Brief Overview About Cryobiopsy Versus Conventional Forceps Biopsy in Endobronchial Tumors

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Abstract

Background: Conventional forceps biopsy is associated with smaller sample size and more crush artifacts. While , Cryobiopsy has a superior diagnostic yield due to its ability to obtain larger-sized biopsies with less crush artifacts in comparison to forceps biopsy. This technique is safe, with no radiation risk, no danger of electrical accidents, and a little risk of bleeding.

Keywords: Cryobiopsy , Forceps biopsy , Endobronchial tumors

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Introduction

Invasive procedures such as brochoscopic biopsy, bronchial washing, and bronchial brushing are broadly used in the diagnosis of lung cancers.[1]

The cryotechniques, such as cryobiopsy, cryotherapy and cryorecanalization are modern methods used for the diagnosis and treatment of pulmonary diseases. Typically, the equipment consists of three main components: a console, the cryogen and cryoprobe. The details provided by the console are the value of cryopressure, the temperature at the tip of the probe and the duration of application. [2]

The cryogens used to achieve temperatures as low as −70 °C to −89 °C, and even −196 °C, are carbon dioxide or nitrous oxide. These low temperatures can be reached in seconds. The Joule–Thompson effect stands at the center of this technology, in which a compressed gas exists with a high flow and expands quickly, creating low temperatures that lead to the adhesion of the surrounding tissue to the cryoprobe.[3]

The tissue sample is then removed during the freeze-thaw cycle. There are different cryoprobes available, rigid, semi-rigid or flexible, with multiple diameters of the tip of 1.9, 2.4 or 5.5 mm and a length between 50 cm and 90 cm. [4]

The disadvantage of removing the cryoprobe en bloc with the bronchoscope has been overcome by the introduction of the disposable cryoprobes with a size of 1.1mm, which can be removed through the working channel of the bronchoscope.[5]

The disposable cryoprobes also come in sizes of 1.7 and 2.4 mm and represent a viable option, overcoming the potential loss of cooling performance and the risk of cross-contamination that comes with the re-usable cryoprobes.[6]

The indications of cryobiopsy are:

- Biopsy of malignant endobronchial growth tumors.[7]
- Tangential biopsy of malignant infiltrating tumors that are hard to sample using conventional forceps biopsy.[8]
- Biopsy of benign tumors.[9]
- Transbronchial biopsy in diffuse interstitial lung diseases and peripheral lung nodules.[10]

Internationally, lung cancer remains the principal cause of cancer-related deaths in both men and women. The incidence and mortality of this disease is closely related to cigarette smoking patterns. Among the reasons for the high mortality rates are unequal access to healthcare and sociocultural barriers that can cause delayed diagnosis and treatment. [11]

Lung cancer is classified into two main groups, non-small cell (NSCLC) and small cell type, with two distinct managements. Adenocarcinoma is currently the most frequent histologic subtype and the incidence increases in parallel with the incidence of lung cancer in women. [13][12]

Squamous cell lung cancer represents the subsequent most common subtype, histologically characterized by squamous pearl formation, intercellular bridging and keratin production. Small cell lung cancer is known for a more aggressive clinical course with extensive metastases and paraneoplastic syndromes. [14]

With the emergence of precision medicine, testing for molecular markers such as epidermal growth factor receptor (EGFR) insertions and deletions, Kirsten rat sarcoma (KRAS) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements has become mandatory. [13][12]

In advanced stages of non-small cell lung cancer, EGFR and ALK mutations predict a better prognosis and sensitivity to target therapy. Immunotherapy have revolutionized the management of NSCLC and testing for programmed death-ligand 1 (PD-L1) in these patients is highly recommended.[15]

In order to improve the prognosis of lung cancer patients, a complete characterization of the tumor needs to performed, with the determination of all the molecular alterations that can be targeted by novel therapies. Therefore, using a biopsy method that provides safe and adequate lung tissue sampling, without morphological alterations, such as cryobiopsy, could provide a better choice for these patients. [16]

At present, bronchoscopy is the gold-standard in diagnosing endobronchial tumors. It allows macroscopic tumor assessment and sample collection by endobronchial biopsy, lavage or bronchial brushing. Although the biopsy is collected under direct visualization, sometimes the diagnosis cannot be confirmed and the bronchoscopy needs to be repeated. [17]

Among the disadvantages of forceps biopsy are the small sample sizes and the crush artefacts that influence the quality of the histopathological analysis. The traditional approach of endobronchial lesions by flexible bronchoscopy with conventional forceps biopsy has a diagnostic yield of 72–88%. When associating forceps biopsy with brushing, lavage and needle aspiration, the diagnostic yield increases. A correlation has been made between the diagnostic yield and the size of the biopsy sample.[18]

Cryobiopsy could have a decisive role in improving the diagnostic of lung cancer, by providing larger and better-preserved samples for both endobronchial and peripheral tumors. The number of molecular markers that need to be determined from the biopsy sample of lung cancer patients increases constantly, therefore, focusing on adequate sampling is of utmost importance. [19]

Only a few studies have been published regarding the improved diagnosis of lung cancer by cryobiopsy,

alone or in combination with other methods. There is currently no standardization regarding the adequate number of cryobiopsy samples or the time of freezing necessary for an acceptable sample. Furthermore, the concerns regarding procedure related complications in lung cancer patients, such as bleeding and pneumothorax, need to be properly addressed. [20]

Cryobiopsy allows endobronchial tumoral tissue sampling and extraction of the sample while still being frozen, attached to the tip of the cryoprobe. Several studies in literature attempted to make a comparison between the diagnostic yield of cryobiopsy and the conventional forceps biopsy in endobronchial lesions. [21]

A prospective, randomized, single-blinded, controlled, multicenter study included 600 patients in eight centers and defined the diagnostic yield as the number of diagnostic procedures divided by the sum between the number of diagnostic procedures and the number of nondiagnostic procedures. [22]

The diagnostic yield for endobronchial forceps biopsy was 85.1%, while for cryobiopsy it was 95.0% ($p < 0.001$), proving the superiority of cryobiopsy in lung cancer patients. A smaller, but recent study, that included 47 patients, reported a higher diagnostic yield of cryobiopsy compared to the forceps biopsy ($p = 0.001$), with no reported severe complications. Two forceps biopsies and a single cryobiopsy were performed for each patient with a randomized sequence.[23]

A study reported a diagnostic yield of cryobiopsy in lung cancer of 96.77%. The authors performed a comparative analysis of forceps biopsy and cryobiopsy by sampling the same tumoral lesion in 22 patients (3 endobronchial forceps and 2 cryobiopsies with 2–3 s freezing time). [24]

The mean volume of the tissue sample was significantly larger in cryobiopsy (0.696 cm^3 versus 0.0373 cm^3 with forceps biopsy ($p = 0.0014$), free of artifacts and the method was overall safe. The high diagnostic yield could be explained by the sampling technique and the deeper sedation used, that could be responsible for a more accurate targeting of the tumor. A study reported a diagnostic yield of 74% for central tumors when using conventional forceps biopsy. [25]

A study have performed bronchoscopy with three forceps biopsies and one cryobiopsy in each of the 41 patients of their prospective study. The tumor sample was pulled with cryoprobe after a 20 s freezing time. The results have shown that cryoprobe biopsies were better than forceps biopsies (92% vs. 78%) in central tumors. Regarding the complications, there was no statistically significant difference between the two types of biopsy. Cold saline, adrenaline and argon plasma coagulation were used to resolve the bleeding.[26]

Although there are various papers concerning the diagnostic performance of cryobiopsy for endobronchial lesions, the procedure protocols differ between centers, therefore having an impact on the reported diagnostic yield. [27]

A prospective study conducted on 50 patients with visible endobronchial tumors, non-diagnostic by conventional forceps biopsy, aimed to establish the optimal number of cryobiopsies needed to diagnose endobronchial malignancies. A total of four cryobiopsies were taken from 49 patients. The results reported a significant difference ($p = 0.031$) between one and two biopsies, however the third and fourth biopsies were found to be redundant.[28]

Advantages of Cryobiopsy

Among the most important advantages that the cryobiopsy offers, when compared to conventional forceps biopsy, is a high diagnostic yield for endobronchial malignant lesions, of up to 95%. The quality of the samples collected with the cryoprobe have a greater quality because of the following:[29]

- the larger size and volume of the collected sample.[30]
- the well-preserved tissue samples for histopathologic, molecular and genetic analysis.[31]

- less crush artifacts.[32]

The size of the sample can be determined by the operator by increasing the freezing time. The larger size of the cryoprobe samples can facilitate an accurate diagnosis, therefore enabling the possibility of target- or immuno-therapy for lung cancer patients and increasing the changes for the patients to receive the best personalized care. It can also reduce the number of additional sampling examinations needed to reach a diagnosis and the need for repeated bronchoscopies.[33]

Given the higher morbidity and mortality of surgical biopsies, TBLC can be easily adopted as a much safer and cost-effective alternative, with a high diagnostic yield. In comparison with video-assisted thoracoscopic surgery (VATS), in diffuse lung disease, TBLC proved to have a decreased median time of hospitalization (2.6 versus 6.1 days, $p < 0.0001$) and a decreased mortality as a result of adverse events (0.3% versus 2.7%).[34]

This novel bronchoscopy method could play a major role in the management of lung diseases, particularly in lung cancer, in the near future.[35]

Limitations and Complications of Cryobiopsy

The complications related to the surgical lung biopsy (SLB) along with the low diagnostic yield of conventional transbronchial forceps biopsy have increased the need for better biopsy methods. Unfortunately, there is a lack of uniformity in reporting the hemorrhage severity among different studies and retrospective studies can be vulnerable to reporting bias when data collection is incomplete. There are no predetermined parameters for categorizing major complications. In addition, reporting in high-volume academic centers may not be fully representative of all bronchoscopy centers.[36]

Among the studies that described cryobiopsy for endobronchial lesions, A study reported no pneumothorax or pneumomediastinum, only mild and moderate bleeding in both procedures, with no significant statistic difference between them.([37]

A study reported 34.1% and 36.6% hemorrhage following forceps and cryoprobe biopsies, respectively ($p > 0.05$). Moderate bleeding occurred after cryobiopsy in two patients and was managed by argon plasma coagulation. Another study showed an increased risk of bleeding when more than three cryobiopsies were obtained (OR = 2.758).[38]

A study reported a case where they performed a lobectomy for both controlling the bleeding and treating the cancer. One patient in this study has also developed pneumonia. Two studies used endobronchial blockers and two reported using an endobronchial balloon, Fogarty or B5-2c Olympus Medical. [39]

Increasing diagnostic yield of bronchoscopy in lung cancer represents an important step in improving the management of this pathology and the survival rates. This narrative review confirmed that cryobiopsy can be an extremely useful tool in the diagnosis of endobronchial tumors, as well as suspect PPLs by means of TBLC. It also adds a great value in obtaining tangential samples in tumors that infiltrate the bronchi and are more difficult to sample by conventional forceps biopsy. [40]

The quality and quantity of the cryobiopsy samples, with fewer crush artifacts and larger volume, does not only optimize the histopathological diagnosis, but also allows a better possibility for complete molecular characterization of the sample. In the current era, where cancer therapy is based on precision medicine, this technique could improve the chances for the lung cancer patients.[41]

The limitations of this paper come from the fact that most of the comprised studies are retrospective, with only two studied being designed in a randomized controlled manner. The studies may have been biased in patient selection in that they included many cases that could be approached with a conventional cryoprobe that is too rigid, or a thick GS and a therapeutic bronchoscope. [42]

Therefore, it may not be meaningful to compare the diagnostic yield of cryobiopsy and forceps biopsy in peripheral lung lesions. Further research is needed to provide a meta-analysis of the current data

regarding the true diagnostic yield of cryobiopsy in central and peripheral lung masses and the true value of r-EBUS.[43]

Lung cryobiopsy is a cost-efficient method with a lower complication and mortality rate in comparison with SLB. When guided by fluoroscopy and/or radial EBUS, an increase in diagnostic yield of peripheral tumors can be noticed, together with a decrease in complications associated with this method. In conclusion, cryobiopsy should be considered as a diagnostic approach in patients with endobronchial tumors, as well as peripheral lesions with high suspicion of lung cancer.[44]

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