard of care for the disease, and consent was waived due to the retrospective nature of the study.

Operative Technique

All patients had multi-slice CT scans of the chest done within 4 weeks prior to the procedure, with a slice thickness of 1 mm and an interval of 0.8 mm. The digitized information from each patient's CT scan was imported into the electromagnetic navigation system in which virtual bronchoscopy images were reconstructed. The target anatomic landmarks such as the main carina, right and left upper lobe, middle lobe, and left lower lobe were identified, and thus, radiological mapping was completed. After data processing, all the information was uploaded to the electromagnetic navigation system. iLogic 7.0 ENB platform (superDimension; Medtronic), the Edge extended working channel catheter (Medtronic, Inc.) with 180- or 90-degree angles, and the standard locatable guide were used in all cases.

The CBCT is a high-resolution 2D detector adapted for use with a C-arm. During the procedure, imaging was performed using an angiographic system (Artis Zeego; Siemens Healthcare, Malvern, PA, USA) equipped with a 40 × 30-cm detector. The CBCT imaging protocol used (DynaCT) was characterized by the following parameters: 8 s rotation time, 200° gantry rotation, 0.5°/projection, 396 total projections, and a detector dose of 0.36 μGy/frame. Using 3D cross-sectional images, the target was identified (Fig. 2b) and manually contoured on workstation in multiple orthogonal planes using dedicated software (Syngo iGuide Toolbox; Siemens), and then superimposed on live fluoroscopy to provide real-time imaging (Fig. 2c). Two dedicated holders attached to the bronchoscopy were utilized to hold the bronchoscope in position so that the operators could leave the room during CBCT scan as shown in Figure 1.

All subjects participating in the study underwent total intravenous anesthesia, neuromuscular paralysis, and mechanical ventilation with volume control (endotracheal tube size 8–9, PEEP between 10 and 20 mmH_2O). Continuous telemetry, pulse oximetry, and capnography were used for monitoring patient status during the entire procedure.

All the procedures were performed under general anesthesia in a hybrid OR equipped with a C-arm system with CBCT capabilities. Following intubation, a bronchoscope (BF-1T180; Olympus) was introduced into the airway, and then, a curved steerable catheter (Edge Firm Tip; Medtronic) was inserted into the working

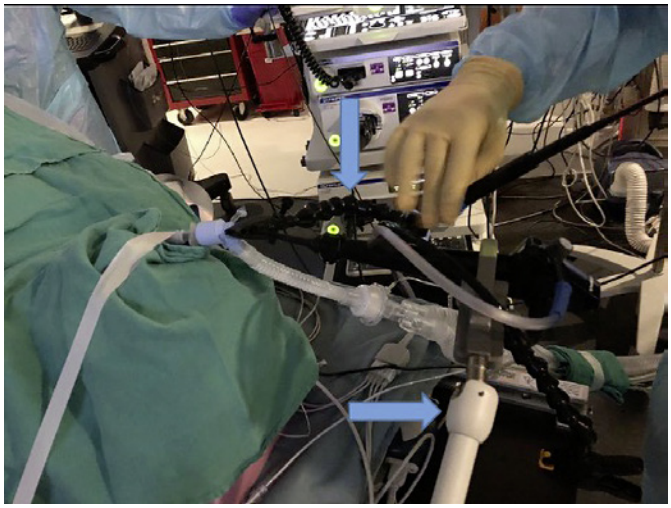

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Fig. 1. Bronchial holders (arrows) for a patient performing electromagnetic navigation with CBCT. CBCT, cone-beam computed tomography.

channel and navigated to the lesion using the ENB system followed by radial-probe EBUS to confirm location. An inspiratory breath-hold maneuver with the adjustable pressure-limiting valve set at 20 cm H_2O was performed by the anesthesiology provider in both groups. This mimics the inspiratory breath hold done during a CT scan.

In the ENB-only group, once successfully navigated to the nodule with ENB and confirmed with radial-probe EBUS, tissue samples were obtained. In the ENB-only cases, conventional C-arm fluoroscopy was used. In the ENB-CBCT group, once navigated to the lesion using ENB system and confirmed by radial-probe EBUS, the aspirating needle was inserted. This was followed by the breath-hold maneuver with adjustable pressure limiting to perform CBCT to identify the position of the nodule with respect to the fine needle aspiration tip, as shown in Figure 2a. This was followed by manual segmentation on the workstation in multiple orthogonal planes and superimposition of nodule on live fluoroscopy using dedicated software (Syngo iGuide Toolbox; Siemens). Based on needle tip location on CBCT (Fig. 2b), necessary adjustments were performed under live fluoroscopy. Once satisfied with the location of the needle (Fig. 2c), tissue samples were obtained under live fluoroscopy. Repeat CBCT was performed only if deemed necessary.

Tissue samples were obtained using multimodality tools, including cytology brush, fine needle for aspiration, biopsy forceps, and targeted bronchoalveolar lavage. Furthermore, all patients underwent EBUS-guided transbronchial needle aspiration for mediastinal staging following ENB or ENB-CBCT. Rapid on-site pathologic examination was used for all cases. Tissue samples and cytology specimens were eventually evaluated by a dedicated lung pathologist.

Study Outcomes

The primary outcome was the diagnostic yield of ENB-CBCT as compared with ENB alone for peripheral lung lesions. The procedure was deemed as diagnostic only if a specific malignant or benign diagnosis of the lesion was made. Normal lung parenchyma, atypical cells, or nonspecific inflammation was considered nondiagnostic biopsies. The overall diagnostic yield was calculated by adding the number of true positives for both malignancy and benign disease in the numerator and dividing by the total number of procedures performed for each arm of the study.

Statistical Analysis

Demographic and medical data were recorded. Continuous outcomes are presented as means or medians based on the assessment of normality (Shapiro-Wilk test). Parametric (*t* test) and nonparametric (Wilcoxon rank-sum test) tests were applied to compare the data based on the normality assessment. Dichotomic outcomes are presented in proportions and were compared with the χ^2 test. A p value <0.05 was considered as statistically significant. A stepwise multivariate regression model was performed based on the type of procedures including the following variables: target size, distance to the pleura, the presence of bronchus sign, and diagnostic yield. Data were analyzed using STATA Release 14 (StataCore, College Station, TX, USA).

Results

Thirty-one patients had ENB-CBCT, and 31 patients had only ENB for peripheral lung lesions. In the ENB-CBCT group, the mean age was 67.7 ± 8.2 years, 19 (61.3%) were men, and 15 (48.4%) were active smokers. Patients in the ENB group had a mean age of 64.5 ± 7.3 years, 28 (90.32%) were men, and 11 (35.5%) were active smokers. Baseline demographics and clinical characteristics are shown in Table 1.

The median size of the lesion for the ENB-CBCT group was 16 (IQR 12.6–25.5) mm as compared with 21.5 (IQR 16–27) mm in the ENB group (p = 0.2). Regarding the distance from the pleura, the ENB-CBCT group was 8 (IQR 0–20) mm as compared with 19 (0–28) mm in the ENB group (p = 0.3). The bronchus sign was present in 18 (58.1%) patients undergoing biopsy with ENB-CBCT as compared with 13 (41.9%) in the other group (p = 0.20). Most of the lesions were in the left lower lobe (41.2%) for the ENB-CBCT group and in the right upper lobe for the ENB group (35.5%). The median time for the procedure was shorter in patients in the ENB-CBCT group with 74 min (IQR 61–87 min) compared with 90 (IQR 72–119) min in the ENB group (p = 0.02). Regarding the pathology results, squamous cell carcinoma was the most common diagnosis in the ENB-CBCT group (29.0%) and lung adenocarcinoma in the ENB group (19.4%). The diagnostic yield for ENB-CBCT was 74.2% compared with 51.6% for ENB (p = 0.05). On the stepwise multivariate regression model adjusting for target size, distance from the pleura, and the presence of bronchus

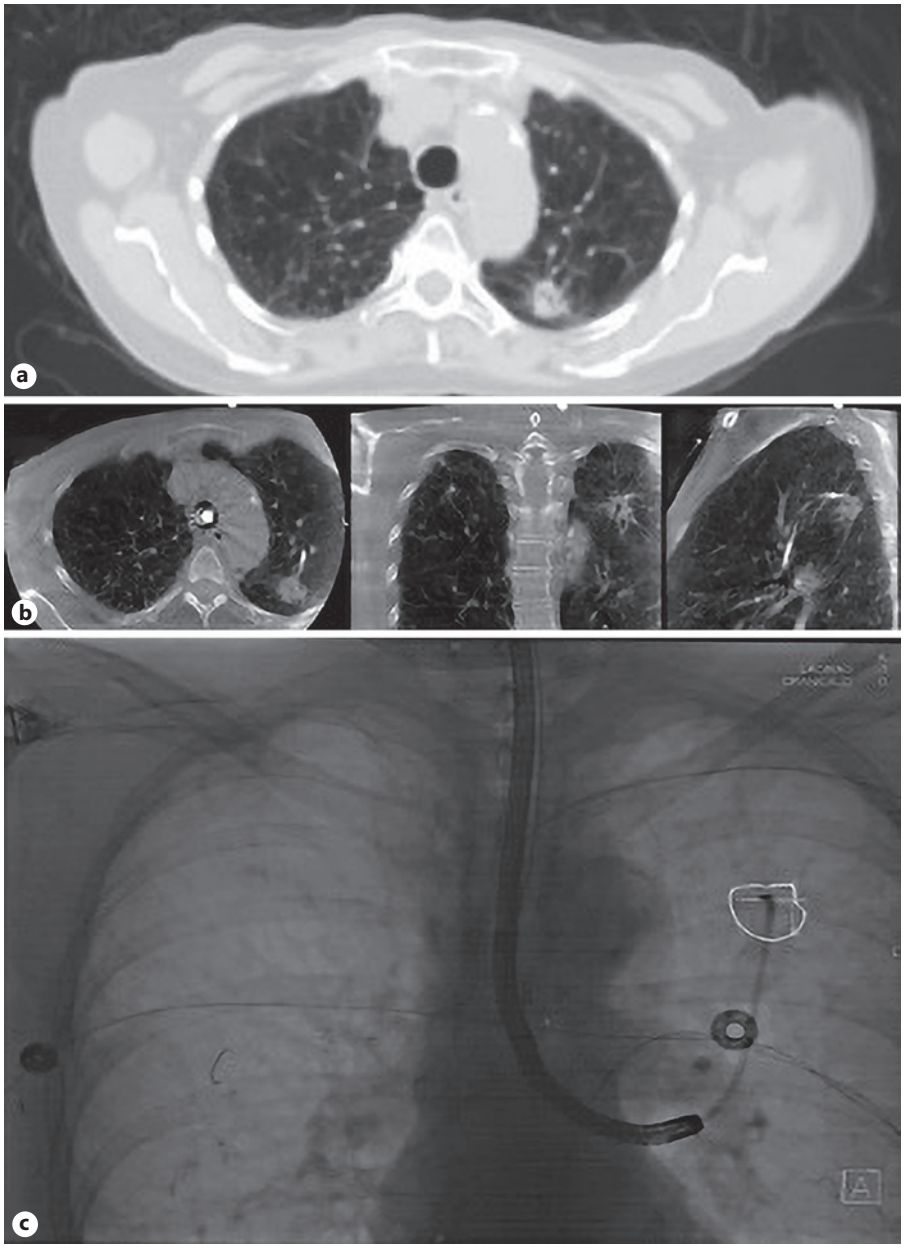

Fig. 2. CBCT-guided bronchoscopy case. CT chest of a LUL lung nodule (**a**); axial, coronal, and sagittal planes showing needle in proximity with the lung nodule target (**b**); fluoroscopy image showing guide sheath with needle in the LUL lesion (lesion is not visible by fluoroscopy) (**c**). CBCT, cone-beam computed tomography; CT, computed tomography; LUL, left upper lobe.

sign, we found an odds ratio for the diagnostic yield of 3.4 (95% CI 1.03–11.26, $p = 0.04$) in the ENB-CBCT as compared with ENB. In the ENB-CBCT group, 9 patients underwent a second CBCT scan due to initial unsuccessful navigation or atelectasis. None of the patients had >2 CBCT. Pneumothorax occurred in 2 patients in each group, respectively (6.5%). The diagnostic yield of TBBx, FNA, brush, and bronchoalveolar lavage was 73.9, 65.2, 52.2, and 21.8% in the ENB-CBCT group, respectively; and 75, 62.5, 56.3, and 18.75% in the ENB group, respectively. Clinical outcomes are shown in Table 2.

Discussion

This retrospective review of 62 patients with peripheral pulmonary nodules undergoing biopsy with ENB-CBCT as compared to ENB demonstrated 22.6% absolute increase in diagnostic yield. To the best of our knowledge, this is a first study comparing ENB-CBCT and ENB alone. The diagnostic yield was conservatively calculated by including only true positives for both malignant and benign diseases, and nonspecific diagnosis was not included. After performing a stepwise regression model adjusting for

Table 1. Baseline characteristics and clinical demographics

	ENB, $n = 31$	ENB-CBCT, $n = 31$	p value
Mean age (SD), years	64.5 (7.3)	67.7 (8.2)	0.1
Men, *n* (%)	28 (90.3)	19 (61.3)	0.008
Smoker, *n* (%)	11 (35.5)	15 (48.4)	
Former smoker, *n* (%)	16 (51. 6)	15 (48.4)	
Never smoker, *n* (%)	2 (6.5)	1 (3.2)	
Target size, median (IQR), mm	21.5 (16–27)	16 (12.6–25.5)	0.2
Distance from the pleura, median (IQR), mm	19 (0–28)	8 (0–20)	0.3
CT density, *n* (%)			
Solid	18 (58.1)	19 (61.3)	
Subsolid	4 (12.9)	7 (22.6)	
Cavitary	2 (6.5)	1 (3.2)	
Ground glass	0 (0)	1 (3.2)	
Bronchus sign	13 (41.9)	14 (45.2)	
Target location, *n* (%)			
LLL	3 (9.7)	3 (9.7)	
LUL	9 (29.0)	13 (41.9)	
RLL	8 (25.8)	7 (22.6)	
RUL	11 (35.5)	8 (25.8)	

IQR, interquartile range; SD, standard deviation; ENB, electromagnetic navigation bronchoscopy; CBCT, cone-beam computed tomography; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RUL, right upper lobe.

Table 2. Clinical outcomes

	ENB, $n = 31$	ENB-CBCT, $n = 31$	p value
Benign diagnoses, *n* (%)			
Granuloma	1 (3.2)	2 (6.5)	
Radiation fibrosis	1 (3.2)	0 (0)	
Organizing pneumonia	2 (6.5)	3 (9.7)	
Malignant diagnoses, *n* (%)			
Lung adenocarcinoma	6 (19.4)	8 (25.8)	
Squamous cell cancer	2 (6.5)	9 (29.0)	
Nonsmall cell lung cancer	1 (3.2)	1 (3.2)	
Large cell neuroendocrine tumor	1 (3.2)	0 (0)	
Small cell lung cancer	1 (3.2)	0 (0)	
Nondiagnostic, *n* (%)	15 (48.4)	8 (25.8)	
Target visible with fluoroscopy, *n* (%)	13 (41.9)	8 (25.8)	0.06
Bronchoscopy time, median (IQR), min	90 (72–119)	74 (61–87)	0.02
Adverse events, *n* (%)	2 (6.5)	2 (6.5)	0.7
Diagnostic yield, *n* (%)	16 (51.6)	23 (74.2)	0.05

ENB, electromagnetic navigation bronchoscopy; CBCT, cone-beam computed tomography; IQR, interquartile range.

Table 3. Summary of published case series describing the utility of CBCT for peripheral pulmonary nodules

	Design	*N*	Technology	Sampling tools	Diagnostic yield	Nodule size	Bronchus sign	Procedure duration
Sobieszczyk et al. [16]	Retrospective case series	22	ENB, CBCT-AF, R-EBUS, TBAT[a]	Needle, forceps, brush, GenCut™ core biopsy	77.2%	21 mm (mean)	Not reported	79.95 min (mean)
Ali et al. [11]	Prospective case series	40	Ultrathin bronchoscope, ENB, CBCT	Forceps, brush, BAL	90%[b]	20 mm (median)	100% (inclusion criteria)	Not reported
Casal et al. [18]	Prospective case series	20	Thin/ultrathin bronchoscope, R-EBUS, CBCT	Needle, forceps, brush, BAL	70%[c]	21 mm (median)	60%	62.5 min (median)
Hohenforst-Schmidt et al. [20]	Prospective case series	33	CBCT-AF	Forceps	<20 mm subgroup: 75% >20 mm subgroup: 67%	<20 mm subgroup 15 mm (mean) >20 mm subgroup 30 mm (mean)	Not reported	Not reported
Bowling et al. [19]	Retrospective case series	14	ENB, CBCT-AF, TBAT	Needle, forceps, brush	71%[d]	23.7 mm (mean)	Not reported	Not reported
Pritchett et al. [15]	Retrospective case series	92 nodules in 74 patients	ENB, CBCT-AF	Needle, forceps, single and triple needle brush, GenCut™ core biopsy, BAL	83.7%[e]	16 mm (median)	39%	Not reported

ENB, electromagnetic navigational bronchoscopy; CBCT, cone-beam computed tomography; CBCT-AF, cone-beam computed tomography scan with augmented fluoroscopy; R-EBUS, radial-probe endobronchial ultrasound; TBAT, transbronchial access tool; BAL, bronchoalveolar lavage. [a] TBAT was used in 7 patients. [b] Nonspecific inflammation was included in calculation. [c] Nonspecific inflammation was considered diagnostic if confirmed by surgical pathology or resolved or improved during the follow-up period. [d] Lung abnormalities with nondefinitive biopsy results that resolved on 6-month follow-up imaging were included in calculations. [e] Nonspecific inflammation was excluded from calculation.

size of the target lesion, distance from the pleura, and the presence of bronchus sign, we found an odds ratio for the diagnostic yield of 3.4 (95% CI 1.03–11.26, $p = 0.04$) in the ENB-CBCT as compared with the ENB group, showing that the results were independent of such factors.

This higher diagnostic yield was also despite the fact that the median nodule size was only 16 mm, nodules were close to the pleura (median distance from the pleura of 8 mm), and the bronchus sign was absent in 42% of patients, which has previously been described to negatively impact diagnostic yield [16]. In addition, the higher diagnostic yield was achieved even though 41.94% of patients in the ENB-CBCT group had pulmonary nodules in the left upper lobe where such location has been reported to negatively impact the diagnostic yield [16].

An unexpected, yet interesting, finding of the study was the median time in minutes for the procedure was shorter in the ENB-CBCT group (74 min) than in ENB only (90 min). Before we start utilizing CBCT for pulmonary nodules, the concern was prolonged procedure, as it requires stabilization of the bronchoscope with a holder, 8 s CBCT scan, segmentation, and projection of nodules on fluoroscopy. We speculate that as navigation became easier and more accurate, and required less failed attempts, ultimately it turned out to be an overall time-saving procedure. The median procedure time of 74 min for ENB-CBCT is comparable to the reported procedure time of 79.9 min by Sobieszczyk et al. [16] and 62.5 min by Casal et al. [18].

There are 2 main factors we believe why ENB-CBCT demonstrated a higher diagnostic yield than ENB alone. First, CBCT allowed for real-time confirmation. ENB, although real time, is a virtual confirmation of the nodule location which completely depends on the location of the nodule at the time of the CT chest utilized for ENB preplanning. It has been well documented that a lung nodule can diverge from its location due to factors such as lung volumes; full inhalation versus tidal breathing; patient positioning, for example, pillow under head or extended arms; and diaphragm position under positive pressure ventilation and paralytics [17]. ENB inherently will navigate to the deviated location for the same reason. CBCT allowed us real-time confirmation of the nodule location relative to the tip of the sampling device, as shown in Figure 2b, while the patient is intubated, anesthetized, and paralyzed, and allowed us to determine whether the tip of the biopsy tool is already in the nodule and if not, then the exact path to navigate to the nodule with the least possible divergence. Second, as nodule was superimposed on fluoroscopy, the live fluoroscopy allowed us to confirm that the tip of the biopsy instruments was staying in the nodule while taking biopsies, as shown in Figure 2c.

Table 3 summarizes recently published case series describing the utility of CBCT for peripheral pulmonary nodules. Sobieszczyk et al. [16] published a retrospective case series of 22 patients with a combination of ENB, R-EBUS, CBCT, and transbronchial bronchial access tool.

They reported a diagnostic yield of 77.2%, which is comparable to our study; however, authors have not clarified how the yield was calculated. Also, the mean size of pulmonary nodules was 21 mm, which is larger than our median nodule size of 16 mm. Ali et al. [11] reported a prospective case series of 40 patients with a combination of ultrathin bronchoscope, ENB, and CBCT achieving a diagnostic yield of 90%, which is higher than our yield. However, the likely explanation for such a high yield is inclusion of nodules with bronchus sign only and inclusion of nonspecific inflammation in diagnostic yield calculation. Casal et al. [18] combined thin/ultrathin bronchoscope, R-EBUS, and CBCT in a prospective series of 20 patients. The median size of the nodules in the series was 21 mm, and the diagnostic yield was 70%. In their series, nonspecific inflammation was considered diagnostic if confirmed by surgical pathology or resolved or improved during the follow-up period, which was different from our study as we excluded inflammation from our diagnostic yield calculation. Hofenforst-Schmidt et al. [20] published one of the earliest series on CBCT and peripheral pulmonary nodules. It was a prospective series of 33 patients divided into subgroups based on nodule size ≤20 and >20 mm. The reported diagnostic yield was 75% in the subgroup of nodules ≤20 mm (mean size 15 mm) and was 67% in the subgroup of nodules >20 mm (mean size 30 mm). Bowling et al. [19] reported a series of 14 patients using a combination of ENB, CBCT-AF, and TBAT, in which they demonstrated a yield of 71% with a median nodule size of 23.7 mm. The authors included nondefinitive biopsy results in yield calculation if the lesion resolved in 6 months. Pritchett et al. [15] published one of the larger retrospective series of 74 patients with 92 nodules combining ENB and CBCT-augmented fluoroscopy. What they described as augmented fluoroscopy is exactly what we described above as nodule superimposed on live fluoroscopy (Fig. 2c). The median lesion size was 16 mm in their series, which was similar to our series; however, their diagnostic yield was 83.7%, which was higher than that in our study by 9.5%. This could be due to their larger sample size.

As CBCT is not routinely used in interventional pulmonology yet, it may be difficult to get hospitals invest in CBCT dedicated to bronchoscopy suites. However, CBCT is increasingly used in other specialties such as interventional radiology, intervention cardiology, vascular surgery, and neurosurgery. Hence, a cost-effective way would be to collaborate with other specialties in the hospital to have access to CBCT. We collaborated with interventional radiology in our institution.

Our study has limitations that are inherent to a retrospective study, although this is the first study comparing ENB to ENB-CBCT and demonstrated a positive impact on diagnostic yield using CBCT. Due to the small sample size, wide confidence intervals in our main outcome were expected. However, we found a statistically significant difference between both groups, reassuring that an actual difference exists and showing a promising approach to peripheral lung lesions with a low rate of adverse events. Also, we used multimodality sampling in both arms, and such an approach might not be even needed and could increase procedure costs. Future studies should also consider whether multimodality sampling techniques are necessary, especially when CBCT is used and the instrument is confirmed to be in the peripheral lung lesion. We did not assess radiation with CBCT and fluoroscopy; however, there are several studies demonstrating that radiation with CBCT and augmented fluoroscopy is within an acceptable range [15, 18–20]. For instance, Casal et al. [18] reported a case series of CBCT-guided transbronchial peripheral lung nodule biopsies with the primary objective of estimating radiation dose. They demonstrated the mean estimated effective radiation dose to patients resulting from CBCT and fluoroscopy combined ranged between 11 and 29 mSv, depending on utilized conversion factors [18], which is comparable to average radiation from CT-guided diagnostic and therapeutic procedures of chest and abdomen [21, 22]. The radiation will vary based on factors like number and duration of CBCT acquisition, length of the field covered, manufacturer, and duration of fluoroscopy [15, 18, 23]. Steinfort et al. [23] demonstrated reduction in radiation dose by reducing imaging interval and inferosuperior field dimensions. Finally, CBCT is only available for proceduralists in a handful of expert centers, making the likelihood of widespread use of such combined procedures low.

Conclusion

The use of intraprocedural CBCT in conjunction with ENB may significantly increase diagnostic yield for peripheral pulmonary nodules by providing real-time confirmation of various lung biopsy tools. The safety profile is similar to other peripheral bronchoscopy platforms and better than the percutaneous lung biopsy approach. The above findings need to be confirmed in multicenter prospective trials.

Statement of Ethics

This study was approved by Tulane University Institutional Review Board (IRB number 2019-2112), and informed consent was waived.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

F.K. and S.T. share co-first authorship and are the guarantors of the content of the manuscript, including the data and analysis, and participated in data analysis, manuscript writing, and manuscript review; J.P.U.B., S.F.B., R.A., U.K., and A.M. participated in data analysis and manuscript review; and M.T. and R.K. participated in data collection and manuscript review.

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