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CHEST

Initial clinical evaluation of stationary digital chest tomosynthesis in adult patients with cystic fibrosis

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Abstract

Objective The imaging evaluation of cystic fibrosis currently relies on chest radiography or computed tomography. Recently, digital chest tomosynthesis has been proposed as an alternative. We have developed a stationary digital chest tomosynthesis (s-DCT) system based on a carbon nanotube (CNT) linear x-ray source array. This system enables tomographic imaging without movement of the x-ray tube and allows for physiological gating. The goal of this study was to evaluate the feasibility of clinical CF imaging with the s-DCT system.

Materials and methods CF patients undergoing clinically indicated chest radiography were recruited for the study and imaged on the s-DCT system. Three board-certified radiologists reviewed both the CXR and s-DCT images for image quality relevant to CF. CF disease severity was assessed by Brasfield score on CXR and chest tomosynthesis score on s-DCT. Disease severity measures were also evaluated against subject pulmonary function tests.

Results Fourteen patients underwent s-DCT imaging within 72 h of their chest radiograph imaging. Readers scored the visualization of proximal bronchi, small airways and vascular pattern higher on s-DCT than CXR. Correlation between the averaged Brasfield score and averaged tomosynthesis disease severity score for CF was -0.73, $p = 0.0033$. The CF disease severity score system for tomosynthesis had high correlation with FEV1 (r = -0.685) and FEF 25–75% (r = -0.719) as well as good correlation with FVC (r = -0.582).

Conclusion We demonstrate the potential of CNT x-ray-based s-DCT for use in the evaluation of cystic fibrosis disease status in the first clinical study of s-DCT.

Key Points

- *Carbon nanotube-based linear array x-ray tomosynthesis systems have the potential to provide diagnostically relevant information for patients with cystic fibrosis without the need for a moving gantry.*

We are requesting dual first authorship for E. Taylor Gunnell and Dora Franceschi. These students contributed equally to the design, implementation, analysis, and write up of this study.

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- *Despite the short angular span in this prototype system, lung features such as the proximal bronchi, small airways and pulmonary vasculature have improved visualization on s-DCT compared with CXR. Further improvements are anticipated with longer linear x-ray array tubes.*
- *Evaluation of disease severity in CF patients is possible with s-DCT, yielding improved visualization of important lung features and high correlation with pulmonary function tests at a relatively low dose.*

Keywords Tomography · Nanotubes, Carbon · X-rays · Cystic fibrosis · Scoring methods

Abbreviations

AFVR	Adapted fan-beam volume reconstruction
CF	Cystic fibrosis
CNT	Carbon nanotube
DCT	Digital chest tomosynthesis
FEF 25–75%	Forced expiratory flow at 25–75% of the pulmonary volume
FEV1	Forced expiratory volume during the first second
FVC	Forced vital capacity
ICCs	Intra-class correlation coefficients
LCA	Lateral costophrenic angles
PFTs	Pulmonary function tests
s-DCT	Stationary digital chest tomosynthesis

Introduction

Cystic fibrosis (CF) is one of the most common life-limiting genetic disorders within the Caucasian population. Progressive lung disease is the main cause of morbidity and mortality in patients with CF, with damage to the lung parenchyma caused by repeated infections and chronic inflammation. Therefore, early diagnosis of infection is important to enable early intervention and prevent irreversible lung damage [1]. Though computed tomography (CT) offers the highest resolution 3D imaging of the lungs, relatively high radiation doses limit repeated measures. Chest radiographs are generally used to monitor disease progression but can be relatively insensitive to detection of early disease [2]. Radiation dose considerations are increasingly important, especially since patients born with CF today now have a life expectancy of 70 years [3]. New short-echo-time techniques paired with hyperpolarized gas inhalation are improving the potential utility of magnetic resonance imaging (MRI); however, the high cost and limited availability of these advanced techniques restrict their utility [4].

Digital chest tomosynthesis (DCT) is an imaging technique in which a 3D image of the chest is reconstructed using x-ray projection images acquired over a limited scanning angle, typically 30–60 degrees [5, 6]. The use of DCT in thoracic imaging has advantages over both conventional chest radiography and computed tomography. Digital chest tomosynthesis generates coronal slices through the thorax with a spatial resolution superior to coronal CT images [5, 6]. The utility of DCT has been explored as an alternative imaging technique for lung cancer screening and the evaluation of cystic fibrosis [7, 8]. Studies by Steyern and colleagues have demonstrated the potential value of DCT as an alternative to CT [9–11].

We have developed a stationary digital chest tomosynthesis (s-DCT) system based on a carbon nanotube (CNT) field emission x-ray source technology. In contrast to conventional x-ray tubes, our x-ray source relies on field emission to generate electrons at room temperature. This technology allows two important advantages over a conventional x-ray source. First, multiple x-ray sources can be packed in close proximity, enabling the creation of an array of x-ray focal spots. Second, the field emission source allows generation of precise x-ray pulses from the individual sources on demand. Thus, a linear x-ray imaging array may be substituted for the conventional moving x-ray source in DCT to provide x-ray projections from multiple directions. In turn, this can shorten imaging times and reduce blur caused by gantry motion. The ability of the system to generate x-ray pulses on demand enables the potential of respiratory gating [12].

The goal of this study was to evaluate the potential of CNT linear x-ray source arrays to perform CF imaging. In the first-in-human prospective imaging study we compared the s-DCT system against conventional radiographs in the evaluation of CF disease status. Our secondary aim was to explore the correlation between s-DCT findings and pulmonary function tests (PFTs).

Materials and methods

This study was approved by the UNC Institutional Review Board. Informed consent was obtained from each patient before enrollment.

Subject characteristics

CF subjects were enrolled through collaboration with our institutions Cystic Fibrosis and Pulmonary Diseases Research and Treatment Center. Adult patients with a history of CF who were undergoing clinically indicated conventional chest radiographs and PFTs were recruited for the study. Exclusion criteria included (1) pregnancy, (2) age < 18 years old, (3)

body mass index > 33 and (4) patients with unstable lung disease. Patients were imaged with the s-DCT system within 3 days of the clinical chest radiograph.

s-DCT and chest radiography imaging systems

The s-DCT is based on a repurposed linear CNT x-ray source array combined with a high-speed digital x-ray detector (Fig. 1). The linear x-ray array consists of 29 cathodes spaced an average of 10 mm apart. The anode consists of a tungsten target. There is 2.5 mm aluminum filtration. The imaging setup uses a source-to-detector distance of 130 cm to achieve a 12-degree angular coverage. All 29 projections are acquired over a 6-s scan time with subjects in a supine (AP) position during a full inspiratory breath hold. The tube voltage is 80 kVp and can produce an x-ray pulse width up to 130 ms. The tube voltage limitation is a function of this particular x-ray tube, which was repurposed from other non-medical applications. The measured focal spot size is 2.5 mm 0.5 mm [13, 14]. The flat panel silicon detector is 35 cm × 43 cm with a 139-mm pixel size and acquisition time of 5 fps. The system resolution was 1.7 cycles/mm in scan direction and 3.4 cycles/mm in the perpendicular direction. The entrance dose for adult patients was 0.6 mGy [14]. Conventional chest radiography was performed on a Fuji machine with a Siemens digital detector. Clinically acquired upright PA images used for the study were acquired with a typical source to detector distance of 182 cm and automatic exposure. Typical tube voltages used ranged from 117–125 kVp and 11–14 mAs.

s-DCT image reconstruction

The acquired projection data were reconstructed using Adapted Fan-beam Volume Reconstruction (AFVR) with custom code written in MATLAB (Mathworks Inc.). The method was optimized for our linear source array by transforming the 3D cone-beam reconstruction into a series of 2D fan-beam volume reconstructions. The AFVR provides fast reconstruction, under 6 min, while utilizing a model-based iterative algorithm for improved image quality [15]. Slice width of 2.5 mm was used. This generated 75 image slices per imaging stack with no gap.

s-DCT reader study and qualitative analysis

Three board-certified radiologists with no prior experience in interpreting chest tomosynthesis were trained in image interpretation via case study of images not included in this analysis. The radiologists had an average of 10 ± 11.3 years' experience. Readers were trained with ten s-DCT cases from another concurrent study that included both CF related and non-CF related findings. For study images the readers independently rated the imaging technique, quality of the s-DCT images and contemporaneous radiographs. Imaging technique was scored based on patient positioning, presence of motion blur and quality of full inspiration effort. Image quality was subjectively quantified by rating the reproduction of the lung fields, trachea, proximal bronchi (including the main stem bronchus and primary branches), small airways, diaphragm and lateral costophrenic angles (LCA) as well as vascular pattern. Each observer assigned a numerical score from 1 to 5, with 1 representing poor quality and 5 representing high quality.

The observers then scored radiographs using the Brasfield score [16] for disease severity and s-DCT images based on a CF disease severity score system for tomosynthesis [17]. This tomosynthesis scoring system evaluated the severity and extent of five common pathological findings in cystic fibrosis: overinflation, bronchial wall thickening, parenchymal lesions, bronchiectasis and mucus plugging. The overinflation score evaluated the lungs as a whole; all other components were scored by quadrant. The lungs were divided into quadrants at the level of the first division of the left main bronchus. The maximum scores were 4 for overinflation, 16 for bronchial wall thickening, 16 for parenchymal lesions, 32 for bronchiectasis and 32 for mucus plugging, with a maximum total score of 100, with higher scores indicating more severe disease [17].

The readers were blinded to patient demographics, clinical status and spirometry data. Image series were presented in random order; radiographs and s-DCT images of the same patient were shown non-consecutively. Tomosynthesis sets were viewed by scrolling through the entire image stack.

Statistical analysis

Statistical analysis was performed by a dedicated biostatistician using SAS/STAT (SAS) software. A reader factor was included in the model. Ordinal data (image technique data) were analyzed with a repeated ordinal logistic model (PROC GENMOD). The model takes into account the ordinal rank (1 to 5). The score method was applied to estimate p values, which extends the linear model to a multinomial model. The interaction of reader and technique was included in a model only when significant. The association between the Brasfield and Tomosynthesis scores and correlation of scores with spirometry are reported as Pearson correlation coefficients. Spirometry data were not available for one patient. The intra-class correlation coefficients (ICCs), quantifying the reliability of the measurement for Brasfield and tomosynthesis scoring, were calculated using a two-way random effects model, with absolute agreement and a single rater. Comparison of ICCs was performed using the Konishi-Gupta modified Z-test.

Results

A total of 14 patients with cystic fibrosis, aged 19 to 47 years, mean age 27.38 ± 10.02 years, were imaged using the s-DCT system (Fig. 1) following clinically indicated chest radiography and pulmonary function tests (Table 1). All subjects underwent s-DCT imaging within 24 h of CXR, except one subject whose imaging was performed within 72 h (see Video, Supplemental Material 1, which demonstrates the complete s-DCT image sequence).

Technique evaluation

Overall, readers gave significantly higher scores for CXR than s-DCT when evaluating technical parameters including full inspiration, motion blur and patient positioning (Table 2). These scores were reader independent for all three parameters. In general, readers gave a wider range of scores for s-DCT.

Image quality evaluation

Stationary tomosynthesis had significantly higher reader quality scores when evaluating proximal bronchi, small airways and vascular pattern (Table 3). Readers tended to give higher image quality scores to CXR than s-DCT for lung fields and diaphragm/LCA. The techniques were not significantly different when evaluating the trachea. Reader effects were not significant except when evaluating the proximal bronchi, diaphragm and LCA. Regarding the proximal bronchi score, the difference of scores between the methods is not similar across readers, which could explain the interaction of reader and technique. Reader 1 gave only scores of 5 (excellent) to all subjects while readers 2 and 3 graded the images more severely. Both reader 2 and 3 gave significantly higher rates for s-DCT than CXR: reader 2 gave a majority of '3' to CXR and a majority of '5' to s-DCT, while reader 3 gave respectively '3' and '4.' When evaluating the diaphragm and LCA, readers 1 and 3 gave higher rates to CXR than s-DCT, while reader 2 gave generally higher rates to s-DCT than CXR.

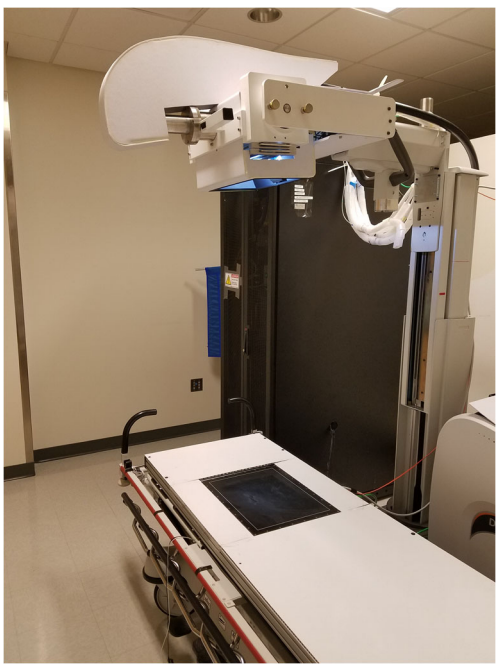

Fig. 1 The stationary digital chest tomosynthesis system (s-DCT) linear x-ray array is aligned with the patient imaging bed (stretcher). The detector is integrated into the stretcher bed

Table 1 Patient pulmonary function tests for recruited patients

	FVC	FEV1	FEV1/FVC ratio	FEF 25–75%
CF001	5.18	3.34	64	2.09
CF002	4.8	3.45	72	2.40
CF003	6.5	4.37	67	2.69
CF004	4.15	3.24	78	2.93
CF005	4.41	3.07	70	1.82
CF006	3.62	2.66	74	2.06
CF007	4.98	3.43	69	2.05
CF008	4.26	3.59	84	4.15
CF009	1.96	1.32	67	0.78
CF010	4.82	3.81	81	3.58
CF011	2.71	1.77	65	1.11
CF012	5.71	4.2	74	3.23
CF013	3.81	3.18	84	3.54

Values for FVC and FEV1 are in liters. Values for FEF 25–75% are in l/s. Subject population $n = 13$

Brasfield score and tomosynthesis score

The correlation coefficient between the averaged Brasfield score and averaged reader tomosynthesis disease severity score for CF was -0.73, $p = 0.0033$. The negative correlation is due to the inverted direction of the tomosynthesis severity scores and Brasfield scores. Lower Brasfield scores correspond to more severe disease, while lower tomosynthesis scores are seen in less severe disease (Figs. 2 and 3). Intraclass correlation coefficients for tomosynthesis and Brasfield scoring were 0.80 and 0.79, respectively. These values were not significantly different; comparison yielded $p = 0.51$.

Pulmonary function tests

The CF disease severity score system for s-DCT has significant correlation with almost all pulmonary function tests, including forced expiratory volume during the first second (FEV1; -0.685), forced expiratory flow at 25–75% of the pulmonary volume (FEF 25–75%; -0.719), with a more modest correlation with forced vital capacity (FVC; -0.582) (Table 4).

Table 2 Imaging technique

		Median score			*p*-values	
		Reader 1	Reader 2	Reader 3	Technique	Reader
Full inspiration	CXR	5	5	5	0.0015	0.0123
	s-DCT	5	4	3		
Motion blur	CXR	5	5	5	0.002	0.0044
	s-DCT	4.5	5	3		
Patient positioning	CXR	5	5	5	0.0246	0.0083
	s-DCT	5	5	4		

Readers gave significantly higher scores for CXR when evaluating imaging technique, likely because of the more simplified imaging process (single view versus 29). Reader scores for these parameters were reader independent for all three parameters

Discussion

This study is the first evaluation of stationary tomosynthesis imaging in CF patients. Tomosynthesis generates image slices with high-fidelity replication of in-plane structures and has been shown to offer more accurate assessment of subtle lung lesions as well as changes in the airways and parenchyma [8, 18, 19]. Bronchial wall thickening, mucus plugging, and bronchiectasis are known to be better delineated with conventional tomosynthesis than with radiography [17].

In our application, CNT s-DCT received significantly higher scores on image quality than conventional radiography in visualizing structures of interest in cystic fibrosis, such as the proximal bronchi, small airways and vascular pattern. We found no difference in image quality between s-DCT and CXR when visualizing the trachea. These findings are similar to reports of conventional chest tomosynthesis and CF, including that of Choo et al, who reported the sensitivity of conventional DCT was higher than chest radiography in detecting airway lesions [18]. The diagnostic accuracy of DCT (90.91%; 94.70%) was also reported as significantly better than that of radiography (78.03%; 82.58%, all $p < 0.05$) [18]. In the work by Galea and colleagues, the sensitivity and specificity were 0.65 and 0.39 for CXR and 0.91 and 1 for DCT in detecting pulmonary and hilar lesions compared with chest x-ray [20]. These results suggest that an s-DCT system with the same geometry as a conventional tomosynthesis system would be capable of more accurately scoring disease severity than conventional radiography. There are no technical or engineering limitations to building a carbon nanotube x-ray source tube that enables this geometry.

CT provides improved sensitivity and specificity compared with tomosynthesis, but the high cost and high effective dose make regular CT examinations prohibitive. The effective dose of published DCT tomosynthesis systems, 0.13 mSv, is equivalent to that of a standard two-view radiograph (0.06 to 0.25 mSv), but much less than even a low-dose thoracic CT examination (typically 1–4 mSv) [21–26]. In the work by Johnsson et al, use of DCT instead of CT resulted in a substantial dose reduction of almost 2 mSv [27]. Our system has an entrance dose of 0.6 mGy; this is comparable to the entrance dose of standard chest x-ray systems (0.31 to 0.88 mGy) and conventional chest tomosynthesis systems (0.31 to 1.27 mGy) [28, 29]. Our system can achieve further dose reductions by developing more advanced reconstruction techniques and utilizing a more optimized x-ray tube.

Our results show a high correlation between the Brasfield score and the tomosynthesis score for cystic fibrosis, suggesting a similar but not exactly equivalent evaluation of disease severity. With other studies showing higher sensitivity and specificity of tomosynthesis compared with conventional thoracic radiographs, we hypothesize that the correlation is not closer to 1 because our s-DCT system detects lung features that are not evident on CXR [18, 20]. This trend of correlation coefficients was found in other CF tomosynthesis evaluations as well [17]. Despite the new nature of the technique,

Table 3 Image quality

	Lung fields	Trachea	Proximal bronchi	Small airways	Diaphragm and LCA	Vascular pattern
Technique	0.0249†	0.3608	0.0329*	0.0028*	0.0303†	0.0071*
Reader	0.0035	< 0.0001	< 0.0001	0.0012	0.019	0.001
Interaction of reader and technique	NS	NS	0.0033	NS	0.0095	NS

Readers gave s-DCT higher scores when evaluating image quality for proximal bronchi, small airways and vascular pattern.
*p values indicate statistically significant differences in technique, favoring tomosynthesis.
†p values indicate statistically significant differences in technique, favoring CXR. Image quality of the trachea was not statistically different between CXR and s-DCT. Reader effects were not significant except when evaluating proximal bronchi and diaphragm and LCA

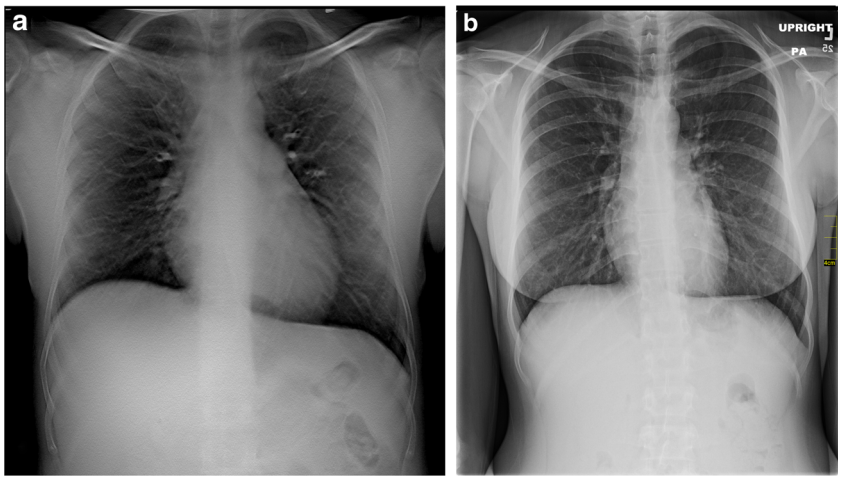

Fig. 2 Mild severity CF, corresponding to a 21 on the Brasfield scoring system and 14 on the tomosynthesis scoring system. A single image from the tomosynthesis examination (**a**) demonstrates improved visualization of bronchial wall thickening and mucous plugging compared with the conventional radiograph (**b**)

intraclass correlation coefficients were found to be comparable for tomosynthesis scores. More detailed assessments and larger patient populations, however, are necessary to further evaluate differences in the two approaches.

The correlation of the tomosynthesis disease severity score with pulmonary function tests further indicates the reliability of the s-DCT approach. Both imaging methods were found to have statistically significant correlations with PFTs (FVC, FEV1 and FEF 25–75%) with no statistical difference between the correlation coefficients of the two modalities. These data confirm the potential of s-DCT to provide greater imaging detail while still correlating well with other diagnostic information. While the measurements from PFTs are typically considered the most clinically relevant in CF patients [30, 31], our study suggests the potential utility of s-DCT to characterize disease in patients who are unable to perform PFTs, typically young children [32–34]. Recent studies have shown that detecting disease at an early age prior to clinical presentation may be important in altering the disease course of CF [35]. In contrast to conventional tomosynthesis, our CNT-based x-ray tubes can also perform prospective gated imaging, which would increase the temporal resolution (and thus disease detection) in young populations that cannot perform breath holds at a minimum radiation dose and relatively low cost [36]. Since our study only included a small range of the disease severity scale (the highest tomosynthesis score was 38 out of 100), further study must be done to quantify the correlation of tomosynthesis with PFTs in extreme disease states. This will allow us to better understand the relationship between the two measures and especially how it may relate to more subtle areas of disease. Ultimately, this technique may need to be evaluated compared with high-resolution CT.

Readers scored CXR as having higher image quality than s-DCT when evaluating full inspiration and the degree of motion blur. Our prototype s-DCT system acquires images in the AP configuration, which likely contributes to this perception despite equivalent breathing instructions. Motion blur in s-DCT images is also likely introduced by a combination of longer imaging times, cardiac motion, (which cannot be compensated without more time consuming cardiac gating) and imperfect breath holds, which may be reduced by improved subject training and operator experience. Differences in

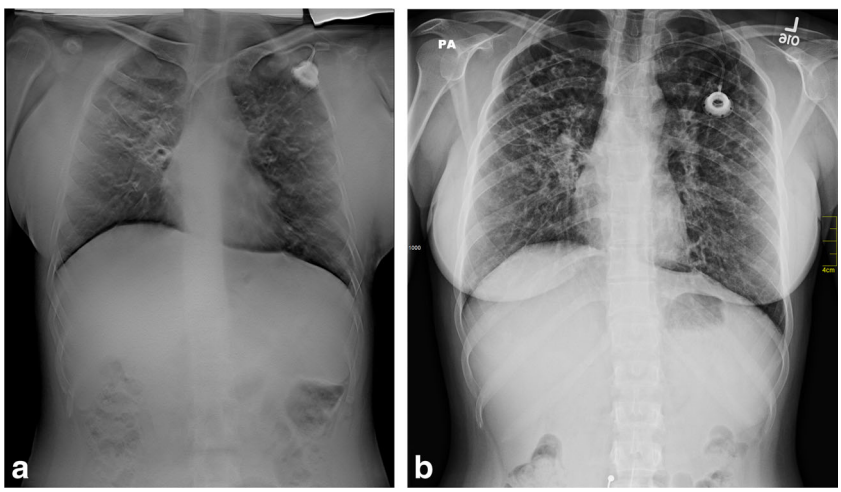

Fig. 3 Severe CF, corresponding to a 15 on the Brasfield scoring system and 33 on the tomosynthesis scoring system. A single image from the tomosynthesis examination (**a**) demonstrates improved visualization of bronchial wall thickening, bronchiectasis and mucous plugging compared with the conventional radiograph (**b**)

Table 4 Pulmonary function correlation

Pulmonary Function Tests Pearson Correlation Coefficients					
		FVC	FEV1	FEV1 FVC ratio	FEF 25–75
Average s-DCT	CC	-0.5818	-0.68506	-0.41015	-0.71886
	p-value	0.037	0.0098	0.1639	0.0056
Average Brasfield	CC	0.68117	0.79454	0.47496	0.78121
	p-value	0.0104	0.0012	0.101	0.0016

Tomosynthesis has high correlation with FEV1, FEF 25–75% and good correlation with FVC. $P < 0.05$ indicates that the correlation coefficient is significantly different from 0. Subject population $n = 13$

patient positioning were also likely due to the technologist learning curve for the new modality. The higher scores given to CXR when evaluating the lung fields, diaphragm and LCA are presumably due to motion blur at the lung bases as a result of imperfect breath hold and cardiac motion. Proximal bronchi, small airways and vascular pattern, all of which are important when assessing disease severity in CF patients, scored better on s-DCT than CXR.

Conventional DCT relies on the translation of a standard x-ray tube across an arc in front of the patient. This translation time typically requires 10 to 15 s, acquiring approximately 60 images. As a result, conventional DCT systems are severely limited in their ability to image patients who are unable to hold their breath for the entire imaging time [6]. These limitations preclude its use in patients such as young children or patients with severe respiratory compromise. A method to perform low-dose gated tomosynthesis imaging could have the potential to offer clinicians insight into the disease status of these patients without excessive doses of radiation. We are currently in the process of evaluating the system for gated tomosynthesis imaging, which could potentially be used to assess disease presence in young patients before they become symptomatic [37].

Study limitations

The main limitation of the current s-DCT system is the small angular span (12° vs. 30–60° in conventional DCT systems), a function of the repurposed tube. The small angular span leads to less effective out-of-plane suppression or increased artifact spread function. In a study by Gomi et al, an increased angular span was shown to significantly increase the detectability index of artificial pulmonary nodules [38]. Interestingly, small angular spans have been shown to be better for evaluation of small structures, such as microcalcifications in breast tomosynthesis [39, 40]. We anticipate that future use of a tube that offers a wider angular span will offer clinical results comparable to other published chest tomosynthesis studies. Longer length tubes have been manufactured for non-medical imaging applications, and we do not anticipate any difficulty adapting these for medical use in the future. Furthermore, faster detector readout could also substantially reduce imaging time without causing a resolution penalty like with conventional moving sources. It should be emphasized that our s-DCT system is a prototype that would require modifications to be ready to be evaluated against an approved chest imaging system. Another study limitation involves the lack of effective dose estimations. We were unable to acquire these values, which makes dose comparisons with other systems difficult. The entrance dose for this system however is similar to conventional DCT systems. Additionally, the small number of patients in this trial makes robust conclusions difficult to attain.

Conclusions

We demonstrate the potential for CNT-based linear x-ray source arrays for use in clinical studies in this first-in-human study of stationary digital chest tomosynthesis for cystic fibrosis. Despite the limitations imposed by this repurposed tube, this study has shown that stationary chest tomosynthesis imaging has the potential to become a useful tool in the evaluation of CF patients and opens the door to low-cost early detection of CF in the pediatric population. Prospective respiratory-gated imaging trials with the s-DCT imaging system are ongoing.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Yueh Lee MD, PhD.

Conflict of interest The authors of this manuscript declare relationships with the following companies:

Drs. Lee, Zhou and Lu are co-inventors of the stationary chest tomosynthesis imaging system evaluated in this study. Dr. Zhou has equity ownership and serves on the board of directors of Xintek, Inc., to which the technologies used or evaluated in this article have been or will be licensed. Dr. Lu has equity ownership in Xintek, Inc. All of these relationships are under management by the University of North Carolina's COI committees.

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Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- experimental
- performed at one institution

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