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Diagnostic Yield of Cone-beam–Derived Augmented Fluoroscopy and Ultrathin Bronchoscopy Versus Conventional Navigational Bronchoscopy Techniques

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Background: **Pulmonary nodules suspicious for lung cancer are frequently diagnosed. Evaluating and optimizing the diagnostic yield of lung nodule biopsy is critical as innovation in bronchoscopy continues to progress.**

Methods: **This is a retrospective cohort study. Consecutive patients undergoing guided bronchoscopy for suspicious pulmonary nodule(s) between February 2020 and July 2021 were included. The cone-beam computed tomography (CBCT)+ radial endobronchial ultrasound (r-EBUS) group had their procedure using CBCT-derived augmented fluoroscopy along with r-EBUS. The CBCT+ ultrathin bronchoscope (UTB)+r-EBUS group had the same procedure but with the use of an ultrathin bronchoscope. The r-EBUS group underwent r-EBUS guidance without CBCT or augmented fluoroscopy. We used multivariable logistic regression to compare diagnostic yield, adjusting for confounding variables.**

Results: **A total of 116 patients were included. The median pulmonary lesion diameter was 19.5 mm (interquartile range, 15.0 to 27.5 mm), and 91 (78.4%) were in the peripheral half of the lung. Thirty patients (25.9%) underwent CBCT+UTB, 27 (23.3%) CBCT, and 59 (50.9%) r-EBUS alone with unadjusted diagnostic yields of 86.7%, 70.4%, and 42.4%, respectively ($P < 0.001$). The adjusted diagnostic yields were 85.0% (95% CI, 68.6% to 100%), 68.3% (95% CI, 50.1% to 86.6%), and 44.5% (95% CI, 31.0% to 58.0%), respectively. There was significantly more virtual navigational bronchoscopy use in the r-EBUS group (45.8%) compared with the CBCT+UTB (13.3%) and CBCT (18.5%) groups, respectively. CBCT procedures required dose area product radiation doses of 7602.5 μGym^2.**

Conclusion: **Compared with the r-EBUS group, CBCT + UTB + r-EBUS was associated with higher navigational success, fewer nondiagnostic biopsy results, and a higher diagnostic yield. CBCT procedures are associated with a considerable radiation dose.**

Key Words: navigational bronchoscopy, lung nodules, augmented fluoroscopy

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Pulmonary nodules suspicious for lung cancer are frequently identified on chest imaging and have an incidence likely to increase as lung cancer screening is adopted and as eligibility expands.[1] Management of intermediate risk nodules may require biopsy.[2] The ultimate goal for patients with pulmonary nodules requiring biopsy is to achieve a high diagnostic yield with the safest possible modality while allowing for simultaneous mediastinal lymph node staging. Reported diagnostic yields of transthoracic needle biopsy are higher compared with guided bronchoscopy, but at the cost of a higher complication rate and without the ability to stage the mediastinum.[3] As such, guided bronchoscopy combined with curvilinear endobronchial ultrasound (c-EBUS) is often the appropriate initial approach.

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However, the accurate diagnosis of indeterminate pulmonary nodules remains challenging despite the advent of several guided bronchoscopy technologies.[4,5] The accuracy of guided bronchoscopy for intermediate risk nodules is near 50% in some of the limited randomized controlled trial data available, as well as rigorously performed registry studies.[6–8] Evaluating and optimizing the diagnostic yield of this procedure is critical, as innovation in bronchoscopy continues. Comparative studies are especially warranted, as many procedural options now exist with mostly descriptive, single-arm study designs available to evaluate their efficacy.[5]

One recent innovation in guided bronchoscopy is the use of augmented fluoroscopy (AF) and intraprocedural cone-beam computed tomography (CBCT) scanning, which can be combined with other forms of navigation and/or radial endobronchial ultrasound (r-EBUS). Limited data suggest a high diagnostic yield that could be superior to historical controls.[9–11] This procedural guidance may overcome many theoretical pitfalls of navigational bronchoscopy such as computed tomography (CT)-to-body divergence, lack of tool-in-lesion confirmation (TIL), respiratory motion, and positional changes to the bronchoscope with the insertion of stiff biopsy instruments.[12] To evaluate the performance of this new technology, we report the comparative diagnostic yield of cone-beam computed tomography–derived augmented fluoroscopy (CBCT AF) combined using r-EBUS with or without an ultrathin bronchoscope (UTB) versus r-EBUS alone in a retrospective cohort study.

METHODS

Patients and Sample Size

Consecutive patients were captured through electronic medical record review at a single health system across 3 hospitals covered by a single interventional pulmonary service. All guided bronchoscopy procedures performed between February 2020 and June 2021 were screened for inclusion in the cohort. This study period allowed for 80 cone-beam CT bronchoscopies to be completed. Assuming an absolute difference in diagnostic yield of 30% between r-EBUS only procedures and CBCT AF procedures, 39 patients in each cone-beam CT group would provide 80% power to detect the difference with an α error level of 0.05.

Inclusion criteria included patients over 18 years of age, with lung lesions measuring between 8 and 50 mm on preprocedure CT scan in largest dimension, who underwent bronchoscopy to sample the lung lesion for diagnosis. Exclusion criteria included lung nodules accessible by c-EBUS, lung nodules that resolved at the time of index intraprocedural CBCT, patients with endobronchial tumor, and patients without adequate clinical follow-up to assess outcomes, as defined below. The study was approved by the Institutional Review Board (#848770).

Exposures—Procedures

Diagnostic bronchoscopies were separated into 3 groups. Patients who had their procedure done using a therapeutic or thin bronchoscope (see below) with r-EBUS were assigned to the r-EBUS group. Patients who had their procedure using CBCT AF were assigned to 1 of 2 CBCT AF groups depending on the bronchoscope used. If an UTB was used (BF-MP190F, distal end diameter: 3.0 mm, working channel diameter: 1.7 mm; Olympus, Tokyo, Japan), the procedure was assigned to the CBCT + UTB + r-EBUS group. If the BF-1TH190 (distal end diameter: 6.2 mm, working channel diameter: 2.8 mm; Olympus, Tokyo, Japan) or the BF-P190 scope (distal end diameter: 4.2 mm, working channel diameter: 2.0 mm; Olympus, Tokyo, Japan) was used, the procedure was assigned to the CBCT + r-EBUS group.

r-EBUS Alone Group

The flexible bronchoscope was inserted via a laryngeal mask airway or endotracheal tube to perform an airway exam and navigate to the lung nodule under general anesthesia. After navigating to the lesion of interest, r-EBUS with or without a guide sheath using an endoscopic ultrasound system (Olympus) and a 20-MHz radial ultrasound probe (17S; Olympus) was performed under fluoroscopic guidance.

CBCT Groups

The flexible bronchoscope was inserted via an endotracheal tube to perform an airway exam and navigate to the lung nodule under general anesthesia. After navigating to the lesion of interest, r-EBUS with or without a guide sheath using an endoscopic ultrasound system (Olympus) and a 20-MHz radial ultrasound probe (17S probe; Olympus) were performed under fluoroscopic guidance. The CBCT AF work flow is outlined in Figure 1. The CBCT AF was performed using a

robotic angiography system (Artis zeego, Siemens Healthineers, Forchheim, Germany). A non-contrast CBCT was acquired during breath hold using either a 4 second or 6 second acquisition protocol, during which 250 to 400 projection images are obtained over a 200-degree rotation. Multiplanar images were reconstructed on a dedicated workstation, and stroke-based segmentation software (Syngo X Workplace, Siemens Healthineers, Forchheim, Germany) was used to delineate and segment the lesion used for AF. A breath hold was performed during all CBCT imaging by holding an end inspiratory pressure that generated 8 cm^3/kg of volume as measured during the volume control ventilation mode used during the procedure. Patients were ventilated with 10 cm H_2O of positive end expiratory pressure, on volume control of 8 cm^3/kg ideal body weight. Patients with upper or right middle lobe lesions were kept supine. Those with lower lobe lesions were placed in semilateral decubitus position to elevate posterior and basilar lower lobe lesions using bedsheet rolls.

For AF, the initial CBCT images were used to segment the lesion of interest using the adjoining workstation (syngo X-Workplace; Siemens) and the accompanying overlay software (syngo iGuide Toolbox; Siemens). This produces a live, 2-dimensional highlighted lesion on fluoroscopy used during the remainder of the procedure (Fig. 2). Beyond the initial intraprocedural CBCT scan used to create AF, repeated CT scans were performed at the discretion of the physician to either confirm TIL or adjust navigation (Fig. 1).

Study Setting

Procedures in all the three groups were performed simultaneously over the study period by the same physicians (D.M.D., K.C.M., C.T.H., A.R.L., and A.R.H.) across 3 hospitals in 1 health system. Virtual navigational bronchoscopy (VNB —Archimedes, Bronchus Medical), guide sheaths, and thin bronchoscopes were available at all 3 hospitals and used at the discretion of the proceduralist. CBCT, the associated AF, and UTBs were only available at 1 hospital during the study period. Patients evaluated in the practice had their bronchoscopy subsequently performed at 1 of the 3 hospitals based on availability, patient preference, and physician preference.

A standard approach was taken for biopsy instruments used in all procedures: nodules adjacent to a segmental airway in the inner half of the thorax were sampled by brushing, transbronchial needle aspirate (21 G PeriView FLEX needle; Olympus, Tokyo, Japan), and a bronchoalveolar lavage. All other lesions were sampled with the same tools plus the addition of transbronchial biopsies. All procedures included fluoroscopy guidance. No procedures used rapid onsite evaluation.

Outcome and Exposure Variables

The primary outcome was diagnostic accuracy of the guided bronchoscopy, accounting for all samples obtained, and was defined as true positives plus true negatives divided by the total number of nodules sampled. A true positive require a pathologic diagnosis of malignancy, whereas a true negative required a biopsy that demonstrated a specific benign pathology that explained the lung nodule (eg, granulomas, organizing pneumonia, etc.) or nonspecific pathology (acute and/or chronic inflammation) that was either confirmed on subsequent biopsy (surgical or transthoracic needle biopsy), improved on follow-up chest CT, or demonstrated >2 years total of radiographic stability (this was possible if the index CT scan diagnosing the nodule predated the study start date by at least 8 mo). Procedures were considered nondiagnostic when the target lesion could not be successfully located, cytology and pathology results of atypical cells, or when only normal pulmonary elements (blood, alveolated lung parenchyma, and endobronchial epithelial cells) were seen on pathology/cytology. False negatives included nodules where sampling showed nonspecific pathology and the nodule was confirmed as malignant on subsequent biopsy (surgical or transthoracic needle biopsy), empirically treated with stereotactic body radiation therapy for high risk of malignancy, grew during the radiographic follow-up period, or did not resolve on subsequent imaging within 1 year of the procedure. We also performed a sensitivity analysis using a more conservative definition for diagnostic yield: malignant diagnoses + specific benign diagnoses/total.[13]

Demographic and clinical data collected included sex, age, any current or former smoking, and the type of malignant or benign disease diagnosed after final chart review. Data on covariates that were plausible confounders for diagnostic yield were collected. This included the presence of a bronchus sign on preprocedural CT scan, use of VNB, nodule size (largest dimension on axial CT scan), nodule location, visibility of

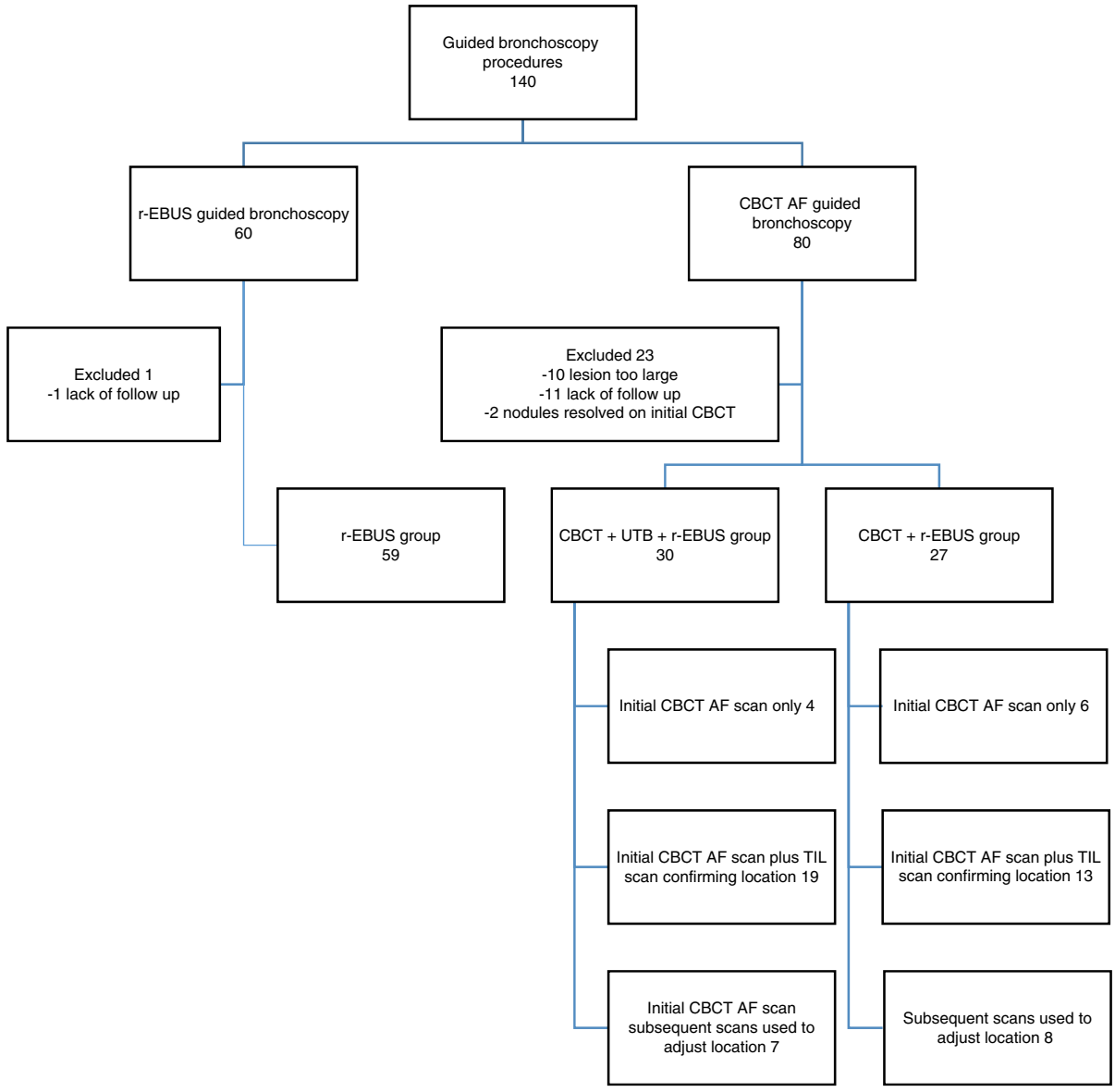

FIGURE 1. CBCT groups study flow. CBCT indicates cone-beam computed tomography; CBCT AF, cone-beam computed tomography–derived augmented fluoroscopy; r-EBUS, radial endobronchial ultrasound; UTB, ultrathin bronchoscope; TIL, tool-in-lesion.

lesion on fluoroscopy, guide sheath use, r-EBUS view and nodule location in peripheral half of the lung as judged by investigator measurements of hilum to pleural distance compared with hilum to lesion distance. More sophisticated measurements of the nodule's location in the thorax were deferred owing to a lack of well-established standardized measurement.

Secondary outcomes included the sensitivity for lung cancer, negative predictive value, safety, final diagnoses, radiation dose and number of intraprocedural CBCT scans for the CBCT procedures, and fluoroscopy time for r-EBUS group. The specific safety end points included rate of pneumothorax, bleeding requiring hospitalization or unplanned readmission, and respiratory failure. Final diagnoses were categorized as presumed benign if no specific pathology was obtained at any time during the patient's clinical course and the nodule proved to be stable with >2 years of follow-up or resolved on subsequent imaging. Final diagnoses were categorized as presumed malignant if no specific pathology was obtained by the end of the follow-up period, and the nodule was either treated empirically with stereotactic body radiation therapy or systemic therapy,

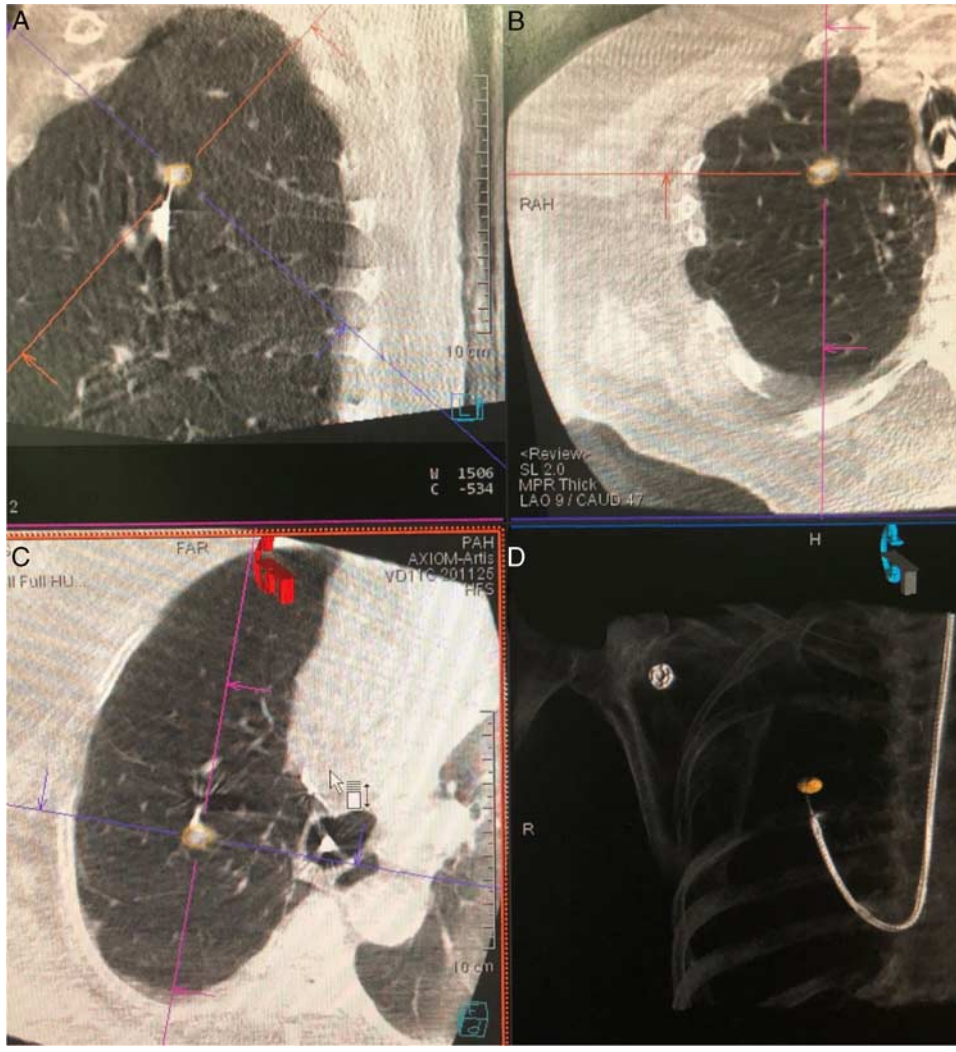

FIGURE 2. Cone-beam computed tomography–derived augmented fluoroscopy used during diagnostic bronchoscopy of a non-small cell lung cancer. Cone-beam computed tomography tool-in-lesion view with needle seen entering nodule from sagittal (A) and axial views (C). Segmenting the lesion in axial view after the initial intraprocedural cone-beam computed tomography scan (B). Augmented fluoroscopy used as live guidance during biopsy maneuver (D).

or surgery was planned for a growing nodule. Radiation dose was recorded in dose area product (μGym^2) and converted to radiation effective dose (mSv) using a conversion factor of 0.17 that has previously been described for a Siemens CBCT system.[14]

Statistical Analysis

We used descriptive statistics to evaluate patient demographics and clinical characteristics. Continuous variables were described with medians and interquartile ranges (IQRs) and categorical variables with frequencies and percentages. Differences in demographic and clinical characteristics and complication rates among the procedural groups were summarized using the Wilcoxon rank-sum test for continuous variables and the Pearson χ^2test for categorical variables.

We reported diagnostic yield proportions as percentages and compared unadjusted diagnostic yields using the Pearson χ^2 test. We used multivariable logistic regression to calculate adjusted diagnostic yields, accounting for patient demographics (age, sex, and smoking status), lesion characteristics (size, lobar location, and presence of bronchus sign), and procedural characteristics (use of virtual navigation, fluoroscopy, or guide sheath; r-EBUS view). Sensitivity for detecting lung cancer, negative predictive value, and prevalence of malignancy are reported as percentages with 95% confidence intervals. Statistical significance was defined with a 2-sided

$P < 0.05$, and all analyses were conducted using Stata/MP 17.0.

RESULTS

A total of 140 patients were identified for potential inclusion (Fig. 1). After applying all inclusion and exclusion criteria, 57 cases using CBCT were eligible. Demographic data and exposure variables are listed in Table 1. There was significantly more VNB use in the r-EBUS group (45.8% vs. 18.5%, $P = 0.02$; 45.8% vs. 13.3%, $P = 0.002$) compared with the CBCT + r-EBUS and CBCT + UTB + r-EBUS groups, respectively. As expected, there was no guide sheath use in the CBCT + UTB + r-EBUS arm. There were also significant differences in the location of the nodules and median age.

Unadjusted diagnostic accuracy favored the CBCT + UTB + r-EBUS group compared with the CBCT + r-EBUS ($P = 0.140$) and r-EBUS groups ($P < 0.001$) (Table 2). After adjusting for all measured confounding variables, diagnostic

TABLE 1. Demographics and Clinical Characteristics of Patients Undergoing Diagnostic Bronchoscopy

	Total (n = 116)	r-EBUS (n = 59)	CBCT + r-EBUS (n = 27)	CBCT + UTB + r-EBUS (n = 30)	
Variable			**n (%)**		***P***
Age, y	—	—	—	—	0.046
25–61	30 (25.9)	8 (13.6)	9 (33.3)	13 (43.3)	—
62–68	31 (26.7)	18 (30.5)	7 (25.9)	6 (20.0)	—
69–73	28 (24.1)	16 (27.1)	4 (14.8)	8 (26.7)	—
74–89	27 (23.3)	17 (28.8)	7 (25.9)	3 (10.0)	—
Sex	—	—	—	—	0.440
Female	61 (52.6)	30 (50.8)	17 (63.0)	14 (46.7)	—
Male	55 (47.4)	29 (49.2)	10 (37.0)	16 (53.3)	—
Smoking status	—	—	—	—	0.470
Not active	25 (21.6)	12 (20.3)	8 (29.6)	5 (16.7)	—
Active	91 (78.4)	47 (79.7)	19 (70.4)	25 (83.3)	—
Pulmonary lesion diameter, mm	—	—	—	—	0.360
7–15	36 (31.0)	15 (25.4)	11 (40.7)	10 (33.3)	—
16–19	22 (19.0)	14 (23.7)	4 (14.8)	4 (13.3)	—
20–27	29 (25.0)	17 (28.8)	3 (11.1)	9 (30.0)	—
28–47	29 (25.0)	13 (22.0)	9 (33.3)	7 (23.3)	—
Pulmonary nodule location	—	—	—	—	0.021
Right upper lobe	29 (25.0)	19 (32.2)	3 (11.1)	7 (23.3)	—
Right middle lobe	10 (8.6)	4 (6.8)	6 (22.2)	0	—
Right lower lobe	25 (21.6)	12 (20.3)	6 (22.2)	7 (23.3)	—
Left upper lobe	30 (25.9)	14 (23.7)	4 (14.8)	12 (40.0)	—
Left lower lobe	22 (19.0)	10 (16.9)	8 (29.6)	4 (13.3)	—
Bronchus sign present	—	—	—	—	0.500
No	29 (25.0)	12 (20.3)	8 (29.6)	9 (30.0)	—
Yes	87 (75.0)	47 (79.7)	19 (70.4)	21 (70.0)	—
Virtual navigation used	—	—	—	—	0.002
No	80 (69.0)	32 (54.2)	22 (81.5)	26 (86.7)	—
Yes	36 (31.0)	27 (45.8)	5 (18.5)	4 (13.3)	—
Visible on fluoroscopy	—	—	—	—	0.450
No	44 (37.9)	21 (35.6)	13 (48.1)	10 (33.3)	—
Yes	72 (62.1)	38 (64.4)	14 (51.9)	20 (66.7)	—
Guide sheath used	—	—	—	—	< 0.001
No	38 (32.8)	5 (8.5)	7 (25.9)	30 (100)	—
Yes	78 (67.2)	54 (91.5)	20 (74.1)	0	—
Peripheral half of the lung	—	—	—	—	0.470
No	25 (21.6)	12 (20.3)	8 (29.6)	5 (16.7)	—
Yes	91 (78.4)	47 (79.7)	19 (70.4)	25 (83.3)	—
r-EBUS view	—	—	—	—	0.970
No view	26 (22.4)	13 (22.0)	7 (25.9)	6 (20.0)	—
Concentric	45 (38.8)	24 (40.7)	9 (33.3)	12 (40.0)	—
Eccentric	45 (38.8)	22 (37.3)	11 (40.7)	12 (40.0)	—

CBCT indicates cone-beam computed tomography; r-EBUS, radial endobronchial ultrasound; UTB, ultrathin bronchoscope.

accuracy was significantly better in the CBCT + UTB + r-EBUS group compared with the r-EBUS group and not significantly different from the CBCT + r-EBUS group (vs. r-EBUS $P = 0.011$; vs. CBCT + r-EBUS $P = 0.238$). In the sensitivity analysis, the trend toward CBCT + UTB + r-EBUS having a higher diagnostic yield than the other 2 groups continued (Table 2). The rate of nondiagnostic bronchoscopies was much higher in the r-EBUS group (40.7%) compared with the CBCT + UTB + r-EBUS (0%), and CBCT + r-EBUS (18.5%) groups. Across all the 3 procedure arms, there was a lower diagnostic yield in the cases using VNB (Table 3).

Diagnostic yield for each procedure group overall and by baseline covariates are shown in Table 3. Final diagnoses for all patients are listed in Table 4. The prevalence of lung cancer was 49.1% with an additional 6% having metastatic cancer. This was consistent across groups, with the prevalence of malignancy being 70.0% (53.6% to 86.4%), 59.3% (40.7% to 77.8%), and 62.3% (50.4% to 75.1%) in the CBCT + UTB + r-EBUS, CBCT + r-EBUS, and r-EBUS groups, respectively. The remaining 44.9% of nodules were benign.

Sensitivity for lung cancer favored the CBCT groups at 81.0% (64.2% to 97.7%) and 81.3% (62.1% to 100%) in the CBCT + UTB + r-EBUS and CBCT + r-EBUS groups, respectively, compared with 43.2% (27.3% to 59.2%) in the r-EBUS group. Similarly, negative predictive value favored the CBCT groups at 69.2% (44.1% to 94.3%) and 78.6% (57.1% to 100%) in the CBCT + UTB + r-EBUS and CBCT + r-EBUS groups, respectively, compared with 51.1% (36.2% to 66.1%) in the r-EBUS group.

The only complications seen in the study were pneumothorax and pneumomediastinum. There was a 16.7% complication rate in the CBCT + UTB + r-EBUS group comprised entirely of 5 pneumothoraxes with 2 requiring chest tube placement. There was a 3.7% complication rate in the CBCT + r-EBUS group derived from a single pneumothorax, and a 6.8% complication rate in the r-EBUS group comprised of 3 pneumothoraxes and 1 pneumomediastinum with no interventions required. The difference in complication rate was not statistically significant ($P = 0.17$). No patients in the study had respiratory failure or bleeding that required any maneuvers beyond suctioning.

Median radiation dose in the CBCT groups was 7042 μGym^2 (IQR: 4249.3 to 9970). This includes both CBCT scans and fluoroscopy imaging during the entire procedure. This translates into a radiation effective dose of 11.97 mSv (IQR: 7.22 to 16.95). In the r-EBUS group, the median fluoroscopy time was 2.2 minutes (IQR: 1 to 4). The median number of intraprocedural CBCT scans was 2 (range: 1 to 4).

DISCUSSION

This is one of the few comparative studies exploring methods to sample indeterminate pulmonary lesions. To the best of our knowledge, this is the first comparative study that compares CBCT AF to another form of guided bronchoscopy, where a TIL repeat CBCT was frequently used. In this single-center cohort study, CBCT- + UTB- + r-EBUS-guided bronchoscopy showed a consistent trend toward a higher diagnostic accuracy compared with the CBCT + r-EBUS and r-EBUS groups using both a strict and more

TABLE 2. Unadjusted and Adjusted Diagnostic Yield Estimates by Type of Diagnostic Bronchoscopy

	Diagnostic Yield, % (95% CI)					
	r-EBUS		CBCT + r-EBUS		CBCT + UTB + r-EBUS	
Diagnostic Yield Calculation	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Primary definition TP + TN/total	42.4 (29.8–55.0)	44.5 (31.0–58.0)	70.4 (53.1–87.6)	68.3 (50.0–86.6)	86.7 (74.5–98.8)	85.0 (68.6–100.0)
Conservative definition TP + SPB/total	32.2 (20.3–44.1)	32.6 (20.3–44.9)	51.9 (33.0–70.7)	50.8 (33.2–68.3)	86.7 (74.5–98.8)	84.3 (69.3–99.3)

*Adjusted for age, sex, smoking status, pulmonary lesion diameter and location, presence of bronchus sign, use of virtual navigation, fluoroscopy, guide sheath, and peripheral location.

CBCT indicates cone-beam computed tomography; r-EBUS, radial endobronchial ultrasound; SPB, specific benign diagnosis; TN, true negative; TP, true positive; UTB, ultrathin bronchoscope.

TABLE 3. Diagnostic Yield by Baseline Characteristics, Overall and by Type of Diagnostic Bronchoscopy

	Total (n = 116)	r-EBUS (n = 59)	CBCT + r-EBUS (n = 27)	CBCT + UTB + r-EBUS (n = 30)
Variable		**Cases, No./Total No. (%)**		
Overall diagnostic yield	70/116 (60.3)	25/59 (42.4)	19/27 (70.4)	26/30 (86.7)
Age, y				
25–61	24/30 (80.0)	5/8 (62.5)	8/9 (88.9)	11/13 (84.6)
62–68	18/31 (58.1)	9/18 (50.0)	3/7 (42.9)	6/6 (100.0)
69–73	13/28 (46.4)	4/16 (25.0)	3/4 (75.0)	6/8 (75.0)
74–89	15/27 (55.6)	7/17 (41.2)	5/7 (71.4)	3/3 (100.0)
Sex				
Female	39/61 (63.9)	14/30 (46.7)	12/17 (70.6)	13/14 (92.9)
Male	31/55 (56.4)	11/29 (37.9)	7/10 (70.0)	13/16 (81.3)
Smoking status				
Not active	17/25 (68.0)	4/12 (33.3)	8/8 (100.0)	5/5 (100.0)
Active	53/91 (58.2)	21/47 (44.7)	11/19 (57.9)	21/25 (84.0)
Pulmonary lesion diameter, mm				
7–15	20/36 (55.6)	4/15 (26.7)	8/11 (72.7)	8/10 (80.0)
16–19	9/22 (40.9)	5/14 (35.7)	1/4 (25.0)	3/4 (75.0)
20–27	19/29 (65.5)	8/17 (47.1)	2/3 (66.7)	9/9 (100.0)
28–47	22/29 (75.9)	8/13 (61.5)	8/9 (88.9)	6/7 (85.7)
Pulmonary nodule location				
Right upper lobe	17/29 (58.6)	8/19 (42.1)	2/3 (66.7)	7/7 (100.0)
Right middle lobe	9/10 (90.0)	3/4 (75.0)	6/6 (100.0)	—
Right lower lobe	14/25 (56.0)	5/12 (41.7)	4/6 (66.7)	5/7 (71.4)
Left upper lobe	18/30 (60.0)	6/14 (42.9)	2/4 (50.0)	10/12 (83.3)
Left lower lobe	12/22 (54.5)	3/10 (30.0)	5/8 (62.5)	4/4 (100.0)
Bronchus sign present				
No	16/29 (55.2)	3/12 (25.0)	5/8 (62.5)	8/9 (88.9)
Yes	54/87 (62.1)	22/47 (46.8)	14/19 (73.7)	18/21 (85.7)
Virtual navigation used				
No	52/80 (65.0)	14/32 (43.8)	15/22 (68.2)	23/26 (88.5)
Yes	18/36 (50.0)	11/27 (40.7)	4/5 (80.0)	3/4 (75.0)
Visible on fluoroscopy				
No	23/44 (52.3)	6/21 (28.6)	8/13 (61.5)	9/10 (90.0)
Yes	47/72 (65.3)	19/38 (50.0)	11/14 (78.6)	17/20 (85.0)
Guide sheath used				
No	28/38 (73.7)	1/5 (20.0)	5/7 (71.4)	26/30 (86.7)
Yes	42/78 (53.8)	24/54 (44.4)	14/20 (70.0)	NA
Peripheral half of the lung				
No	16/25 (64.0)	4/12 (33.3)	8/8 (100.0)	4/5 (80.0)
Yes	54/91 (59.3)	21/47 (44.7)	11/19 (57.9)	22/25 (88.0)
r-EBUS view				
No view	9/26 (34.6)	0/13 (0.0)	4/7 (57.1)	5/6 (83.3)
Concentric	33/45 (73.3)	15/24 (62.5)	7/9 (77.8)	11/12 (91.7)
Eccentric	28/45 (62.2)	10/22 (45.5)	8/11 (72.7)	10/12 (83.3)

CBCT indicates cone-beam computed tomography; r-EBUS, radial endobronchial ultrasound; UTB, ultrathin bronchoscope.

liberal definition of diagnostic yield. After controlling for potential confounding variables, this trend continued. Differences between the CBCT + UTB + r-EBUS and CBCT + r-EBUS groups were not all statistically significant. The improvement in diagnostic yield in the CBCT groups compared with the r-EBUS group seemed to be driven by improved navigational success, higher diagnostic yield for nodules <2 cm, and fewer nondiagnostic samples.

There are several ways the CBCT groups have plausible advantages when sampling peripheral lung nodules. First, the AF may have benefit as a navigational bronchoscopy technique compared with VNB or no navigation. This technique has been studied in single-arm studies with promising initial results.[10,15] In a recent study by Yu et al,[10] CBCT AF was compared with r-EBUS alone in a cohort design showing an improvement in diagnostic yield despite the vast majority of patients in the study only have 1 CBCT during the procedure. As such, 10/57 (17.5%) of CBCT procedures in our study required only an initial intraprocedural CBCT

TABLE 4. Final Diagnoses

Malignant diagnoses	
Lung adenocarcinoma	40
Squamous cell carcinoma of the lung	9
Small cell carcinoma	3
Carcinoid tumor	5
Metastatic adenocarcinoma	1
Metastatic leiomyosarcoma	1
Metastatic thyroid carcinoma	1
Metastatic melanoma	1
Metastatic squamous cell carcinoma	1
Pleomorphic carcinoma	1
Presumed malignant nodule based on growth	3
Presumed malignant nodule treated with SBRT	5
Presumed malignant nodule with systemic therapy given	3
Benign diagnoses	
Organizing pneumonia	3
Lung infarction from pulmonary embolism	1
Presumed benign nodule with >2 y of radiographic stability	5
Presumed benign nodule with resolution on follow up imaging	9
Non-necrotizing granulomas	
Sarcoidosis	5
Nontuberculous mycobacterium	1
Nonspecific, resolved on follow-up imaging	1
Necrotizing granulomas	2
Ig4 disease	1
Acute inflammation with >2 y of radiographic stability	1
Acute or chronic inflammation with resolution on follow-up imaging	11
Sclerosing pneumocytoma	1
Hamartoma	1

Ig indicates immunoglobulin; SBRT, stereotactic body radiation therapy.

for AF navigation. Furthermore, the use of the ultrathin scope in the CBCT + UTB + r-EBUS group likely led to a further improvement in diagnostic yield. In randomized controlled studies, there has been additional benefit of the ultrathin scope during virtual navigational bronchoscopy.[16,17] Third, the ability to use additional CBCT scans to demonstrate a TIL view can confirm the biopsy location in real time and be used to adjust navigation. In fact, 15/57 (26.3%) of CBCT procedures were adjusted based on a second intraprocedural CBCT scan. Any combination of these factors could have contributed to the highly successful navigation to the target lesion in the CBCT groups compared with the r-EBUS group. Lastly, only patients in the CBCT groups were ventilated with an open lung strategy, which may have helped lung biopsy yield regardless of method used to navigate toward and sample the lesion by pneumatically stenting open small airways and preventing atelectasis. This may have also led to a higher pneumothorax rate, although previous data collected using a smaller sample size did not demonstrate similar results.[18]

The improvement in negative predictive value explains some of the increase in diagnostic yield in the CBCT groups compared with the r-EBUS group by increasing the number of true negatives. It is possible that minute adjustments in biopsy tool position aided by TIL repeat CBCT scans helped acquire higher quality samples that affected benign more so than malignancy lesions. The paucity of data gathered during this study does not suggest that phenomenon as the TIL CBCT scan confirmed a biopsy tool engaged in the lesion for 9 of the 16 true negatives (56.3%) compared with 4 of the 7 (57.1%) in the CBCT groups.

This study suggests the learning curve for experienced interventional pulmonologists to use CBCT AF may be quite shallow. There were no CBCT AF cases performed at our institution before the study period. Despite the lack of experience with the technique, the uncorrected combined diagnosed yield of all CBCT procedures of nearly 80% is higher than aforementioned historical controls. Another way this learning curve may have manifested was an increase in procedure time. There was likely an increase in procedure time in the CBCT groups compared with the r-EBUS group; however, this was not measured reliably enough to be included in our analysis.

The effective radiation dose in the CBCT AF arm is not insignificant at roughly 4-fold the average annual background dose of 3 mSv per year. The median dose during a CBCT AF procedure was about 10% of the recommended limit for medical radiation exposure over someone's lifetime.[19] Unfortunately, we were unable to quantify the radiation dose delivered in the r-EBUS group as the information was not stored for clinical use in the electronic medical record, as it was in the CBCT AF groups. That being said, fluoroscopy time in the r-EBUS group and the radiation dose in the CBCT AF groups were consistent with previous reports.[9–11,14,18] Specifically, radiation dose was very similar in our study to reports during transthoracic needle biopsy and CBCT AF bronchoscopic biopsy when using a very similar CBCT system.[14,18] As expected, our dose was higher than a previous report using CBCT AF bronchoscopy to biopsy lung nodules when the vast majority of patient did not have a

repeat CBCT scan to document a TIL image.[10] For reference, our effective radiation dose was very similar to the range demonstrated during cardiac catheterization (11.8 to 14.8 mSv) using a variety of techniques.[20] Compared with diagnostic CT scans, our radiation effective dose was comparable to traditional CT scan protocols of the chest where median doses range between 8.2 and 22 mSv depending on the protocol.[21] These median doses are all much higher than a low-dose CT chest that has an approximate dose of 2 mSv.[22] Notably, no effort to reduce the radiation dose was made during this study. There are actionable variables related to software processing systems, lower radiation dose settings that can depend on the capabilities of the radiation modality hardware itself, collimating the radiation image to focus on the lesion of interest, and restricting certain forms of magnification that will reduce radiation dose.[23]

There was a higher pneumothorax rate in the CBCT + UTB + r-EBUS group that did not reach statistical significance. One could assume CBCT guidance may reduce pneumothorax rate by giving the physician real-time feedback regarding the distance between the biopsy tools and the pleura. Open lung ventilation protocols used during CBCT procedures and more aggressive pursuit of peripheral nodules in the CBCT + UTB + r-EBUS group may have mitigated this potential benefit. A larger sample size in future studies will be needed to clarify the relationship between CBCT and UTB and pneumothorax rate.

There are several serious limitations to this study. Importantly, this is a retrospective cohort study that allows for indication bias between groups. There undoubtedly are unmeasurable variables related to the reasons a physician planned the procedure for CBCT, UTB, or neither. During the study period, open procedure scheduling permitted any provider to plan any type of guided bronchoscopy for any patient. These factors may have introduced bias toward finding a difference between groups (more routine procedures planned with CBCT to gain more experience with a new technique) or the null hypothesis (more difficult procedures were planned with CBCT + UTB + r-EBUS given its theoretical advantages). Notably, the CBCT groups were compared with a guided bronchoscopy group that did not mandate the use of navigation. One could expect a group undergoing a procedure with r-EBUS alone to have a lower diagnostic yield compared with a procedure that includes more advanced navigational techniques.

Similarly, there was no controlled method to determine when a nodule path could not be navigated successfully. Failed navigation was clearly a factor in the diagnostic yield in the r-EBUS group. It is possible the proceduralist was more willing to undergo repeat navigation attempts in the CBCT groups given the excitement surrounding new technology. Furthermore, CBCT AF procedures were only done at a single institution that also afforded the use of the ultrathin scope. Therefore, the association between CBCT AF and higher diagnostic yield requires more controlled investigation to understand how CBCT itself may improve navigational bronchoscopy. It is therefore possible that institutional factors explain some of the benefit seen with CBCT.

In this single-center retrospective cohort study, guided bronchoscopy with CBCT + UTB + r-EBUS showed a trend toward a higher diagnostic yield compared with CBCT + r-EBUS and r-EBUS groups with a moderate dose of radiation, and potentially higher pneumothorax rate. The difference in diagnostic yield was not statistically significant between all comparisons, notably the CBCT groups, after controlling for potential confounding variables, although a trend remained. These data further support the plausible benefits of CBCT AF +/− UTB for navigational bronchoscopy. Future studies should emphasize comparison arms with more standardization between groups in an effort to elucidate the potential benefit to this technology.

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