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(Review Article)

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Diagnostic and therapeutic applications of Bronchoscopic cryotechniques in lung neoplasms: A literature review

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Abstract

Bronchoscopic cryotechniques have been used since the mid-20th century, initially for therapeutic purposes. Subsequent modifications in the technology led to the emergence of a new biopsy method, which became part of the diagnostic process of various lung diseases. Transbronchial cryobiopsy is widely used for the diagnosis of patients with diffuse parenchymal lung diseases. Due to the lower risk of complications, a shorter hospital stay, and reduced costs, it is a reasonable alternative to surgical lung biopsy. The role of cryobiopsy is also increasing in patients with central and peripheral lung tumors, although there are still significant variations in technical protocols between different centers.

Keywords: **L**ung neoplasms; Cryotherapy; Cryobiopsy; Transbronchial cryobiopsy

1. Introduction

The clinical presentation of airway stenosis due to malignant lesions correlates with the degree of obstruction and its location. Symptoms range from mild dyspnea, cough, and hemoptysis to stridor and life-threatening respiratory failure [1,2]

Bronchoscopic techniques used in malignant central airway obstruction to relieve symptoms and improve quality of life include laser and argon plasma coagulation [3,4], electrocautery [5], photodynamic therapy [6], endobronchial brachytherapy [7], cryotherapy [8], mechanical debulking [9], stenting [10]. The choice depends on factors such as availability, operator experience, the need for immediate effect, and the type of lesion (endoluminal, extraluminal, causing extrinsic compression or mixed) [11].

In 1968, a rigid cryoprobe was used for the first time to treat an endobronchial tumor [12]. Subsequently, with the development of flexible cryoprobes, the application of bronchoscopic cryotechniques increased. To date, endoscopic spray cryotherapy systems are also available [13].

Cryoablation was the first cryotechnique used [14,15]. It is based on the Joule–Thomson principle, where a liquefied gas under pressure expands into a gaseous form, leading to a decrease in temperature. Stopping the flow and reducing the pressure is followed by the release of heat and thawing [13,16]. Repeated cycles of rapid freezing and slow thawing cause cellular and vascular damage, with the end result being the destruction of the target area [12,17]. After several days, subsequent bronchoscopic procedures are necessary to remove necrotic tissue [17,18].

Cryorecanalization is a newer technique that uses cryoadhesion for therapeutic purposes [19-21]. The formation of ice crystals upon freezing of the fluid between the tip of the probe and the target tissue, as well as the fluid within the tissue itself, results in the adhesion of the two surfaces [21]. While still frozen, the cryoprobe is withdrawn along with the

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bronchoscope. This approach allows immediate treatment of the endobronchial lesion and provides faster results compared to the delayed response seen with cryoablation. This makes cryorecanalisation a suitable technique for patients with acute symptoms due to airway obstruction [19]. In addition, biopsy samples with well-preserved cellular structures and tissue architecture can be obtained for subsequent pathoanatomical studies [22-24].

2. Cryorecanalization

Among the advantages of cryorecanalization over other bronchoscopic techniques are lower costs and a low risk of airway perforation due to the cryoresistance of cartilage tissue [19,25]. In addition, the procedure can be performed in an environment with a high oxygen fraction, unlike laser ablation for example [19,25].

Hetzel et al. [19] were the first to evaluate the effectiveness of cryorecanalization in patients with exophytic endobronchial tumors and clinically significant airway stenosis. A cryoprobe with greater freezing power and stability against traction was used compared to the cryoablation probe. All procedures in the study were performed using a flexible bronchoscope, with the duration of each ranging from 9 to 81 minutes (mean 41 ± 16 minutes). According to the investigators, rigid bronchoscopy was not necessary but should be available to manage potential complications.

Partial or complete success was achieved in 83% of cases regardless of tumor type or the location of the airway obstruction (trachea, main or lobar bronchi). In the remaining 17% (10 patients), the stenosis was too extensive, preventing access to the distal respiratory tract, an important predictor of procedural success. To reduce the likelihood of unsuccessful interventions, the authors recommend careful patient selection and pre-procedural assessment of the tracheobronchial tree using imaging techniques such as virtual bronchoscopy and bronchography.

A subsequent study by the same group of investigators [20] reported successful cryorecanalization in 205 of 223 patients (91.1%). According to the authors, increased operator experience and refinement of technique were possible reasons for the higher success rate compared to previous results. In most cases, a flexible bronchoscope and endotracheal tube were utilized (n=194; 86.2%).

Subsequent studies in which cryorecanalization was used reported success rates ranging from 72.5% to 95% [25-27]. Several factors influencing the effectiveness of the technique have been analyzed, such as lesion localization in the central airways [25], the absence of distal atelectasis [20,25,26], the duration of the obstruction [26], and the use of additional methods such as stenting and balloon dilation in cases of mixed lesions [25].

In a study by Ng B et al. [28], most procedures were performed in an outpatient setting (49/54 procedures). An improvement in respiratory function following the procedure (mean increase in FEV1 by 0.28L) and a low bleeding rate (observed in two patients) were reported. There was no significant difference in performance status before and after the intervention. However, the results of another study [29] demonstrated an improvement in performance status in the majority of patients (49/67 patients), enabling subsequent chemotherapy. In addition, patients who received both chemotherapy and cryotherapy had a better survival compared to those who underwent cryotherapy alone.

According to studies published to date, the most frequently observed complications of cryorecanalization are mild and moderate bleeding, with severe and life-threatening events being rare [19,20,25]. Schumann et al. [20] reported an overall bleeding rate of 12%, with mild bleeding in 4% and moderate bleeding in 8% of patients. Additionally, one case of pneumomediastinum was observed in a patient with a tracheal cystadenoma.

In the study by Inaty et al. [25], respiratory failure requiring invasive mechanical ventilation occurred in seven patients, while two patients needed noninvasive ventilation. Furthermore, one patient had a mucosal wall defect following the procedure, without progression to pneumomediastinum or pneumothorax.

A retrospective study of 208 patients conducted in Seoul [27] analyzed the risk factors for bleeding during bronchoscopic cryorecanalization. According to the results, diabetes mellitus (associated with persistent vascular damage and inflammation), respiratory failure before the procedure (suggesting higher-grade stenosis and the need for a more invasive intervention), and the absence of distal atelectasis (leading to hypoxic vasoconstriction) were associated with an increased risk of moderate and severe bleeding events. In contrast to previous reports, there was no significant relationship with the histological variant of the tumor. In one patient with obstruction of both main bronchi due to metastases from renal cell carcinoma, a fatal outcome occurred due to severe bleeding and respiratory failure. In addition, the data suggest that even in more extensive airway involvement and the presence of distal atelectasis, cryorecanalization can be successful. However, multivariate logistic regression analysis did not show a statistically significant association, and further studies are needed.

3. Cryobiopsy

Cryobiopsy enables the acquisition of larger specimens with fewer artifacts caused by mechanical damage compared to conventional forceps biopsy (Figure 1 and 2) [22-24]. In this way, tissue architecture and cellular structures are preserved, allowing for more accurate histological analysis [30-32].

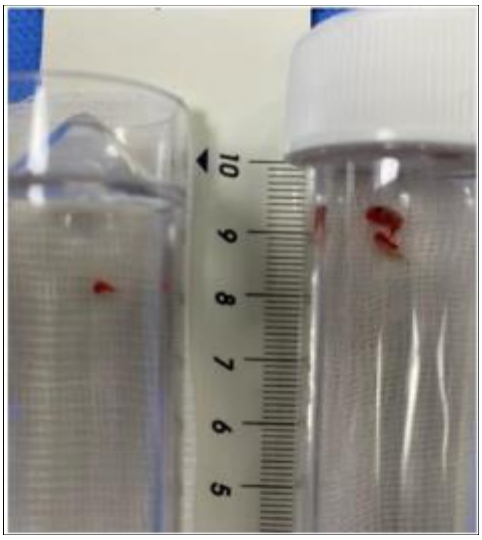

Figure 1 Difference in size between forceps biopsy and cryobiopsy

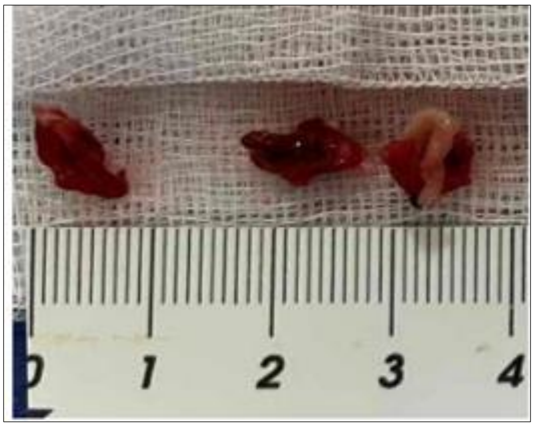

Figure 2 Cryobiopsy samples

3.1. Central pulmonary lesions

Fiberoptic bronchoscopy with forceps biopsy is the gold standard for the diagnosis of endobronchial lesions [33]. The diagnostic yield depends on several factors, including the type of lesion [34], the number of samples obtained [34-36], and the use of additional techniques such as brush biopsy, bronchoalveolar lavage, and endobronchial needle aspiration biopsy [37,38].

Unlike forceps, the cryoprobe can be positioned both perpendicularly and tangentially to the target area, allowing concentric expansion of the freezing zone and sample acquisition from the depth of the lesion (3) [19,21]. This is the reason for the reported higher diagnostic value of cryobiopsy not only in exophytic endobronchial lesions but also in those with mucosal and submucosal infiltration [19].

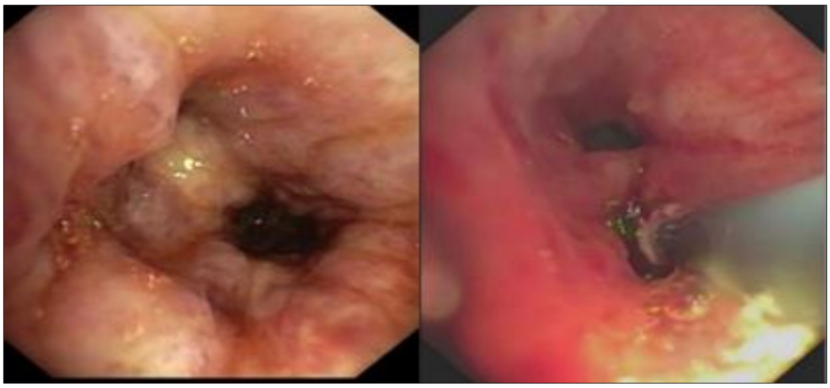

Figure 3 Cryoprobe can be positioned tangentially to the target area

Fewer cryobiopsies are required for histological diagnosis and subsequent genetic and immunohistochemical analysis [39-41]. According to a prospective study [42], two cryobiopsies are the optimal number for making a definitive diagnosis and at the same time for minimal risk of complications. In comparison, according to the recommendations, at least five forceps biopsies are required for visible endobronchial formations in order to achieve maximum diagnostic results [43].

Time to diagnosis is a key factor influencing therapeutic outcomes and survival. In the absence of histological verification of the imaging findings, repeat bronchoscopy or additional invasive procedures are required, which are associated with increased costs, higher risk of complications, and delays in diagnosis. A Czech study [44] found that, in patients with central lung neoplasms, cryobiopsy shortens the time to diagnosis compared to conventional forceps biopsy. The proportion of patients requiring a second or third procedure to establish a diagnosis was lower in the cryobiopsy group (2% vs. 9%).

3.2. Peripheral pulmonary lesions

Transbronchial cryobiopsy is widely used for diagnosing patients with diffuse parenchymal lung diseases [45,46]. With its advantages in terms of shorter hospital stay, lower costs, and lower risk of complications, it may be an alternative to surgical biopsy in selected patients with peripheral lung neoplasms [47,48]. Various factors that may influence the diagnostic yield have been analyzed, such as the size and location of the lesions [49-51], fluoroscopic visibility [50], use of radial probe endobronchial ultrasound (RP-EBUS) with or without a guide sheath [49,52,53], orientation of the lesions to the ultrasound probe [49,54], presence of a bronchus sign [41,50,55], probe size [49,55,56], and operator experience [41,47].

One of the limitations of cryobiopsy is the difficulty in accessing certain lung regions, particularly the upper lobes, due to the rigidity of the cryoprobe [50,57]. In an attempt to overcome this limitations, newer disposable cryoprobes with smaller outer diameters and enhanced flexibility have been developed [49,55,56]. In addition, the 1.1 mm diameter cryoprobe can be removed along with the biopsy tissue in certain conditions (such as using an optimal activation duration and a bronchoscope with a sufficiently large working channel) [54]. In this way, the bronchoscope remains in the airway throughout the procedure, ensuring better control. Any bleeding can be promptly assessed, and hemostasis methods can be applied.

Radial probe endobronchial ultrasound (RP-EBUS) is a guided imaging technique that can also be utilized for transbronchial cryobiopsy of peripheral lesions [51,53,54]. Due to its ability to perform lateral biopsies, the cryotechnique enhances diagnostic yield in eccentrically and adjacently oriented RP-EBUS lesions. [54].

3.3. Complications

According to the available studies, the most common complications associated with cryobiopsy of lung lesions are mild to moderate bleeding [19,20,39,40]. Various factors that may influence the incidence of bleeding have been investigated. In a study of patients with endobronchial tumors [42], a higher risk was reported when more than three cryobiopsies were taken. The use of radial probe endobronchial ultrasound (RP-EBUS) allows for the visualization of large blood vessels, potentially minimizing the risk of hemorrhagic complications [58]. Some investigators use an endobronchial blocker [57] or a two-bronchoscope technique [59] during transbronchial cryobiopsy to further reduce the bleeding rate.

4. Conclusion

Bronchoscopic cryotechniques play a significant role in both the diagnostic and therapeutic management of pulmonary neoplasms. Cryobiopsy provides high-quality specimens with well-preserved cellular structures and tissue architecture for more precise pathoanatomical studies. Among the key advantages of cryorecanalization are its relatively low cost, minimal risk of airway perforation, and the ability to perform the procedure in environments with high oxygen concentrations. Furthermore, the incidence of severe and life-threatening complications associated with these procedures is reported to be low.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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