

# The Safety and Feasibility of Radial Endobronchial Ultrasound-guided Transbronchial Cryobiopsy in Diffuse Pulmonary Infiltrate Diseases

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## Research article

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# Abstract

**Background** Transbronchial lung cryobiopsy (TBLC) has emerged as a new bronchoscopic procedure which can improve specimen size and obtain crush artifact-free tissue to increase diagnostic yield in various diffuse parenchymal lung diseases (DPLDs). However, TBLC has been associated with a higher incidence of complications, and variability in diagnostic yield. Radial probe endobronchial ultrasound (R-EBUS) may be able to overcome these problems. We evaluated the safety and feasibility of TBLC in combination with R-EBUS to diagnose DPLDs.

**Methods** We conducted this retrospective study at a single medical center from January 2015 to March 2019. Patients with DPLDs who underwent R-EBUS to locate target lesions and confirm the absence of adjacent vessels, followed by sampling with conventional transbronchial lung forceps biopsy (TBLB) and cryobiopsy (TBLC) were enrolled. TBLC and TBLB samples were sent to the pathology department for diagnostic analysis. The sample size, diagnostic yield and complications after the procedure were recorded.

**Results** A total 30 patients with DPLD were analyzed, of whom 17 had diffuse lung infiltrates and 13 had pulmonary nodules/masses. The overall diagnostic rate was 80% (24/30) and the diagnostic yield increased from 46.7% with the forceps biopsy to 73.3% after adding cryobiopsy ( $p=0.038$ ). Compared to conventional transbronchial biopsy with forceps, cryobiopsy provided a larger specimen and sample volume (40 mm<sup>3</sup> vs 6 mm<sup>3</sup>;  $p<0.001$ ). Twenty-two (73.3%) patients had mild bleeding, two (6.7%) had moderate to severe bleeding, and one (3%) had pneumothorax. Ten patients who initially had non-diagnostic results by TBLB received a definite diagnosis after adding TBLC. Among these patients, eight (8/10) were ultimately diagnosed with interstitial lung disease (ILD) ( $p<0.001$ ).

**Conclusions** TBLC with R-EBUS guidance increased the diagnostic yield in patients with DPLD, particularly in those with ILD. The samples obtained by TBLC were significantly larger and there were no severe complications after the procedure. Larger studies are needed to confirm the safety and feasibility of R-EBUS-guided TBLC.

## Introduction

Transbronchial lung cryobiopsy (TBLC) has emerged as a new bronchoscopic procedure which can improve specimen size and obtain crush artifact-free tissue compared with transbronchial lung biopsy (TBLB) performed with conventional forceps.[1–4] TBLC aims to obtain a specimen from the lung parenchyma, and is indicated for patients with diffuse parenchymal lung diseases (DPLDs) and pulmonary masses or nodules. In the diagnosis of interstitial lung disease (ILD), Pajares et al reported that TBLC provided a higher diagnostic yield than TBLB (74% vs. 34%).[5] With regards to the application of TBLC for pulmonary masses or nodules, specimens obtained by TBLC have been shown to be consistently larger than those obtained by TBLB and that this is preferential for mutation analysis and

molecular testing, although no statistically significant difference has been reported in the diagnostic yield between TBLC and TBLB.[6]

Although TBLC can provide a larger and artifact-free tissue sample for diagnosis, concerns over a higher risk of bleeding and pneumothorax compared to TBLB have been reported.[7] In recent years, radial probe-endobronchial ultrasound (R-EBUS)-guided TBLC has been used to identify target lung parenchyma without adjacent blood vessels, and it has been shown to reduce the risk of bleeding. However, few studies have assessed the feasibility and safety of R-EBUS-guided TBLC in the diagnosis of DPLDs and peripheral pulmonary lesions (PPLs). Berim et al indicated that the simultaneous use of R-EBUS and fluoroscopy could reduce the risk of bleeding complications with TBLC in patients with suspected ILD.[8] In addition, Gnass et al reported that the complication of pneumothorax occurred in one patient (5%) and mild bleeding in a few patients in the diagnosis of ILD with a combination of TBLC and R-EBUS, but no cases of moderate to severe bleeding.[9] The diagnostic yield of R-EBUS with TBLC in patients with ILD has been reported to be around 80%.[9, 10] The diagnostic rate of PPLs with R-EBUS with TBLC has been reported to range from 62.5% to 83%, with a moderate bleeding rate of 3% to 32%.[11]

Most previous studies have been limited by the lack of a control group. Therefore, we conducted this retrospectively study of 30 patients with DPLDs or PPLs who underwent R-EBUS-guided TBLB followed by R-EBUS-guided TBLC. The purpose of this study was to assess the efficacy and feasibility of R-EBUS-guided TBLC in the diagnosis of patients with DPLDs or PPLs, and identify the patients who would benefit from R-EBUS-guided TBLC due to the larger diagnostic yield.

## Patients And Methods

Between January 2015 and March 2019, 30 patients with DPLDs or PPLs who underwent R-EBUS to locate target lesions and confirm the absence of adjacent vascular structure, followed by sampling with conventional R-EBUS tools and cryobiopsy at our institution were included in this study. Diffuse lung infiltrates on chest computed tomography (CT) images may present as ground glass opacities, reticular and alveolar patterns. All procedures were conducted in our bronchoscopy room, and bronchoscopy was performed under conscious sedation with pulse oximeter and EKG monitoring. The clinical data of the patients, including age, sex, lesion location, pathological diagnosis, image size, image characteristics, specimen size, and complications were retrospectively analyzed. This study was approved by the China Medical University Hospital Institutional Review Board (CMUH103-REC1-112), and written consent was obtained from all patients.

All 30 patients underwent flexible bronchoscopy (BF-1T260; Olympus; Tokyo, Japan) with a transbronchial biopsy, and cryobiopsies were performed according to the standard protocol of China Medical University Hospital Intervention Pulmonology teams. The patients received local anesthesia with 2% xylocaine and conscious sedation with midazolam before the procedure. EBUS was performed using an endoscopic ultrasound system (EU-M30; Olympus) and a 20-MHz miniature radial probe (UM-S20-20R; Olympus). CT scans were performed in all patients prior to diagnostic bronchoscopy. Neither

navigation bronchoscopy nor fluoroscopy was performed. The EBUS radio probe was inserted into the target bronchus according to the radiographic findings.

Once the target lesion had been identified on EBUS, sampling was first performed using the traditional diagnostic method with a forceps biopsy and bronchus washing. We then performed a cryobiopsy with a cryoprobe (ERBE Cryoprobe 1.9 mm diameter or 2.4 mm diameter), with a uniform freezing time of 4 seconds for each cryobiopsy. After freezing, the cryoprobe and bronchoscope were removed with the frozen lung sample attached to the probe. The frozen samples were then thawed in normal saline and fixed in formalin. Each patient had three transbronchial biopsies of their lung lesions with forceps and one to two with the cryoprobe. The bronchoscope was reintroduced to assess bleeding at the biopsy site. The severity of bleeding was classified into three groups as follows: (1) nil: slight, self-limited without any interventions; (2) mild: a vasoactive drug (adrenaline) was administered into the airway to treat the bleeding; and (3) moderate to severe: argon plasma coagulation (APC) or electrocautery were used to manage the bleeding. After the procedure, the specimens were sent to the Department of Pathology where they were assessed by two independent pathologists. The final diagnosis was made by multidisciplinary discussion, including experts in pulmonology, radiology, and lung pathology.

## Statistical Analysis

The data were compiled and analyzed using commercial statistical software MedCalc version 15.6.1 (MedCalc, Mariakerke, Belgium). All continuous variables were reported as mean and standard deviation. Differences in continuous variables were compared using the Mann-Whitney U-test for non-normally distributed data. Categorical variables were reported as the number of patients and percentage. Differences in categorical variables were examined using the chi-square test or Fisher's exact test. McNemar's test was used to examine differences in diagnostic yield between forceps biopsies and cryobiopsies. All tests of significance were two sided, and a p value 0.05 was considered to be statistically significant.

## Results

Thirty patients (18 men and 12 women) with a mean age of 62 years were included in this retrospective study. Among them, 17 patients with DPLDs and 13 patients with PPLs were referred for R-EBUS-guided TBLC. A definite diagnosis after diagnostic bronchoscopy was established in 24 patients. Adenocarcinoma (eight patients) was the most common pathological diagnosis, followed by organizing pneumonia (seven patients). Invasive mucinous carcinoma was diagnosed in two patients. Lymphoma, pulmonary alveolar proteinosis, IgG4 disease, xanthogranulomatous inflammation, cryptococcus, granulomatous, and leiomyosarcoma were diagnosed in one patient each, and six patients had non-specific pathologic findings with chronic inflammation (Table 1). The locations of the biopsies are summarized in Table 2. The right lower lobe (11 patients) was the most frequently biopsied site, followed by the left lower lobe (10 patients), right upper lobe (five patients), and lingual lobe (four patients).

Compared to TBLB with forceps, TBLC provided a larger specimen and sample volume (40 mm<sup>3</sup> vs 6 mm<sup>3</sup>; p < 0.001) (Figure 1). Biopsy specimens obtained with the cryoprobe were considered to be diagnostic in 22 patients (22/30,73.3%), compared to 14 patients (14/30,46.7%) with forceps biopsies. The diagnostic yield increased from 46.7% with the forceps biopsy to 73.3% after adding cryobiopsy (p = 0.038). A definite diagnosis was made in 12 patients by both forceps biopsy and cryobiopsy; six patients had non-diagnostic results even after a forceps biopsy and cryobiopsy. In 10 patients with initially non-diagnostic specimens obtained by forceps biopsy, a definite diagnosis was achieved after adding cryobiopsy. However, in two patients with initially definite diagnostic specimens obtained by forceps biopsy, non-diagnostic specimens were obtained after adding cryobiopsy (Table 3). Table 4 shows detailed information on sample size and the diagnosis of the 12 patients with inconsistent diagnostic results with forceps biopsy and cryobiopsy.

The study patients were divided into two groups: (1) those with initially non-diagnostic specimens by forceps biopsy who then had a definite diagnosis after adding cryobiopsy; (2) those who still had the same diagnostic results or non-diagnostic specimens after adding cryobiopsy. Table 5 summarizes the clinical basic characteristics of these two groups. The only variable that was significantly different between these two groups was a diagnosis of ILD (15% vs 80%; p < 0.001). There were no significant differences in other variables including initial image presentation (diffuse lung infiltration or nodules/masses), size of the target lesion on CT scan, characteristics of the EBUS image (within or not within), diagnosis of malignant disease, and size of specimen (forceps biopsy or cryobiopsy) between the two groups. These results suggested that adding cryobiopsy increased the diagnostic yield in patients with ILD.

With regards to the safety of the technique, one patient had pneumothorax which resolved after chest tube drainage, and the patient was subsequently discharged. In total, 22 (73.3%) patients had mild bleeding, and two (6.7%) patients had moderate to severe bleeding. All cases of bleeding were controlled by norepinephrine injection or argon plasma coagulation (Table 6). No severe complications were recorded after the procedure.

## Discussion

The current study showed that the addition of R-EBUS-guided TBLC to conventional TBLB increased the diagnostic yield from 46.7% to 73.3%, especially in patients with a diagnosis of ILD. In 10 patients with initially non-diagnostic specimens obtained by TBLB, a definite diagnosis was achieved after adding TBLC. Among these patients, eight were ultimately diagnosed with ILD. Cryobiopsy provided larger tissue specimens than forceps biopsy (40 mm<sup>3</sup> vs 6 mm<sup>3</sup>; p < 0.001) without uncontrolled complications such as near-fatal pneumothorax and bleeding.

Few studies have investigated R-EBUS-guided TBLC for DPLDs and PPLs.

The novel method of combining R-EBUS and TBLC can be advantageous for patients with ILD and pulmonary masses/nodules by increasing the diagnostic yield. In 2013, Schuhmann et al were the first to report the use of R-EBUS-guided TBLC in pulmonary masses/nodules. They reported that the specimen obtained by TBLC (11.17 mm<sup>2</sup>) was significantly larger than that obtained by TBLB (4.69 mm<sup>2</sup>) ( $p < 0.001$ ). However, there was no significant difference in the diagnostic yield between TBLC (23/31; 74.2%) and TBLB (19/31; 61.3%) ( $p = 0.42$ ).<sup>[6]</sup> In addition, Armura et al reported that TBLC could provide specimens of sufficient quantity and quality for DNA sequencing by NGS, with diagnostic accuracy rates of 87% for TBLC and 82.6% for TBLB.<sup>[12]</sup> Hibare et al reported diagnostic accuracy rates of 67.9% (19/28) in patients with PPLs with R-EBUS-guided TBLC and 75% (21/28) in those with R-EBUS-guided TBLB. However, the difference in diagnostic yield was not statistically significant ( $p = 0.562$ ).<sup>[13]</sup>

For ILD, surgical lung biopsy (SLB) is currently the gold standard when noninvasive modalities such as laboratory data and imaging findings cannot be used to make a definite diagnosis. TBLC has recently emerged as an alternative diagnostic tool, with lower mortality and morbidity compared with SLB<sup>[14]</sup> and a higher diagnostic yield than TBLB.<sup>[5]</sup> The diagnostic yield of TBLC to diagnose ILD has been reported to range from 66% to 86%.<sup>[14–16]</sup> A meta-analysis assessed the performance of TBLC for diagnosing diffuse lung infiltrate diseases, and showed a diagnostic yield of 72.9% with a mean tissue size of 23.4 mm<sup>2</sup>.<sup>[17]</sup> The diagnostic yield seems to be reasonable, however safety concerns have been raised. Nevertheless, few studies have investigated R-EBUS-guided TBLC for ILD. Gnass et al reported a diagnostic yield of 80% in patients with ILD using a combination of R-EBUS and TBLC.<sup>[9]</sup>

In the current study, the diagnostic yield increased from 46.7% with a forceps biopsy to 73.3% after adding cryobiopsy. In order to identify the patients who may benefit from TBLC, we divided them into two groups: (1) those with initially non-diagnostic specimens by forceps biopsy who then had a definite diagnosis after adding cryobiopsy; and (2) those who still had the same diagnostic results or non-diagnostic specimens after adding cryobiopsy. The only significant difference between the two groups was the proportion of ILD patients (80% in group 1 vs 15% in group 2;  $p < 0.001$ ). There were no significant differences in the type of image presentation (DPLD or PPLs), position of the EBUS probe (within or not within), lesion size, tissue sample size, and patients with lung malignancy between the two groups. Therefore, for patients suspected of having a diagnosis of ILD, cryobiopsy can increase the diagnostic yield. This is consistent with previous studies which showed a better diagnostic rate with TBLC compared to TBLB in patients with ILD, but not in patients with pulmonary nodules/masses.<sup>[6, 11, 18]</sup> This may be because cryobiopsy provided a larger specimen than forceps biopsy in this study (40 mm<sup>3</sup> vs 6 mm<sup>3</sup>;  $p < 0.001$ ), which is also consistent with a previous study.<sup>[17]</sup> In the current study, five patients had non-specific pathological findings of chronic inflammation based on the forceps biopsy, and were ultimately diagnosed as having organizing pneumonia after adding cryobiopsy. We reviewed the pathologic picture of these patients, and the presence of Masson bodies in the cryobiopsy specimens was the key factor from which a definite diagnosis of organizing pneumonia was made. This can be explained by the fact that Masson bodies can be seen easily on larger cryobiopsy tissue specimens compared to forceps biopsy tissue specimens.

The complication rate of TBLC without R-EBUS for patients with ILD has been reported to be relatively high, with pooled estimates for moderate to severe bleeding and pneumothorax of 39% and 12%, respectively.[19] Another study reported incidence rates of significant bleeding and pneumothorax of 14.2% and 9.4%, respectively.[17] For patients with PPLs, the complication rate of TBLC has been reported to be relatively lower compared to patients with ILD.[11] The purpose of combining R-EBUS guidance with TBLC is not only to reduce the bleeding rate by locating lung parenchyma without adjacent major vessels, but also to decrease the occurrence of pneumothorax. Gnass et al reported a case series of 20 patients with ILD who underwent R-EBUS-guided TBLC, in which only one patient (1/20) had minor bleeding and one patient (1/20) had pneumothorax.[9] In addition, the bleeding rate was lower than in those with ILD without R-EBUS-guided TBLC. In the current study, one patient (3%) had pneumothorax and required chest tube drainage, and two patients (6%) had moderate to severe bleeding which was controlled by coagulation or argon plasma coagulation. There were no near-fatal complications after receiving TBLC followed by TBLB with flexible bronchoscopy.

In this study, there are two cases where only the forceps biopsy was successful in making a definite diagnosis; one who was diagnosed with a fungal infection, and the other with adenocarcinoma. Both patients had larger specimens with cryobiopsy than forceps biopsy. Dislocation of the cryoprobe is a possible explanation for these cases, because we did not recheck with EBUS before performing cryobiopsy. Therefore, we suspect that a technical error caused the negative cryobiopsy result in these two patients. In our protocol, we did not use a guided sheath (GS) to locate the target lung lesion, which may have contributed to sampling errors. The use of TBLC or TBLB via a GS may overcome this issue.

There are several limitations to this study. First, it was performed at a single tertiary referral medical center and included a small number of patients. Therefore, the results may not be generalizable to other patient populations. Second, the study is retrospective in nature, and there may have been selection bias. Third, there was no control group because every patient received both a forceps biopsy and cryobiopsy under R-EBUS. Therefore, we could not differentiate safety data and ascribe the complication to one of the techniques. In addition, we could not conclude that R-EBUS-guided TBLB or TBLC could reduce the complication rate in patients with DPLDs. However, the life-threatening complication rate in our study was low, and R-EBUS-guided TBLC appears to be safe. Finally, we did not use a GS to locate the target lung lesion in our protocol, which may have influenced the diagnostic rate of this novel method.

## Conclusions

R-EBUS-guided TBLC in patients with DPLDs can increase the diagnostic yield due to larger specimens and preserved architecture, particularly in patients suspected of having ILD. The life-threatening complication rate was low in this study. R-EBUS guidance can be an alternative method to choose the optimal area for cryobiopsy at institutions without fluoroscopy. However, further large-scale prospective trials in a randomized setting are needed.

## Abbreviations

TBLC = Transbronchial lung cryobiopsy; DPLDs = diffuse parenchymal lung diseases;

R-EBUS = Radial probe endobronchial ultrasound; TBLB = transbronchial lung forceps biopsy; ILD = interstitial lung disease; PPLs = peripheral pulmonary lesions; CT = computed tomography; EBUS = endobronchial ultrasound; GS = guided sheath

## **Declarations**

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None

### **Availability of data and materials:**

The datasets used and/or analyzed during the current study are available from the corresponding author on a reasonable request.

### **Author contributions:**

**(I) Conception and design: C.H Chen, C.Y Tu, B.R Wu, W.C Chen**

**(II) Administrative support: W.C Liao, C.Y Tu, C.H Chen,**

**(III) Provision of study materials or patients: C.H Chen, W.C Liao, C.Y Chen, B.R Wu**

**(IV) Collection and assembly of data: W.C Cheng, C.H Chen, W.C Chen**

**(V) Data analysis and interpretation: C.H Chen, W.C Cheng**

**(VI) Manuscript writing: M.F Shen, W.C Cheng**

## **(VII) Final approval of manuscript: W.C Cheng, M.F Shen, B.R Wu, W.C Chen, W.C Liao, C.Y Chen, C.Y Tu and C.H Chen**

### **Ethics approval and consent to participate:**

The study has been approved by China Medical University Hospital Institutional Review Board (CMUH103-REC1-112), and written consent was obtained from all patients.

### **Consent for publication:**

Not applicable

### **Competing interests:**

**The authors declare that they have no competing interests**

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## Tables

Due to technical limitations, the tables are available in the supplementary section.

## Figures

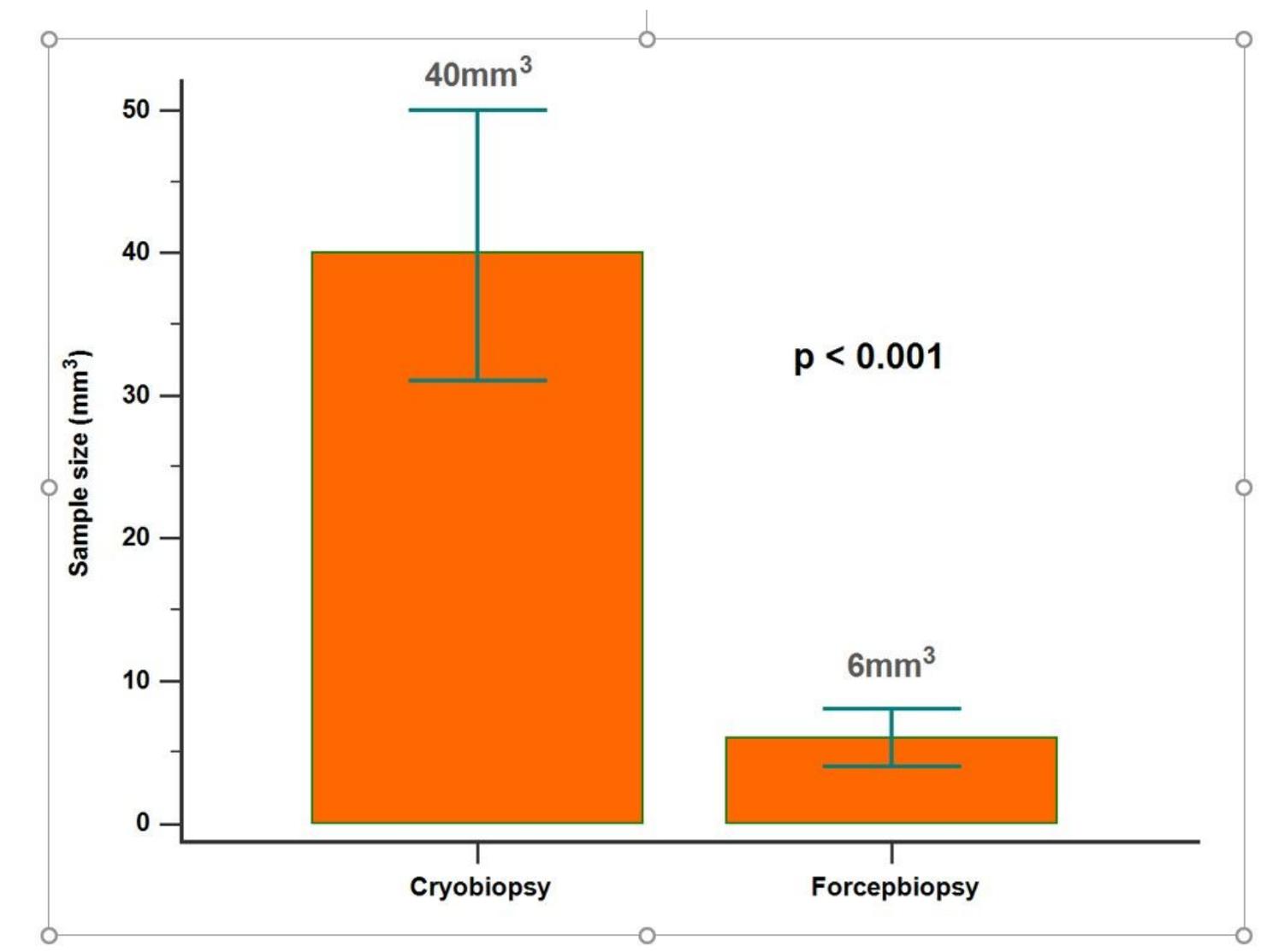


Figure 1

The size of biopsy specimens were obtained with cryoprobe and forceps. Compared to TBLB with forceps, TBLC provided a larger specimen and sample volume (40 mm<sup>3</sup> vs 6 mm<sup>3</sup>; p < 0.001)

## Supplementary Files

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