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Early View

Research letter

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Safety and diagnostic efficacy of cone beam computed tomography-guided transbronchial cryobiopsy for interstitial lung disease: a cohort study

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Take home message:

Cone beam CT (CBCT) can provide 3-dimensional images enabling accurate positioning of cryoprobe. CBCT-guided transbronchial cryobiopsy had a favorable safety profile with low risks of pneumothorax and significant bleeding, with excellent diagnostic yield.

To the Editor:

Transbronchial cryobiopsy (TBCB) is one of the most important procedures for assessment of patients with suspected interstitial lung diseases (ILD) when diagnosis cannot be made based on clinical and radiological assessments [1-4]. Recent reports suggested that TBCB may offer diagnostic value approaching that of surgical lung biopsy [5,6].

The location of the cryobiopsy is strongly associated with procedure-related complications [2,3]. Chest fluoroscopy has been suggested by some clinicians [2,3] to guide TBCB. However, the probe-to-pleura distance is unclear when the probe path is not perpendicular to the P-A plane of the C-arm imaging. A recent meta-analysis [7] observed an overall complication rate of 23.1%, with significant bleeding and pneumothorax reported in 14.2% and 9.4% of patients, respectively. Compared to fluoroscopy, Cone-beam computed tomography (CBCT) can provide 3-dimensional (3D) CT images that approach the image qualities of conventional CT [8]. Using this approach, the probe-to-pleura relationship can be accurately established based on 3D scans, which may improve the safety profile of cryobiopsies. We thus conducted a single-center prospective cohort study (NCT04047667) which was approved by our institution's human research ethics committee.

All patients diagnosed with ILD between September 2018 and August 2019 who met the following eligibility criteria were recommended to undergo CBCT-guided TBCB: > 18 years of age; a diagnosis of ILD could not be established after integration of clinical features; forced vital capacity (FVC) > 50%; and diffusing capacity of the lung for CO (DLCO) > 35%. Patients who met the following criteria were excluded: acute exacerbation in the past 30 days, bleeding diathesis, anticoagulant therapy, current use of antiplatelet drugs, pulmonary hypertension, respiratory failure, liver or kidney disfunction, cardiac insufficiency, and platelet count $< 50 \times 10^9$/L. Written informed consent was obtained from all patients prior to enrollment in the study.

Bronchoscopies were performed through endotracheal tube or rigid bronchoscopy under general anesthesia in a hybrid CBCT operation room. Cryoprobe (ERBE, Solingen, Germany) was advanced as far as possible into the target bronchial segment through the bronchoscopy working channel. The cryoprobe was then retracted 1 cm and the bronchoscopy was fixed on a stand. All medical workers were then moved to the control room and CBCT imaging (Artis Zee III ceiling, Siemens AG, Munich, Germany) was performed. Three-dimensional CT images were acquired and reviewed in axial, coronal, and sagittal planes to accurately assess the cryoprobe position (Figure 1A) within the lung parenchyma and relative to other thoracic structures. Re-positioning of cryoprobe was conducted if necessary to ensure a probe-to-pleura distance of ~1 cm. Cryobiopsy was performed (6-8 s freeze time for 1.9 mm cryoprobe and 4-6 s for 2.4 mm cryoprobe) following probe positioning, using carbon dioxide as the cryogen. After each biopsy, a bronchial blocker was immediately filled to stop the bleeding. Post-procedure CBCT or X-ray imaging was used to screen for acute pneumothorax. Bleeding severity was graded on scale described by Ernst et al [9]. Intensive care unit admission, histopathological diagnosis, and multidisciplinary discussions (MDD) diagnosis, disease progression and death within 30-day after TBCB were followed up.

A total of 155 patients (male-to-female ratio: 1.4 (90/65)) were finally enrolled (Figure 1B), with a mean age of 55.2±12.1 years. Mean FVC was 88.6%±20.5% and mean DLCO was 68.0%±19.5%. Fibrotic patterns on high-resolution CT (HRCT) were found in 67 (43.2%) patients.

Prior to TBCB, 66/155 (42.6%) patients required re-positioning after CBCT guidance. The mean number of CBCT scans conducted throughout the procedure was 2.1±0.7, with a mean radiation exposure of 17.0±7.0 mSv. The radiation exposure significantly decreased from 18.7±0.8 mSv to 10.6±1.4 mSv in the groups receiving post-procedure CBCT and X-ray, respectively (Student's t-test, $p<0.001$). All medical staff were free of radiation exposure.

An average of 3.39±0.96 specimens was obtained, with a mean surface area of 24.5±11.1 mm^2 (long axis diameter: 5.4±1.4 mm, short axis diameter 4.3±1.1 mm). A specific pathological diagnosis (P-diagnosis) was achieved in 134/155 patients (86.5%): 32 (20.6%) had non-specific interstitial pneumonia (NSIP), 19 (12.3%) had usual interstitial pneumonia (UIP), and 15 (9.7%) had hypersensitivity pneumonitis (HP). An MDD diagnosis was possible in 140/155 patients (90.3%): 28 (18.1%) had connective tissue disease-related ILD (CTD-ILD), 23 (14.8%) had HP, 18 (11.6%) had idiopathic pulmonary fibrosis (IPF), and 17 (11.0%) had NSIP. The agreement between P-diagnosis and MDD diagnosis was 80.0%, with a corresponding kappa concordance coefficient of 0.78 (95% confidence interval 0.75-0.80).

The complications of CBCT-guided TBCB are summarized in Figure 1C. The most common complication was procedure-related bleeding. Twenty patients (12.9%) had no bleeding; others had either mild (116/155, 74.8%) or moderate (19/155, 12.3%) bleeding that was immediately controlled by endoscopic measures. No severe bleeding events were reported. Pneumothorax occurred in only three patients (1.9%); all instances were resolved using a chest tube and cured within one week; one of them presented visceral pleura in samples. Acute exacerbation of ILD and temporary post-bronchoscopy fever occurred in one (0.6%) and 11 (7.1%) patients, respectively. No deaths were reported within 30 days after TBCB.

Multivariate logistic regression analyses indicated that the less number of biopsies collected (p=0.007) and fibrotic patterns on HRCT (p=0.002) may be associated with a greater risk of moderate bleeding. No significant associations were observed between various clinical features and the risk of pneumothorax or diagnostic efficacy.

To our best knowledges, this report represents the first prospective study of CBCT-guided TBCB, revealing favorable safety and diagnostic profiles.

Pneumothorax is one of the most common complications of TBCB. Occurrence of pneumothorax could lead to longer hospital stay and more medical cost [6]. In some of reported studies, pneumothorax was a serious, life-threatening complication, which resulted in several deaths [10-13]. Fluoroscopic guidance is presumed to reduce the incidence of pneumothorax by localizing the cryoprobe at a suitable position and is routinely used in TBCB [2,3]. However, numerous studies have shown that fluoroscopy does not significantly reduce the rate of pneumothorax. In a large retrospective cohort study by Ravaglia *et al*. [13], pneumothorax occurred in 19.2% (134/699) of patients after fluoroscopy-guided TBCB, of which 70.1% required chest tube drainage. These analyses suggest that the rate of pneumothorax might be significantly higher in fluoroscopy-guided TBCB than in CBCT-guided procedures. Here, we found the incidence of pneumothorax was only

1.9%. The 3D images generated by CBCT presented an accurate view of the cryoprobe position, enabling us to measure the probe-to-pleura distance. Of the 155 patients enrolled in this study, 66 (42.6%) required repositioning of the cryoprobe prior to biopsy, enabling an optimal probe-to-pleura distance of ~1 cm. Furthermore, the precise localization of cryobiopsy under guidance of 3D CBCT imaging might reduce the influences of clinical factors on pneumothorax. We found no apparent relationship between the rate of pneumothorax and biopsy sites, cryoprobe types, or sample sizes. This was different from previous study [13] which showed collection of > 1 biopsy or use of a 2.4 mm cryoprobe could significantly increase the rate of pneumothorax, even under fluoroscopy guidance.

Bleeding is another common complication encountered in TBCB; the incidence of serious bleeding events has ranged from 0% to 42%. There were no severe bleeding events reported in our study; however, moderate bleeding was observed in 12.3% of patients. Accurate localization by CBCT 3D imaging might be helpful to prevent severe bleeding, as it enabled a consistent cryoprobe-to-pleura distance of ~1 cm, targeting an area that primarily contained only small vessels. Multivariate analysis suggested that the less number of TBCB biopsies and fibrotic patterns on HRCT may be associated with a higher risk of moderate bleeding. The former could be explained by the occurrence of moderate bleeding leading to discontinuation of further biopsy collection. The latter may tell us that it's important to assess fibrotic score on HRCT before TBCB in order to prevent significant bleeding risk.

The use of CBCT guidance significantly reduced TBCB-related complications, with 42.6% of patients requiring repositioning based on CBCT images. However, the addition of CBCT to TBCB may increase radiation exposure for patients, compared to fluoroscopy. In our study, only one CBCT scan was conducted for TBCB procedures in the same lobe, thereby reducing radiation exposure. To optimize probe placement without repeated CBCT scanning, optimization of the probe-to-pleura distance was achieved by repositioning the cryoprobe based on the difference between actual and predicted positions. Subsequent samples in the same area or adjacent segment were then obtained by inserting the cryoprobe at consistent intervals from the location of the first biopsy. As a result, we performed a mean of 3.39 samples per patient, with a mean of only 1.1 CBCT scans necessary to guide TBCB. Furthermore, replacement of post-procedure CBCT with a traditional X-ray significantly reduced the mean radiation exposure to 10.6 mSv.

To the best of our knowledge, this work constitutes the largest cohort study thus far regarding the use of CBCT guidance for bronchoscopy. However, it is limited by non-randomized controlled design.

In conclusion, CBCT-guided TBCB was associated with a favorable safety profile, with low risks of pneumothorax and moderate to severe bleeding. Both histopathological and MDD diagnostic yield were excellent, with a high level of agreement between these metrics.

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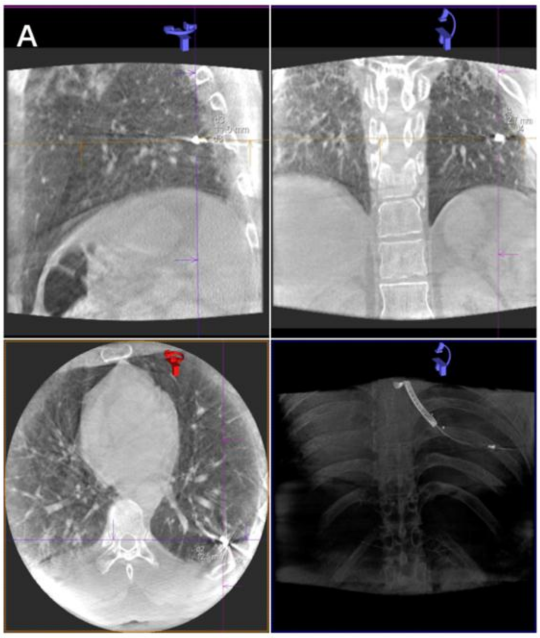
Figure legends

Figure1. A. Three-dimensional (3D) cone beam computed tomography (CBCT) images used to identify the cryoprobe position; B. Clinical characteristics in patients with interstitial lung disease

(ILD) undergoing CBCT-guided transbronchial cryobiopsy (TBCB); C. Safety and diagnostic outcomes of CBCT-guided TBCB.



B. Patient characteristics	Number
Patients	155
Median age, year-old	55.2±12.1
Male-to-female (ratio)	90/65 (1.4)
Smokers (%)	73 (47.1%)
Environmental or occupational history (%)	55 (34.5%)
Mean FVC, % predicted	88.6±20.5
Mean DLCO, % predicted	68.0±19.5
HRCT pattern	
Fibrotic (%)	67 (43.2%)
Non-fibrotic (%)	88 (56.8%)
Cryoprobe	
1.9 mm (%)	48 (31.0%)
2.4 mm (%)	107 (69.0%)
Biopsy site	
Single segment (%)	72 (46.5%)
Multiple segments (%)	83 (53.5%)
Mean sample number	3.39±0.96
Mean sample size	
Surface area, mm^2	24.5±11.1
Long axis diameter, mm	5.4±1.4
Short axis diameter, mm	4.3±1.1
Mean CBCT scanning times	2.1±0.7
Cryoprobe re-position after CBCT (%)	66 (42.6%)
Radiation exposure, mSv	17.0±7.0
Procedure duration, min	38.5±15.3

FVC: forced vital capacity; DLCO: diffusing capacity of the lung for CO; HRCT: high resolution computed tomography; CBCT: cone-beam computed tomography.

C. Outcomes of CBCT-guided TBCB	Number (%)
Patients	155
Complications	
Pneumothorax	3 (1.9%)
Mild bleeding	116 (74.8%)
Moderate bleeding	19 (12.3%)
Acute exacerbation of ILD	1 (0.6%)
Post-bronchoscopy fever	11 (7.1%)
Diagnostic yields	
Pathological diagnosis	134 (86.5%)
MDD diagnosis	140 (90.3%)

CBCT: Cone-beam computed tomography; TBCB: transbronchial cryobiopsy; ILD: interstitial lung diseases; MDD: multidisciplinary discussions.