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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 the 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 intensive care unit 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.

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 the evaluation and sampling of such lesions whenever deemed necessary for 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, 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 from endobronchial cryobiopsies performed in our tertiary care academic kindly add this after institute: "(National Institute of Tuberculosis and Respiratory Diseases, New Delhi)" 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 [intravenous (IV) midazolam and IV fentanyl] without the use of rigid bronchoscope or any artificial airway. Ethical clearance was obtained from the institutional ethical committee.

This study aimed to demonstrate the 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

The following patients were included in the study with the necessary inclusion and exclusion criteria after obtaining informed written consent.

Inclusion criteria

Outpatients and inpatients in whom endobronchial cryobiopsy was performed for visible endobronchial lesions (exophytic, nodular, ulcerative/plaque, mucosal infiltrative lesion) beyond the level of carina were included in the study. The second inclusion criterion was patients who were willing to provide signed informed consent.

Exclusion criteria

The exclusion criteria were as follows: i) severe hypoxemia and hemodynamic instability [systolic blood pressure (BP)≤90 mmHg and diastolic BP≤60 mmHg]; ii) platelet count <100.000/mm^3 and abnormal coagulation profile; iii) patients without an endobronchial tumor (endoscopically non-visible lesion); iv) patients with tracheal and carinal lesions; v) patients in whom anticoagulants could not be stopped due to underlying severe medical condition [liver disease, severe renal impairment (glomerular filtration rate ≤30 mL/kg/min), active bleeding and active pulmonary embolism].

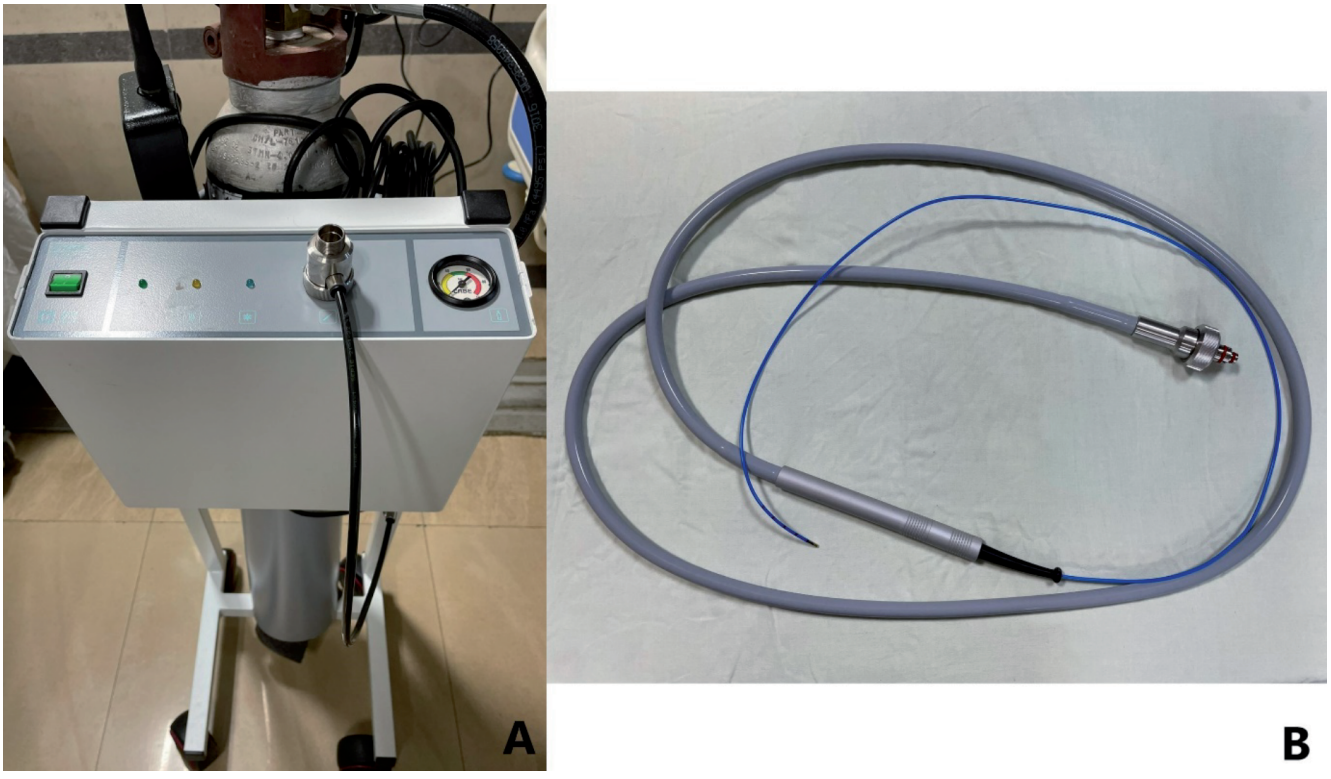

Figure 1. Cryobiopsy equipment (ERBOKRYO CA, ERBE, Tübingen, Germany) (A) with 2.4 mm biopsy probe (B).

Methodology

All patients underwent a comprehensive clinical examination, detailed medical history, and blood investigations, including complete blood profile, liver function test, renal function test, and radiological assessment before the procedure. Evaluation for coagulopathy and thrombocytopenia was routinely done before biopsy. For subjects on anticoagulants and aspirin, we performed the procedure after discontinuing the drug for 2-5 days (depending on the drug the 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 preprocedural consent was obtained from all the participants. Topical anesthesia for the bronchoscopy included three sprays of 10% lignocaine to the pharynx. IV midazolam and fentanyl were used to achieve the desired level of sedation. Low-flow supplemental oxygen was provided through a nasal cannula (low baseline oxygen saturation (SpO2 <90%), or >4% decrease from baseline or SpO2 <90% for >1 min). Continuous monitoring of oxygen saturation, heart rate, BP, and electrocardiogram was done throughout and for the next 2 hours after the procedure. After ensuring that the patient was sedated, a bite block was placed in the mouth. An adult therapeutic video bronchoscope (channel diameter: 2.8 mm, outer diameter: 6.0 mm, Olympus BF-1TQ170, Olympus Corporation, Tokyo, Japan,) 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. Before sampling, a bronchoscopic inspection of the bronchial tree was done. After visualization of the endobronchial lesion, 5-10 mL of cold saline was instilled in 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, Tübingen, 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. The cryoprobe was activated for 3-5 seconds. A flexible bronchoscope and cryoprobe with tissue samples attached to it were 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 it occurred) and to take another sample. Typically, two cryobiopsy samples were taken. If a noticeable degree (which requires 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 the 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. The patient was kept under observation for 2 hours, and post-procedure vitals monitoring was done. The following parameters were included in the analysis: patient characteristics, histopathological diagnosis, and post-biopsy bleeding.

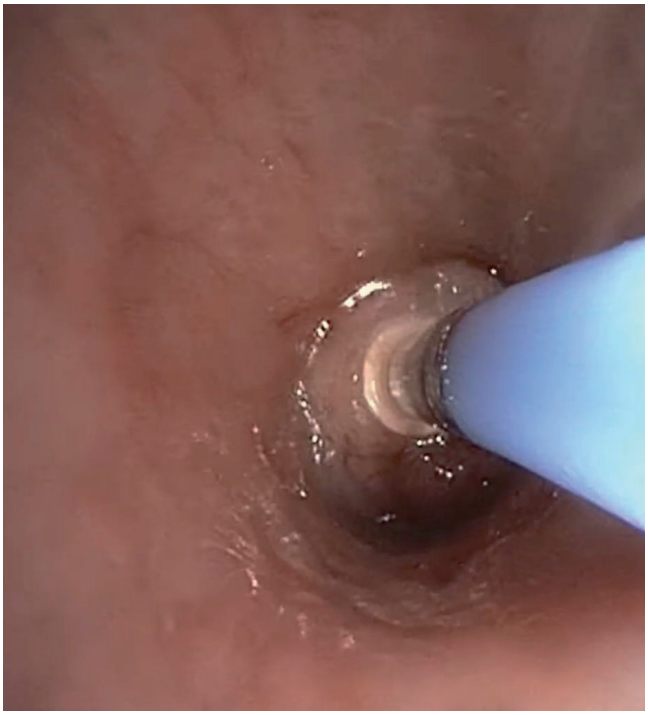

Figure 2. Image showing advancing the cryoprobe tip into the endobronchial mass lesion.

Post-biopsy bleeding was classified as per British Thoracic Society bronchoscopy guidelines and bleeding was managed as per the standard guidelines [8]: i) no bleeding – traces of blood with no need for continuous suctioning, bleeding stops spontaneously; ii) mild bleeding – continued suctioning of blood from the airways, bleeding stops spontaneously; iii) moderate bleeding – intubation of the biopsied segment with the bronchoscope in wedge position. Use of adrenaline or cold saline to stop bleeding; iv) 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 (Microsoft, Redmond, WA, USA). The data were analyzed and statistically evaluated using Statistical Package for Social Studies (SPSS) Windows version 23.0 (IBM, Chicago, USA). Quantitative data were expressed in mean ± standard deviation, while qualitative data were expressed in numbers and percentages.

Results

Among 200 patients enrolled in our study, the majority were male (n=169; 84.5%). The age of the patients enrolled was between 18 and 92 years, and the 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%), and non-small cell lung cancer (not otherwise specified) (n=15; 7.5%). Other diagnoses were tuberculosis (2.5%), carcinoid tumor (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 were reported as non-specific inflammation/inconclusive/necrotic tumor/suppurative inflammation/inflammatory polypoidal hyperplasia, which was considered non-diagnostic. The final histopathological diagnoses of the study participants are listed in Table 1.

No bleeding was observed in 32% of patients (n=64). Bleeding was mild in 41% of 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 the intensive care unit (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 provisional diagnosis for the case.

Table 1. Different histopathological diagnoses 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)

NOS, not otherwise specified.

Table 2. Bleeding observed in the study.

Post biopsy bleeding	Number (%)
No bleeding	64 (32)
Mild	82 (41)
Moderate	52 (26)
Severe	2 (1)

However, in many cases, achieving a definitive diagnosis often necessitates tissue sampling and subsequent histopathological examination. A 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 samples for histological and molecular analysis. The 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 of up to 13 mm in size, which was comparable to previous studies. The diagnostic yield in this study was 93%, which is higher than the FB yield reported in the 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 show that FB can also 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 at finding the optimal number of cryobiopsies required in endobronchial tumors, it was observed that two cryobiopsies were optimal when the 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 the final diagnosis in most cases without the need for additional procedures or repeated bronchoscopy. According to a recent literature review on cryobiopsy in lung cancer diagnosis, it highlighted that cryobiopsy is a 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, the 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 blocker 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%) and lesser than that reported by Khan *et al*. (35%) [6,7]. 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) was reported nil to 18% in earlier studies [5-7,9]. Both patients with 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 similarly without using an artificial airway

or rigid bronchoscope by Ahmed *et al*. had a better safety profile compared to our study. However, this can be attributed to the smaller sample size of the study (n=47) and the number of cryobiopsy samples taken (only one per patient) [6]. Pathology remains crucial for accurate diagnosis, sub-typing the tumors histologically, aiding treatment decisions, and being supported by immunohistochemistry. 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 if 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 the bronchoscope will not have to be removed from the airways for sample retrieval, and bleeding (if it 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 FB, potentially expanding the pulmonologist's range of diagnostic options to obtain sufficient endobronchial samples for a definitive diagnosis.

References

1. Mohan A, Madan K, Hadda V, et al. Guidelines for diagnostic flexible bronchoscopy in adults. Lung India July 2019;36:S37-S89.
2. Muthu V, Babu R, Sehgal IS, et al. Predictors of severe bleeding during endobronchial biopsy: experience of 537 cases. J Bronchol Interv Pulmonol 2019;26:273-9.
3. Rivera MP, Mehta AC, American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:131S-48.
4. Rivera MP, Detterbeck F, Mehta AC, et al. Diagnosis of lung cancer: the guidelines. Chest 2003;123:129S-36.
5. Hetzel J, Eberhardt R, Herth FJF, et al. Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicentre trial. Eur Respir J 2012;39:685-690.
6. Ehab A, Khairy ME, Abdelhamed AM, El-Dosouky MA. Cryobiopsy versus forceps biopsy in endobronchial lesions, diagnostic yield and safety. Adv Respir Med 2017;85:301-6.
7. Khan S, Cherian S, Panchal R, et al. P79 The utility of endobronchial cryobiopsy in the molecular diagnosis of lung cancer. Thorax 2018;73:A144.
8. Du Rand IA, Blaikley J, Booton R, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax 2013;68:i1-i44.
9. Schumann C, Hetzel J, Babiak AJ, et al. Cryoprobe biopsy increases the diagnostic yield in endobronchial tumor lesions. J Thorac Cardiovasc Surg 2010;140:417-21.
10. Rana S, Bhattacharyya D, Katoch CDS, et al. Clinical, radiological, and histopathological profile of patients with endobronchial lesions on fiber-optic bronchoscopy. J Assoc Chest Physs 2018;6 53.
11. Segmen F, Aktaş Z, Öztürk A, et al. How many samples would be optimal for endobronchial cryobiopsy? Surg Endosc 2017;31:1219-24.
12. Wang S, Ye Q, Tu J, Song Y. The location, histologic type, and stage of lung cancer are associated with bleeding during endobronchial biopsy. Cancer Manag Res 2018;10:1251-7.
13. Aktas Z, Gunay E, Hoca NT, et al. Endobronchial cryobiopsy or forceps biopsy for lung cancer diagnosis. Ann Thorac Med 2010;5:242-6.
14. Stastna N, Brat K, Heroutova M, Svoboda M, et al. Endobronchial cryobiopsy may shorten the time to cancer diagnosis: a retrospective study. ERJ Open Res 2023;9:00179-2023.
15. Simon M, Simon I, Tent PA, Todea DA, et al. Cryobiopsy in lung cancer diagnosis-a literature review. Medicina (Kaunas) 2021;57:393.