Original Article

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Internal Medicine Section

Comparison of Cryobiopsy and Forceps Biopsy in Suspected Lung Carcinoma Patients with Endobronchial Lesions: A Cross-sectional Study

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ABSTRACT

Introduction: Forceps Biopsy (FB) is usually used to obtain tissue in endobronchial lesions through a flexible bronchoscope. The mean diagnostic rate of bronchoscopic FB is 74% in central tumours. A limitation of FB is the small tissue size and the occurrence of crush artifacts. In contrast, Cryobiopsy (CB) provides larger samples without such artifacts, which are crucial for accurate histopathological diagnoses.

Aim: To compare the efficacy and safety of CB with FB in endobronchial mass lesions suspected of lung cancer.

Materials and Methods: A cross-sectional study was conducted on suspected endobronchial mass lesions with suspicion of malignancy from October 2015 to March 2017. About 35 patients fulfilling the inclusion criteria were enrolled, and five of these 35 patients were excluded as they were diagnosed with benign lesions. Among these 30 patients, a flexible biopsy was obtained first followed by CB using the same endobronchial cryobiopsy. Data were analysed in terms of tissue viability, mean tissue size, diagnostic yield, complications, and histological diagnosis. Parameters were compared using the Chi-square test (χ^2 test) and Fisher's exact test.

Results: The mean age of the study participants was 58.33±10.12 years. The mean±SD size (diameter) of tissue obtained by CB (0.73±0.47 cm) was higher than that of FB (0.23±0.08 cm) (p-value<0.001). The diagnostic yield obtained by CB was 96.7% compared to 70% in FB (p-value<0.005). Mild bleeding was seen in 86.7% of the CB group and in 60% of the FB group (p-value=0.019). None of the patients in the study experienced moderate or severe bleeding.

Conclusion: CB emerges as a safe and dependable method, offering superior diagnostic outcomes compared to conventional FB with its capability to obtain larger biopsy samples and good-quality tissue while minimal bleeding. CB stands as a viable alternative to FB.

Keywords: Diagnostic yield, Endobronchial cryobiopsy, Safety

INTRODUCTION

Lung cancer continues to rank second in terms of prevalence, with 1 in 10 (11.4%) diagnosed cancers, leading to 1 in 5 (18%) cancer deaths. The number of new cases and deaths from lung cancer is estimated at 2.2 million and 1.8 million, respectively, according to GLOBOCAN 2020. There is a two-fold higher incidence and mortality rate of lung cancer in men than in women [1]. Bronchoscopy remains the predominant method employed for diagnosing lung cancer and is pivotal in determining the stage of the disease. The yield of bronchoscopy is highest for endoscopically visible lesions, with a diagnostic yield ranging between 65-74% [2,3]. The major drawback of the FB technique is the relatively small amount of tissue obtained, with a diameter of approximately 2 mm [4]. Additionally, mechanical compression or crush artifacts from the instrument tip cause alterations to the tissue samples, which affect the quality of histological analysis. Furthermore, immunohistochemical staining can also be limited by the absence of vital tumour tissue [5,6].

Although the yield can be augmented by combining FB with several diagnostic techniques, including brush cytology, needle aspiration, and washing, it consumes more time, involves more anaesthesia complications, and comes at a cost [7]. To make a definite pathological diagnosis and detect target-specific genetic changes in the tumour tissue, larger samples are required, which are becoming increasingly important in lung cancer treatment [8]. CB is the biopsy tool of choice, providing a safe technique capable of obtaining large biopsy samples without causing any morphological alterations (crush artifacts) to the tissue samples, thereby reducing the need for additional sampling techniques or even the need for repeated bronchoscopies [6,8]. CB also provides larger samples that are crucial for specific histopathological diagnosis, as well as for immunohistochemical staining and mutational analysis in the tumour tissue [9]. The present study aimed to evaluate the effectiveness of CB and FB with flexible bronchoscopy for diagnosing endobronchial visible lesions. Also, to demonstrate the feasibility of endobronchial biopsies using the flexible cryoprobe and understand the advantages of CB over FB.

MATERIALS AND METHODS

The study was a time-bound comparative cross-sectional study conducted at the tertiary respiratory care centre (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India) from October 2015 to March 2017 after obtaining ethical approval from the Institutional Research and Ethical Committee (NITRD/PGEC/7277). In this study, patients meeting specific inclusion and exclusion criteria were enrolled following informed written consent.

Inclusion criteria: Individuals demonstrating clinicoradiological features indicative of visible exophytic endobronchial lesions beyond the carina level, and who were willing to provide signed informed consent were included in the study.

Exclusion criteria: Severe hypoxaemia and haemodynamic instability (with systolic blood pressure <90 mmHg and diastolic blood pressure <60 mmHg), platelet count <50,000 cells/mm3 and abnormal coagulation profile, pathological diagnosis of benign lesions and lesions in the trachea, and patients lacking

endobronchial tumours (without endoscopically visible lesions) were excluded from the study.

Sample size: The study's sample size was determined based on the observed yield from CB, approximately 90% [6], compared to 70% from FB [3], indicating a 20% variation between the two procedures. With an average expected yield of 90% from CB (P1) and 70% from FB (P2), and an absolute precision expected of 20% at a 95% confidence level.

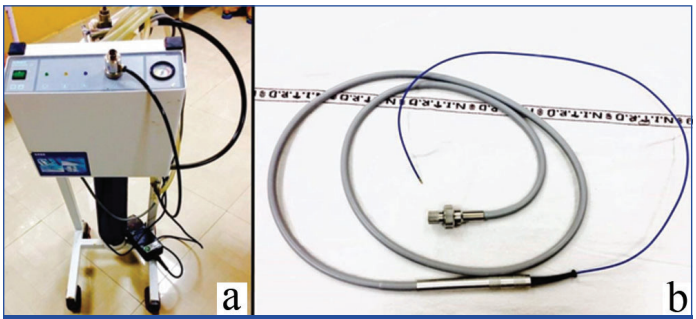
$$n=\frac{(1.96)^2[(0.90)(0.10)+(0.70)(0.30)]}{(0.20)^2}$$

$$n=28.81$$

The formula for sample size calculation yielded n=28.81, rounded up to 30 to facilitate the simultaneous performance of both FB and CB in all patients.

Study Procedure

In this study, all patients with suspected lung carcinoma with radiological features suggestive of endobronchial lesions were taken for bronchoscopy. All interventions were done with a fiberoptic flexible bronchoscope in the study. After local anaesthesia inhalation (2% xylocaine), midazolam (0.05 mg/kg for induction) and fentanyl (1 µg/kg for induction and 25 µg as top-up for maintenance) were used for sedation. A FB was obtained first followed by CB using the same flexible bronchoscope in all patients in the same sitting. The flexible fibreoptic bronchoscope was inserted through the oral mouth gag, and FB was performed using a reusable fenestrated forceps, with about 4-6 forceps biopsies taken. For CB procedures, a flexible cryoprobe was utilised. The CB equipment with the probe employed in the study is depicted in [Table/Fig-1]. The probe was positioned onto the endobronchial lesion, undergoing a freezing phase lasting three seconds followed by a cooling phase of two seconds. Subsequently, after a total of five seconds, the probe was withdrawn along with the bronchoscope, and the frozen biopsy sample was detached from the cryoprobe by immersing it in a saline solution. A maximum of two samples were taken via the cryoprobe. All obtained specimens were immediately fixed in buffered formalin and sent to the institutional pathologist for histopathological examination. The biopsy samples collected from both FB and CB were assigned random numbers to ensure that the pathologist remained unaware of the specific modality employed. All the procedures were conducted without any charges.



[Table/Fig-1]: Cryobiopsy (CB) equipment (Erbe-1) (a) with 2.4 mm biopsy probe (b).

Postbiopsy bleeding was classified according to the British Thoracic Society bronchoscopy guidelines, and bleeding was managed as per the standard guidelines [10]:

No bleeding: Blood traces requiring no continuous suctioning and spontaneously ceasing bleeding.

Mild bleeding: Continued aspiration of blood from the airways results in the cessation of bleeding without the need for external intervention.

Moderate bleeding: Insertion of the bronchoscope into the biopsied segment positioned in a wedge configuration. Application of adrenaline or cold saline to stop bleeding.

Severe bleeding: Placement of a bronchus blocker or catheter, administration of fibrin sealant, resuscitation measures, blood transfusion if necessary, admission to the critical care unit, or potential mortality.

The study documented the baseline characteristics of participants, which encompassed age, gender, smoking status, smoking index {Classified smokers as non severe (<300) and severe (≥300) [11]}, symptoms, Computed Tomography (CT) chest findings, and lesion location. Additionally, various parameters were derived from specimen analysis, such as gross features {lesion location, number of biopsies, and biopsy size measured with slide calipers (diameter)} and microscopic features (including lesion size and tissue viability). The interpretation of biopsy results, including the final diagnosis and the use of Immunohistochemistry (IHC) with markers such as p63, p40, pan-CK, CK-5/6, CD-56, synaptophysin, CK7, Napsin A, and TTF-1 for accurate diagnosis and diagnostic yield were also recorded. The viability of the tissue was assessed based on the morphological characteristics seen on the tissue sections stained. The effectiveness of both the procedures were assessed through diagnostic yield, while bleeding was used to evaluate their safety. The benchmark for definitively labelling cryotherapy as more effective was established by comparing it with biopsy results obtained through forceps.

STATISTICAL ANALYSIS

All data were expressed as numeric values (%). Quantitative data were presented as mean and standard deviation, while qualitative data were expressed as a percentage. Data normality was checked using the Kolmogorov-Smirnov test. In cases where the data were not normal, non parametric tests were used. Proportions were compared using the Chi-square test (χ^2 test) and Fisher's exact test. The level of statistical significance was set at p-value≤0.05.

RESULTS

A total of 35 patients were enrolled in the study. Five patients were diagnosed with benign lesions and were excluded from data analysis. Data from 30 patients were finally analysed among both groups in the study. The majority of the patients (93.4%) belonged to the age group of 41-70 years, with a mean age of 58.33±10.12 years. Among the enrolled participants, the majority were males 27 (90%) and smokers 27 (90%). Cough was the most common presenting symptom in 29 (96.7%) patients. The majority of patients in the study had an endobronchial lesion in the left main bronchus in 9 (30%), followed by the right main bronchus in 7 (23.4%). Characteristics of the study participants are illustrated in [Table/Fig-2].

Parameters	n (%), M±SD
Age (years)	58.33±10.12
Sex	
Male	27 (90)
Female	03 (10)
Smoking	
Smokers	27 (90)
Non smokers	03 (10)
Smoking index	
≥300	23 (85.2)
<300	4 (14.8)
Symptoms	
Cough	29 (96.7)
Weight loss	23 (76.7)
Breathlessness	19 (63.3)
Haemoptysis	14 (46.6)
Chest pain	13 (43.3)
Fever	09 (30)
CT chest findings	
Mass lesion	05 (16.7)

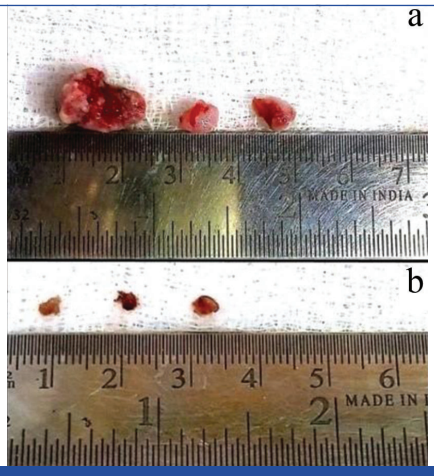
Mass with collapse	12 (40)
Collapse with effusion	01 (3.3)
Collapse	12 (40)
Endobronchial mass location	
Right main bronchus	07 (23.4)
Right upper lobe bronchus	04 (13.3)
Right middle lobe bronchus	02 (6.7)
Left main bronchus	09 (30)
Left upper lobe bronchus	06 (20)
Left lower lobe bronchus	02 (6.7)

[Table/Fig-2]: Baseline characteristics of the study participants.

Out of 30 patients, squamous cell carcinoma was the most common histopathological diagnosis, seen in 12 (40%) by forceps and in 18 (60%) by the CB technique, followed by Small Cell Carcinoma (SCLC) in both techniques. FB could not diagnose malignancy in 9 (30%) of the study participants, while the cryoprobe failed to diagnose malignancy in 1 (3.3%) of the study participants. The diagnosis of the study participants is shown in [Table/Fig-3]. A comparison in the size of the sample obtained by FB and CB is shown in [Table/Fig-4].

Diagnosis	Forceps biopsy n (%)	Cryobiopsy n (%)
Adenocarcinoma	02 (6.7)	02 (6.7)
Squamous cell carcinoma	12 (40)	18 (60)
Small Cell Carcinoma (SCLC)	04 (13.4)	04 (13.4)
Large cell carcinoma	01 (3.3)	01 (3.3)
Poorly differentiated malignant lesion	0	01 (3.3)
Atypical/malignant lesion	02 (6.7)	03 (10)
Undiagnosed	09 (30)	01 (3.3)

[Table/Fig-3]: Type of malignancies diagnosed in the study.



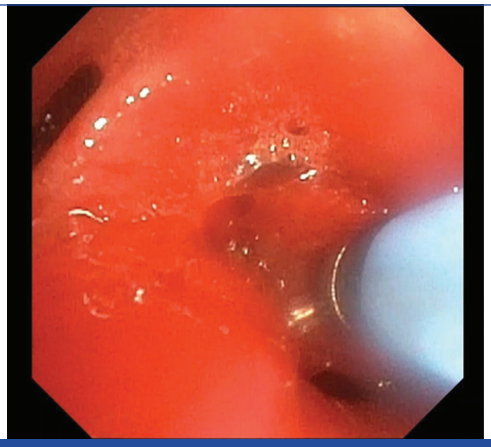
[Table/Fig-4]: Difference in sizes of the samples obtained from (a) Cryobiopsy (CB) and (b) Forceps Biopsy (FB).

In the present study, non viable samples were more common in FB 8 (26.7%) compared to CB 2 (6.7%) (p-value=0.037). The mean size of tissue (diameter) obtained by CB (0.73 cm ±0.47) was higher than by FB (0.23 cm ±0.0809) (p-value<0.0001), and the diagnostic yield obtained by CB was 96.7% compared to 70% in FB (p-value=0.005). IHC was performed on 24 (80%) samples in the CB group and 17 (56.7%) in the forceps method, thus increasing the diagnosis (p-value=0.052). In the study, mild bleeding was seen in 26 (86.7%) by CB technique and 18 (60%) by FB (p-value=0.019). None of the patients in the study had moderate or severe bleeding. No significant difference was seen between FB and CB in diagnosing NSCLC vs SCLC and squamous cell carcinoma vs non squamous cell carcinoma.

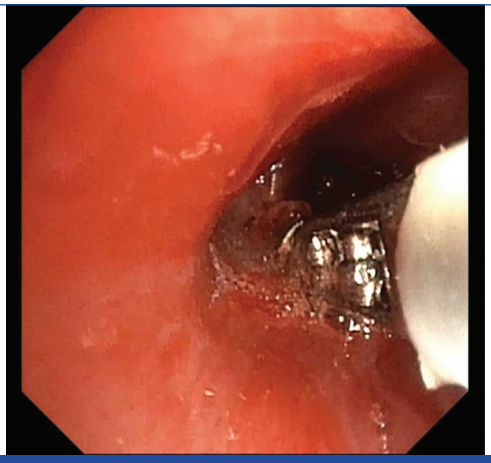
Univariate analysis of the parameters of FB compared with CB is shown in [Table/Fig-5]. The image displaying the acquisition of a biopsy of an endobronchial mass using CB is depicted in [Table/Fig-6], while forceps are shown in [Table/Fig-7].

Parameters	Subgroup	Forceps Biopsy (FB) (n=30) (%)	Cryobiopsy (n=30) (%)	Univariate analysis p-value
Viability	Yes	22 (73.3)	28 (93.3)	**0.037**
	No	8 (26.7)	2 (6.7)	
Diameter of tissue M±SD (cm)		0.23±0.08	0.73±0.47	**<0.001**
Diagnosis	Yes	21 (70)	29 (96.6)	**0.005**
	No	9 (30)	1 (3.4)	
Immunohistochemistry (IHC) reported	Yes	17 (56.7)	24 (80)	0.052
	No	13 (43.3)	6 (20)	
Bleeding	Yes	18 (60)	26 (86.7)	**0.019**
	No	12 (40)	4 (13.3)	

[Table/Fig-5]: Comparison of parameters in Forceps Biopsy (FB) with Cryobiopsy (CB).
The chi-square test and Fisher's-exact test (2-tail) were used for analysis



[Table/Fig-6]: Obtaining a biopsy specimen from the endobronchial lesion situated in the left lower lobe employing a cryoprobe.



[Table/Fig-7]: Acquiring a biopsy sample from the endobronchial lesion located in the left lower lobe utilising forceps.

DISCUSSION

Biopsies from bronchoscopically visible lesions are traditionally extracted using biopsy forceps for pathological diagnosis and molecular analysis. The sensitivity of FB in diagnosing a visible endobronchial mass is approximately 74%; however, the yield can be increased to approximately 89% by combining cytologic methods such as brushing, washing, and needle aspiration, but it is accompanied by an increase in cost and procedural time [3,6,7]. Additionally, several factors also influence its diagnostic yield, including the size, location, pathology, visibility, and, most importantly, the size and quality of the samples obtained [5,12]. The purpose of this study was to compare and assess the efficacy of CB and FB in visible endobronchial mass lesions suspected of lung carcinoma.

Tissue viability: The viability of the tissue was assessed based on the morphological characteristics seen on the tissue sections stained. In present study, the viability of the tissue obtained by CB was 93.3%, which was higher compared to FB (73.3%). The CB technique proved advantageous in obtaining larger tissue samples with reduced crush artifacts compared to traditional methods. Forceps are known to exhibit more crushing and architectural loss compared to CB, resulting in the CB sample being larger in diameter with preserved architecture [13,14]. The samples obtained exhibited excellent quantity and quality, comparable to those from endobronchial tumours [9,14]. This enhancement could potentially lead to pathologists achieving diagnoses more frequently than previously documented.

Tissue size: The mean size of the tissue obtained by CB (0.73±0.47 cm) was higher than that of FB (0.23±0.08 cm). There was a significant difference between the size of the biopsy specimen obtained (p-value<0.001). Aktas Z et al., also had similar findings compared to present study, where the median size obtained by CB was 0.8 cm and 0.2 cm in FB [5]. Similarly, Jabbardarjani H et al., also found a higher mean size in CB (1.6 cm) compared to FB (0.5 cm) [15]. Mohamed ASh et al., in their study, found that the median size by FB (0.6 cm) was lower compared to CB (1.7 cm) [16]. This clearly denotes that CB provides a larger sample to perform both histopathology and IHC in a single sample.

Diagnostic yield: The diagnostic yield obtained in the study by FB was 70% compared to CB, which was 96.7%, and it was statistically significant (p-value<0.005). Similar findings were observed in a study by Mohamed ASh et al., where the diagnostic yield was significantly higher with CB (95%) compared to FB (80%) [16]. Hetzel J et al., reported that a definitive diagnosis was achieved in 85.1% of the patients randomised to conventional FB and 95% of patients who underwent CB [8]. Present study was also comparable to other studies conducted by Aktas Z et al., Schumann C et al., Rubio ER et al., Ehab A et al., Jabari H et al., Nasu S et al., and Moghazy MA et al., showing that CB has a higher diagnostic yield compared to FB [5-7,17-20]. CB not only improves tissue diagnosis, but it also increases the chances of detecting mutations in the tissue. This was proved by a study done by Haentschel M et al., who showed an increased detection rate of Epidermal Growth Factor Receptor (EGFR) mutations compared with FB in central tumours (19.6% versus 6.5%, p-value<0.05) [21]. Present results were in accordance with other studies that demonstrated the cryo-technique provides not only larger but also qualitatively better specimens. Less mechanical damage in the cryo-method might reflect tissue architecture preservation as the cryoprobe only needs to touch the tumour lesion gently.

Histology: Squamous cell carcinoma was the most commonly diagnosed lung carcinoma in present study, seen in 40% of patients by FB and in 60% of patients by CB. Similar findings were observed in studies conducted by Schumann C et al., where squamous cell carcinoma (57.3%) was the most common lung cancer diagnosed among patients undergoing biopsy [6]. Aktas Z et al., in his study, also found that squamous cell carcinoma (61%) was the most common histological diagnosis [5]. In present study, FB could not diagnose malignancy in 30% of patients, while 3.3% (n=1) of patients were not diagnosed by the cryoprobe. No significant difference was seen between FB and CB in diagnosing NSCLC vs SCLC and squamous cell carcinoma vs non squamous cell carcinoma. The single undiagnosed case in CB underwent rigid bronchoscopy, leading to the identification of carcinosarcoma through IHC markers consisting of pan-cytokeratin, p63, p40, desmin, myo-D1, and vimentin. Immunohistochemical analysis was feasible and conducted more on samples obtained through CB (80%) compared to FB (56.7%). This observation supports the notion that CB yields a greater amount of tissue compared to FB, as seen in other studies [7,9,22]. Notably, the freezing and thawing process did not adversely affect tissue viability, including immunohistochemical staining, as reported previously [23,24]. Increased specimen size, and consequently larger volumes, have demonstrated a correlation with enhanced diagnostic yield. With cancer treatment evolving towards greater individualisation, larger tissue samples could prove invaluable in studies involving IHC analysis, mutational analysis, and genetic profiling.

Complications: In present study, simultaneous clotting was achieved in 40% of cases in the FB group and in 13.3% in the CB group. Mild bleeding was observed in 86.7% and 60% of patients who underwent CB and FB, respectively. The difference was significant (p-value=0.019). More bleeding was seen in the current study due to the small sample size and repeated CB followed by FB from the same site. None of the patients in the study experienced moderate or severe bleeding, and there were no deaths or other complications. In a multicentre trial conducted by Hetzel J et al., 51.5% of patients had mild bleeding in the FB group and 61.8% had mild bleeding in the CB group, requiring no intervention [8]. Schumann C et al., in their study, noted that mild bleeding complications occurred in 3.7% of cases [6]. Aktas Z et al., in their study, found that interventions for haemorrhage, including cold water application, Adrenaline (ADR), and Argon Plasma Coagulation (APC) application, were performed in 34.1% of patients in the FB group and 36.6% in the CB group [5]. Segmen F et al., in their study, also noted that the majority of patients undergoing CB had only grade 0 or 1 bleeding, requiring minimal intervention [25]. A study performed by Mohamed ASh et al., reported no cases of moderate to severe bleeding [16]. Similarly, in present study, the majority of patients 26 (86.7%) experienced mild bleeding in the CB group, which was managed with cold saline application as all patients were immunocompetent with no coagulopathy, thrombocytopenia, or uraemia.

Due to the emergence of numerous novel targeted therapeutic approaches, alongside advancements in histological characterisation and molecular classification, lung carcinoma has garnered significant attention in recent times. Pathology remains a key component in accurately histological subtyping of tumours, supported by IHC, and also in treatment decision-making. The need for these additional diagnostic steps emphasises the importance of maximising tissue yield from biopsy procedures. CB enhances diagnostic accuracy by minimising tissue artifacts and obtaining larger samples. The utilisation of a cryo-flexible probe, guided by a flexible bronchoscope, facilitates endobronchial cryobiopsies in both central and more distal airways, contingent upon lesion visibility during bronchoscopic assessment. However, a notable drawback of CB is that the cryoprobe cannot be extracted through the bronchoscope's working channel alongside the specimen. Consequently, the entire bronchoscope, along with the cryoprobe and specimen, must be removed en bloc, necessitating swift reinsertion of the bronchoscope postbiopsy [7]. A superior diagnostic yield can be obtained by performing CB, which is proven in the study despite a smaller sample size.

Limitation(s)

Present study had certain constraints, particularly due to its limited sample size and reliance on data from a single centre. Patients with low platelet counts and elevated International Normalised Ratio (INR) were excluded from the procedure, which restricts the generalisability of present study findings to all patients with endobronchial lesions. Furthermore, this study excludes tracheal lesions due to their propensity to cause bleeding.

CONCLUSION(S)

This study reveals that CB offers distinct advantages over FB in terms of sample size, diagnostic yield, and histopathological quality. Present study findings suggest that CB may provide more accurate and comprehensive tissue samples, facilitating a more precise

diagnosis of lung carcinoma in patients with endobronchial lesions. Additionally, the study underscores the safety profile of CB, with comparable complication rates to FB. These results advocate for the consideration of CB as a preferred diagnostic technique in patients with endobronchial lesions, potentially improving clinical outcomes and treatment decisions.

Author contribution: VG, VV, JKS: Concepts; VG, VV, PS, JKS, VYA: Definition of intellectual content; VG, VV, JKS, KS, SA: Literature research and data analysis; VG, VV, JKS, VYA, SA: Manuscript preparation; VG, VV, PS, JKS, VYA, KS, SA: Manuscript editing; Manuscript review and final approval: All author.

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