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Original Article

Elucidating diagnostic efficacy and safety of the procedure: cryobiopsy of endobronchial lesions with a flexible bronchoscope

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Abstract

When compared to conventional forceps biopsy, the use of a flexible cryoprobe allows for the sampling of endobronchial lesions, yielding well-preserved, circumferential, and substantial specimens, resulting in a higher diagnostic yield, as demonstrated in multiple studies. We evaluated the utility of cryobiopsy in the diagnosis of endobronchial lesions as well as its safety profile in this study. This retrospective study included 200 patients who underwent cryobiopsy for bronchoscopically visible endobronchial lesions between March 2016 and July 2022. Cryobiopsy was performed under conscious sedation using a flexible cryoprobe. Data on baseline patient characteristics, post-biopsy bleeding, and final histopathological diagnosis were collected. We evaluated the procedure's diagnostic yield and safety. The majority of the patients were male (84.5%) and the mean age of the patients was 56.96±13.64 years. In our study, the average size of cryobiopsy specimen was 6.8±1.2 mm. In 93% of cases, a definitive diagnosis was established; the most common diagnosis was squamous cell carcinoma of the lung (42.5%), followed by adenocarcinoma (18.5%) and small cell carcinoma (13.5%). Tuberculosis and sarcoidosis were reported in 2.5% and 1% of cases, respectively. In this study, 1% of patients had severe bleeding that required intubation and ICU admission, while 26% had moderate bleeding that was treated with cold saline and local epinephrine instillation. No mortality was reported in the study. Endobronchial cryobiopsy with a flexible bronchoscope is a safe procedure with a high diagnostic yield. This approach, which has a favorable safety

profile, holds the promise of improving diagnostic and treatment outcomes in lung cancer and other benign lung diseases.

Key words: bronchoscopy, cryobiopsy, endobronchial lesion, diagnostic yield and safety

Introduction

A wide variety of diseases may present as an endobronchial lesion either isolated or in conjunction with pulmonary parenchymal lesions. Diagnostic bronchoscopy is an excellent tool for evaluation and sampling of such lesions whenever deemed necessary for the patient management. Fiberoptic bronchoscopy offers valuable insights into the type, location, and number of endobronchial lesions. Various techniques can be applied for sampling these lesions through the working channel of the flexible bronchoscope such as bronchial washing, transbronchial needle aspiration (TBNA), brush, and endobronchial biopsy [1]. Forceps biopsy (FB) is a commonly used method to obtain tissue samples from endobronchial lesions, with 65-91% diagnostic yield in various studies [2-6]. However, the forceps can only be advanced in the forward direction and tissues from the lateral wall are difficult to obtain.

In contrast, cryobiopsy enables clinicians to perform a tangential biopsy, which includes the lateral area, by touching the lateral portion of the cryoprobe tip against the target lesion. Another downside of FB is the small tissue size and crush artifacts. Cryobiopsy provides larger samples without any crush artifacts. Larger samples are crucial for specific histopathological diagnosis, as well as immunohistochemical staining and mutational analysis in the tumor tissue [7] which is of immense importance in the management of lung cancer. The objective of this study was to evaluate the efficacy of cryobiopsy in diagnosing endobronchial lesions and its procedural safety.

Materials and Methods

Study design and settings

This was a retrospective analysis of prospectively collected data of endobronchial cryobiopsies performed in our tertiary care academic institute from March 2016 to July 2022. Patients with suspected endobronchial lesions [based on clinical history (hemoptysis) and radiological findings (atelectasis, etc.)] beyond the level of carina underwent flexible bronchoscopy under moderate sedation (IV Midazolam and IV fentanyl) without the use of rigid bronchoscope or any artificial airway. Ethical clearance was obtained from the institutional ethical committee.

The aim of this study was to demonstrate safety and diagnostic efficacy of cryobiopsy in endobronchial lesions (exophytic, nodular, ulcerative/plaque, mucosal infiltrative lesion) beyond the level of carina without necessitating a rigid bronchoscope or artificial airway.

Study subjects

Following patients were included in the study with the necessary inclusion and exclusion criteria after taking informed written consent.

Inclusion criteria

1. Outpatients and Inpatients in whom endobronchial cryobiopsy was performed for visible endobronchial lesion (exophytic, nodular, ulcerative/plaque, mucosal infiltrative lesion) beyond the level of carina were included in the study.
2. Patients who were willing to provide signed informed consent.

Exclusion criteria

1. Severe hypoxemia and hemodynamic instability (aystolic BP ≤90 mmHg and diastolic BP ≤60 mmHg).
2. Platelet count <100.000/mm^3 and abnormal coagulation profile.
3. Patients without endobronchial tumour (endoscopically non-visible lesion).
4. Patients with tracheal and carinal lesions.
5. Patients in whom anticoagulants could not be stopped due to underlying severe medical condition [liver disease, severe renal impairment (GFR ≤30 mL/kg/min), active bleeding and active pulmonary embolism].

Methodology

All patients underwent a comprehensive clinical examination, detailed medical history, blood investigations including complete blood profile, liver function test, renal function test, and radiological assessment prior to procedure. Evaluation for coagulopathy and thrombocytopenia was routinely done prior to biopsy. For subjects on anticoagulants and aspirin, we performed the procedure after discontinuing the drug for 2-5 days (depending on the drug patient was taking) and ensuring that the international normalized ratio (INR) was less than 1.5. None of our patients had severe cardiac, renal, or liver disease. Patients were explained about the

procedure in detail and a preprocedural consent was obtained from all the participants. Topical anesthesia for the bronchoscopy included 3 sprays of 10% lignocaine to the pharynx. Intravenous (IV) midazolam and fentanyl were used to achieve the desired level of sedation. Low flow supplemental oxygen was provided through nasal cannula. Continuous monitoring of Spo2, heart rate, blood pressure and ECG was done throughout and for next 2 hours after the procedure. After ensuring that the patient was sedated, a bite block was placed in mouth. Adult therapeutic video bronchoscope (Olympus BF-1TQ170, Olympus Corporation, Japan, channel diameter: 2.8 mm, outer diameter: 6.0 mm) was utilized for bronchoscopy.

The "spray-as-you-go" technique involving 1% lignocaine solution was used for topical anesthesia of vocal cords and tracheobronchial tree in. Prior to sampling, bronchoscopic inspection of the bronchial tree was done. After visualization of the endobronchial lesion, 5-10 ml of cold saline was instilled on the target area with the intent to reduce post-biopsy bleeding and clear the slough. A 1.9-mm or 2.4 mm flexible cryoprobe (length: 780 mm, ERBOKRYO CA, ERBE, Germany) (Figure 1) was inserted through the bronchoscope working channel and gradually advanced to place the cryoprobe tip in direct contact with the target lesion (Figure 2). Tangential cryobiopsy was performed for mucosal infiltrative lesions positioned lateral to the bronchoscope. Cryobiopsy was done in patients having lesions beyond the carina. Cryoprobe was activated for 3-5s. A flexible bronchoscope and cryoprobe with tissue sample attached to it was removed en-block from the bronchial tree. The tissue sample was taken off after submerging the cryoprobe tip in room temperature saline and subsequently transferred to 10% formalin solution for histopathological analysis. The bronchoscope was quickly reintroduced to control the bleeding (if occurred) and to take another sample. Typically, two cryobiopsy samples were taken. If noticeable degree (which require additional intervention i.e., cold saline and diluted epinephrine) of bleeding occurred, the body position of the patient was changed to target-side down i.e., left lateral or right lateral decubitus and fogarty catheter was used in cases with severe bleeding (through the working channel of bronchoscope and was placed above the bleeding lesion for 5-15minutes). Hemostasis was achieved by cold saline and/or local epinephrine (1:10000) instillation. Subsequently, the bronchoscope was removed after performing airway toileting and ensuring adequate hemostasis. Patient was kept under observation for 2 hours and post-procedure vitals monitoring was done. Following parameters were included in analysis: patient characteristics, histopathological diagnosis and post biopsy bleeding.

Post biopsy bleeding was classified as per British Thoracic Society bronchoscopy guidelines and bleeding was managed as per the standard guidelines [8]:

No bleeding: Traces of blood with no need for continuous suctioning, Bleeding stops spontaneously.

Mild bleeding: Continued suctioning of blood from the airways, bleeding stops spontaneously.

Moderate bleeding: Intubation of the biopsied segment with the bronchoscope in wedge position. Use of adrenaline or cold saline to stop bleeding.

Severe bleeding: Placement of bronchial blocker or catheter, resuscitation, blood transfusion, admission to Critical Care Unit or death.

Statistical analysis

The collected data were transformed into variables, coded, and entered in Microsoft Excel. The data were analyzed and statistically evaluated using Statistical Package for Social Studies (SPSS) IBM manufacturer, Chicago, USA, Windows version 23.0. Quantitative data were expressed in Mean±SD (Standard deviation) while qualitative data were expressed in number and percentage.

Results

Among 200 patients enrolled in our study, majority were male (n=169; 84.5%). The age of the patients enrolled was between 18 to 92 years and mean age was 56.96±13.64 years. The size of the cryobiopsy specimen ranged between 5-13 mm with a mean size of 6.8±1.2 mm. A definitive diagnosis was established in 93% of cases (n=186). The most common diagnosis was squamous cell carcinoma (n=85; 42.5%) followed by adenocarcinoma (n=37; 18.5%), small cell lung cancer (n=27; 13.5%), non-small cell lung cancer (not otherwise specified, NOS) (n=15; 7.5%). Other diagnoses were tuberculosis (2.5%), carcinoid tumour (2%), benign epithelial polyp (1.5%), sarcoidosis (1%), undifferentiated carcinoma (1%) and one case of each of the following: pleomorphic sarcoma, mucormycosis, hamartoma, lymphoma, pleomorphic adenoma and leiomyoma. Fourteen samples (n=14) were reported as non-specific inflammation/ inconclusive/necrotic tumor/ suppurative inflammation/ inflammatory polypoidal hyperplasia which were considered non-diagnostic. The final histopathological diagnoses of the study participants are listed in Table 1.

No bleeding was observed in 32% patients (n=64). Bleeding was mild in 41% cases (n=82) and moderate bleeding requiring cold saline and epinephrine instillation occurred in 26% (n=52)

patients. In our study, clinically relevant and severe bleeding necessitating the use of a Fogarty catheter (through the working channel of flexible bronchoscope as endobronchial tamponade) was observed in two cases, accounting for 1% of the total cases. One patient required bronchoscopic endotracheal intubation and mechanical ventilation. Another patient required observation in ICU after cessation of bleeding (Table 2). Complications such as pneumothorax, pneumomediastinum, or mortality were not observed.

Discussion

Bronchoscopists often come across endobronchial lesions during bronchoscopy. The patient's clinical profile encompassing age, sex, smoking history, signs and symptoms, radiological findings, and the appearance of the lesion during bronchoscopy, provide valuable clues for establishing a probable diagnosis for the case. However, in many cases, achieving a definitive diagnosis often necessitates tissue sampling and subsequent histopathological examination. Flexible cryoprobe commonly used for airway tumor debulking and cryotherapy, has been found to be appropriate for obtaining biopsies from visible endobronchial lesions as it provides good quality, artifact free sample for histological and molecular analysis. Most common histopathological subtype in our study was squamous cell carcinoma (42.5%), as previously reported in numerous studies [5,9-12].

In our study, the mean size of the cryobiopsy samples was 6.8±1.2 mm. We obtained tissue samples maximum up to 13 mm in size, which was comparable to previous studies. Diagnostic yield in this study was 93%, which is higher than the FB yield reported in literature (65-91%) [5,6,9,13] and almost similar to the cryobiopsy yield in the studies done by Hetzel et al (95%), Aktas et al. (92%) and Schumann et al. (89.1%) [5,9,13]. FB demonstrates a sensitivity of approximately 74% in diagnosing a visible endobronchial mass [4,7]. Nevertheless, recent studies have that showed FB can also a yield around 85-91% [2]. However, it should be noted that this approach comes with an increase in cost and procedural time. In a study aimed to find the optimal number of cryobiopsies required in endobronchial tumor, it was observed that two cryobiopsies were optimal when diagnostic outcome and complication rates were taken into consideration [11]. Higher diagnostic yield in cryobiopsy is explained by both high quality and larger size of cryobiopsy samples. Also, cryobiopsy can establish final diagnosis in majority of the cases without need of additional procedures or repeated bronchoscopy. According to a recent literature review on cryobiopsy in lung cancer diagnosis, it highlighted that cryobiopsy is highly beneficial tool in diagnosing endobronchial tumors and also shortens the time to

cancer diagnosis [14]. Additionally, it excels in obtaining tangential samples from tumors that infiltrate the bronchial wall, which are more challenging to sample using conventional methods [15]. Cryobiopsy samples not only enhance the histopathological diagnosis in patients with lung cancer, but also provide a greater opportunity for comprehensive molecular characterization of the specimen [7]. In the current landscape of precision medicine-driven cancer therapy, this technique holds the potential to enhance the outcomes of lung cancer patients. Further mutational analysis was done in selective cancer patients in our study and in all such cases, specimen was sufficient in providing molecular testing results.

Bleeding is a common complication of cryobiopsy, but it is readily controlled bronchoscopically with the use of ice-cold saline, topical epinephrine instillation and/or endobronchial blockers placement as described in studies. There is significant variation in the definition of the severity of bleeding in different studies. A higher incidence of bleeding has been reported following cryobiopsy compared to FB in previous literature. Post-biopsy bleeding requiring cold saline and/or vasoconstrictor agent administration varies widely (3%-60%) in different studies [5,6,7,9]. Moderate bleeding requiring iced saline and diluted epinephrine occurred in 26% of cases in our study, which was higher than that reported in a recent study by Ahmed et al. (8.5%) [6] and lesser than that reported by Khan et al. (35%) [7]. All episodes of moderate bleeding in our study were controlled well within the bronchoscopy unit. Severe bleeding requiring interventions (argon plasma coagulation/endobronchial balloon placement or resuscitative measures, ICU admission) were reported nil to 18% in earlier studies [5-7,9]. Both patients of severe bleeding in our study had full recovery and were discharged within 2-5 days; thus, the overall complication rate was low.

A study performed in similar manner without using artificial airway or rigid bronchoscope by Ahmed et al, had better safety profile compared to our study. However, this can be attributed to smaller sample size of the study (n=47) and number of cryobiopsy sample taken (only one per patient) [6]. Pathology remains crucial for accurate diagnosis, sub-typing the tumors histologically, aiding treatment decisions, and being supported by IHC. To maximize tissue yield from biopsy procedures, cryobiopsy is preferred as it avoids tissue artifacts and provides larger samples. The cryo-flexible probe, guided by a flexible bronchoscope, allows endobronchial cryobiopsies of the lesions as long as the lesion is visible during bronchoscopic evaluation. The primary concerns associated with cryobiopsy for endobronchial lesions when utilizing only a flexible bronchoscope predominantly revolve around the potential for significant bleeding. Airway conduits can be used to improve the safety of this procedure

further. The use of a newly available sheathed cryoprobe may further enhance the safety of this procedure as bronchoscope will not have to be removed out of airways for sample retrieval, and bleeding (if occurs) can be quickly managed. Studies are required in this area.

Our study has some limitations, notably its retrospective design and single-center experience. Compared to FB, performing two cryobiopsies necessitated at least three bronchoscopic intubations, resulting in extended procedural time and increased discomfort. The procedure was not performed in cases with platelet counts less than 100.000/mm^3 and raised INR; all these factors limit its generalizability in all patients with endobronchial lesions. This study also excludes tracheal lesions due to their tendency to bleed and the requirement for a rigid bronchoscope.

Conclusions

Our study provides evidence that endobronchial cryobiopsy, when performed using a flexible bronchoscope, is a highly productive and safe procedure, characterized by an exceedingly low rate of serious adverse events. Samples obtained through cryobiopsy are well preserved and are large enough to provide histopathological, immunohistochemical and molecular testing results. In carefully selected patients, this technique can serve as an acceptable alternative to forceps biopsy, potentially expanding the pulmonologist's range of diagnostic options to obtain sufficient endobronchial samples for a definitive diagnosis.

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Abbreviations:

FB- Flexible Bronchoscopy

OPD- Outpatient Department

IPD- Inpatient Department FB- flexible bronchoscope

ICU- Intensive Care Unit

ECG- Electrocardiogram

IV-Intravenous

Figure 1: Cryobiopsy equipment (Erbe) (A) with 2.4mm biopsy probe (B)

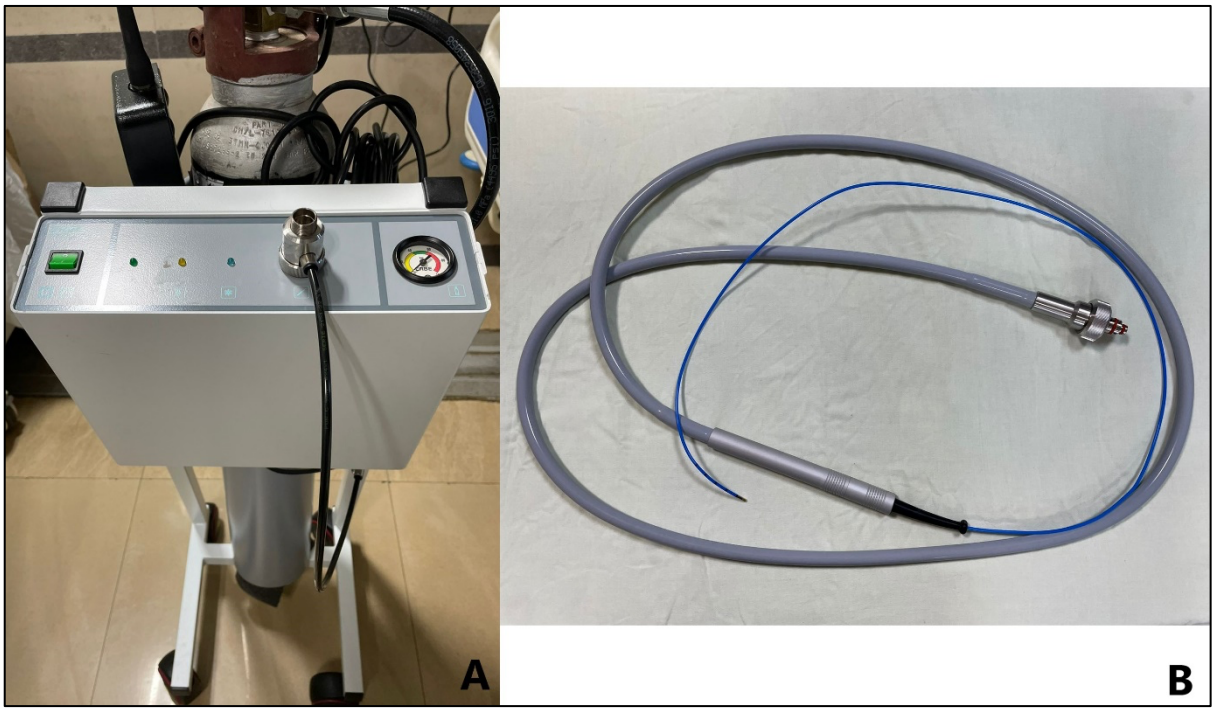

Figure 2: Image showing advancing the cryoprobe tip into endobronchial mass lesion

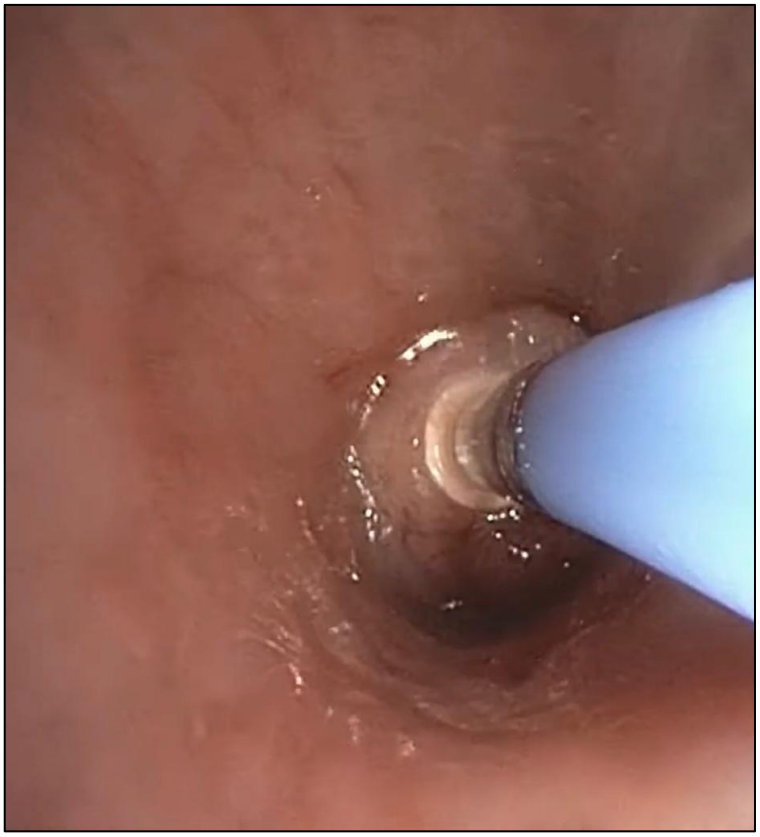

Table 1: Different histopathological diagnosis obtained in the study

Histopathological Diagnosis	Number (%)
Squamous cell carcinoma	85 (42.5)
Adenocarcinoma	37 (18.5)
Small cell lung cancer	27 (13.5)
Non-Small cell lung cancer (NOS)	15 (7.5)
Tuberculosis	5 (2.5)
Carcinoid	4 (2)
Benign Epithelial Polyp	3 (1.5)
Sarcoidosis	2 (1)
Undifferentiated carcinoma	2 (1)
Pleomorphic Sarcoma	1 (0.5)
Mucormycosis	1 (0.5)
Hamartoma	1 (0.5)
Lymphoma	1 (0.5)
Pleomorphic Adenoma	1 (0.5)
Leiomyoma	1 (0.5)
No Final diagnosis	14 (7)

Table 2: Bleeding observed in the study

Post biopsy bleeding	Number (%)
No bleeding	64 (32%)
Mild	82 (41%)
Moderate	52 (26%)
Severe	02 (1%)