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ORIGINAL ARTICLE

The Diagnostic Yield of Bronchoscopic Cryobiopsy Compared to Conventional Forceps Biopsy in Endobronchial Tumors

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ABSTRACT

Background: Conventional Forceps biopsy is associated with smaller specimen sizes and more crushed artifacts. Recently, cryobiopsy has been suggested to be associated with higher diagnostic yield due to its ability to obtain larger biopsies with less crush artifacts when compared to conventional biopsy techniques. This study aimed for assessment of the diagnostic yield of cryobiopsy compared to the forceps biopsy for endobronchial lesions.

Methods: In this cross sectional study, 48 patients with endobronchial lesions underwent bronchoscopic forceps biopsy and cryobiopsy, at the Chest Department, Faculty of Medicine, Zagazig University, and the specimens were sent for histopathological analysis. **Results:** Two methods showed statistically significant differences as regards the diagnostic yield as all the cryoprobe biopsies (100%) were diagnostic while only (81.3%) of forceps biopsies were diagnostic (P value = 0.002).

Conclusions: Cryobiopsy yielded larger tissue specimens, resulting in a higher diagnostic yield and a lower prevalence of non-diagnostic results compared to forceps biopsy.

Keywords: Cryobiopsy, Forceps biopsy, Endobronchial tumors.

INTRODUCTION

Globally, lung cancer is the leading cause of cancer-related mortality, accounting for over a million fatalities per year [1]. Diagnosing lung cancer is a challenge either clinically (cough, hemoptysis, unresolved or recurrent pneumonia, lung abscess, malignant pleural effusion, mediastinal syndrome, or other presentations) or by imaging where it appears as solitary lung nodule or lobar collapse or cavitating mass or pleural effusion by chest x-ray and/or CT chest [2].

Currently, bronchoscopy is the gold standard for tissue sampling of endobronchial tumors [3]. It allows sample gathering by endobronchial biopsy, bronchial brushing, or bronchoalveolar lavage, and microscopic tumor assessment [4]. Conventional bronchoscopic forceps biopsy is still considered an international technique for tissue sampling for histopathological analysis of

lung biopsies. Smaller specimen sizes and greater crush artifacts restrict the diagnostic yield of forceps biopsies and influence the histopathological analysis quality. The diagnostic yield is enhanced when forceps biopsy is performed in conjunction with bronchial brushing, lavage, or needle aspiration [5]. However, this combined technique results in increasing procedural time and cost. Bronchoscopic cryobiopsy is a novel minimally invasive bronchoscopic technique for obtaining biopsy [6]. It involves the bronchoscopic placement of a flexible cryoprobe inside the endobronchial lesion, freezing the probe, and cropping out the tissue frozen around the tip. Cryobiopsy yields tissue specimens larger than the traditional forceps biopsy, resulting in a significantly higher diagnostic yield with fewer crush artifacts [7-9]. This study aimed for assessment of the diagnostic yield of

bronchoscopic forceps biopsy and cryobiopsy in endobronchial lesions.

METHODS

From March 2023 to December 2023, at Zagazig University Hospitals' Bronchoscopic Unit of the Chest Department, we performed this cross-sectional study on 48 patients with endobronchial lesions who underwent bronchoscopic forceps biopsy and cryobiopsy. Approval for performing the study was obtained from the Chest Department, Faculty of Medicine, Zagazig University, after the institutional review board of Zagazig University (ZU-IRB) approval under code IRB#:10366/25-1-2023. Written informed consent was taken from all patients. This study included 48 patients with suspected endobronchial lesions who were subjected to bronchoscopic cryobiopsy and forceps biopsy in the same session.

Inclusion criteria: Patients > 18 years old with suspected endobronchial lesions based on clinical and radiological data.

Exclusion criteria: Hemodynamic instability (hypotension or uncontrolled hypertension), uncorrected bleeding diathesis (INR >1.5), unsuitability for stopping anticoagulation drugs for 1-7 days before the procedure, suspected bronchial artery aneurysms or lung metastasis of renal cell carcinoma due to risk of bronchial bleeding, significant hypoxemia despite the application of supplemental oxygen, acute exacerbation of chronic obstructive pulmonary diseases, serious underlying cardiac condition (uncontrolled arrhythmias, unstable angina, myocardial infarction in the past month, decompensated heart failure).

All patients were subjected to full history taking, including demographic data, associated comorbidities, full clinical examination, and routine laboratory investigations.

Patient preparation: 4 to 6 hours of fasting were routinely done before the bronchoscopy procedure for all patients.

Application of anesthesia [10]: The procedure was done under local anesthesia and conscious sedation. Patients were instructed to puff back an atomizer spray containing a 2% xylocaine solution that had been administered to both nostrils. Additionally, xylocaine is spritzed straight into the mouth of the patient. Using a detachable and sterile angle nozzle, two or three

measured dose sprays (20-30 mg) are then directed onto the cords. Conscious sedation was done by appropriate doses of a benzodiazepine, e.g., midazolam (Dormicum amp, F. Hoffman la Roch, Egyptian pharmaceutical trading company). Intravenous 5-10 mg of this drug was administered.

Technique of Bronchoscopy [3]

A 2.6 mm working channel (BF-IT 10; Olympus America; Melville, NY) flexible fiberoptic bronchoscope was used in the bronchoscopy procedure in conjunction with the flexible cryoprobe.

Cryo-equipment [11]

The cryo-equipment is comprised of a high-pressure cryogenic cylinder, a cryo-machine console that regulates the cryogen flow, and a catheter with a cryoprobe at one end to directly freeze the target tissue. The bronchoscopist controlled and activated the cryogen flow via the catheter, moving it from the cylinder to the cryoprobe with a foot pedal.

The cryo-machine used was ERBE Cryo CA (Erbe, Elektromedizin GmbH, Waldhoemlestrasse 17,72072 Tuebingen, Germany).

Endoscopy Room: In the respiratory endoscopy unit, bronchoscopy was safely carried out in a sterile environment with sufficient patient monitoring and the necessary resuscitation equipment on hand. The autoclave and its accessories were used to sterilize the flexible bronchoscope.

Bronchoscopy Procedure [3]: The operator and assistant hands were scrubbed, and surgical masks, gowns, and gloves were worn. Supplementary oxygen was provided to the patient to maintain oxygen saturation above 90%. The patient was positioned in the supine position. Following the administration of local anesthesia, the bronchoscope was coated with 2% xylocaine gel and guided into a nostril under direct eyesight. It was then passed along the nasal floor through the most visible aperture between the turbinates. Never push the instrument; light pressure was necessary. The bronchoscope should be removed, and the other nostril should be attempted if it does not advance easily.

If the bronchoscope's shaft couldn't fit through the patient's nasal approaches, the specialist would have them place a bite block between their teeth or gums so the device could be passed into

their oropharynx. By bending the tip downwards as the instrument was advanced, the glottis and larynx were revealed. Observations were made on the vocal cords' position and movement in relation to respiration.. Most patients found the section of the treatment where the bronchoscope went through their vocal cords to be the most unpleasant, and they often experienced a brief feeling of apnea. The suction channel was used to administer an additional 2% lignocaine once the cords had been passed.

Biopsy technique [12] :Using reusable fenestrated forceps FB-21C or FB-52C-1; Olympus Corp, Hamburg, Germany, 3-4 biopsies were conducted using the usual method of forceps biopsy. The cryoprobe was utilized using carbon dioxide as the cryogen for cryobiopsy, which consists of 1-2 biopsies. The endobronchial lesion was covered with the flexible cryoprobe, and the freezing process was started. The ice front was allowed to reach the bronchial wall for three to five seconds. After that, the frozen tissue was removed from the probe tip by thawing it in a sterile 0.9 percent sodium chloride water bath and then placed in formalin. The cryobiopsy and forceps biopsy were performed simultaneously.

After removal of the biopsy, the biopsy sites were inspected for any bleeding, which must be controlled.

The severity of the bleeding at the biopsy site was evaluated using the following scale: minor, self-limiting bleeding; moderate, requiring vasoactive drug injection or ice cold saline; and severe, requiring electrocautery or argon plasma coagulation intervention [10]

Any complications, e.g., pneumothorax, hemoptysis, shock, and death, were recorded if they occurred. Days of hospital stay after the procedure were also recorded.

Pathological evaluation [5]: Specimens were described grossly and were placed in a cassette containing tissue that was being processed into a paraffin block. Hematoxylin and eosin stain were used to prepare the tissue on the slide for histological evaluation. Biopsies obtained by both techniques were compared in terms of size (surface area in mm²), grading of crushed cells (artifacts), and diagnostic yield. Histopathological grading of crushed cells (tissue viability, integrity): A well-integrated, viable biopsy" was intended to be negative if there were

no crushed cells. A biopsy was classified as 1+ if crushed cells were discovered in less than 5% of it, 2+ if they were found in between 5 and 25% of it, and 3+ if they were found in more than 25% of it.

Statistical analysis:

Collected data were computerized and statistically analyzed using IBM SPSS 23.0 for Windows (SPSS Inc., Chicago, IL, USA) and the Jamovi project (2022) (Version 2.3). Qualitative data is represented in the form of numbers and percentages (N. %), while quantitative data after testing of normality using the Shapiro-Wilk test: Data that is regularly distributed are displayed as mean±SD, while data that is skewed are displayed as median (interquartile range). And range from minimum to maximum value. Inferential statistics: At the level of significance value (P value): $P > 0.05$ (Non-significant), $P \leq 0.05$ (Significant). For qualitative data, Fisher's exact test and the chi-square test were applied, while for quantitative data that was normally distributed, a t-test was used. Skewed data: Mann-Whitney test & Kruskal-Willais were used.

RESULTS

This cross-section study included 48 patients with suspected endobronchial lesions who were subjected to bronchoscopic cryoprobe biopsy and forceps biopsy in the same session. The mean age of patients was (58.9 ± 9.51). Regarding gender of the patients (70.8%) of patients were males, while (29.2%) were females.

As shown in Table (2) regarding the lesion sites, the results showed that the most common sites are the left upper & right upper lobe bronchus (25% & 20.8, respectively), followed by the left main & right main bronchus (20.8% & 14.6%, respectively), then the left lower & right lower lobe bronchus (10.4 & 4.2%, respectively), then trachea 4.2%.

As shown in Table (3) regarding the biopsy characters and the diagnostic yield, the biopsy size and diameter were significantly larger with cryoprobe than with forceps ($P < 0.001$). Regarding the presence of crushed cells, there was a highly statistically significant difference between the two procedures, with forceps biopsies showing a higher presence of crushed cells ($P < 0.001$).

However, when it came to bleeding at the biopsy bed, there was no significant difference between the two methods ($P > 0.05$). Regarding the type of bleeding intervention, there was no statistically significant difference between the two methods ($P > 0.05$).

Regarding the diagnostic yield, there was a statistically significant difference between the

two methods as all the cryoprobe biopsies (100%) were diagnostic, while only (81.3%) of forceps biopsies were diagnostic ($P \text{ value} = 0.002$). N.B. 2 cases were complicated by severe bleeding while taking forceps biopsy, so cryobiopsy had not been taken during the procedure.

Table 1: Demographic data and clinical presentation among studied patients

Variable	All patients (n=48)
Age (years) Mean \pm SD (range)	58.9 \pm 9.51 (22 – 75)
Sex (N. %)	
Male	34 (70.8%)
Female	14 (29.2%)
Clinical presentation (N. %)	
Dyspnea	48 (100%)
Chest pain	5 (10.4%)
Cough	48 (100%)
Hemoptysis	30 (62.5%)
Expectorations	45 (95.7%)
Fever	3 (6.3%)
Weight loss	26 (54.2%)
Associated comorbidities (N. %)	
Diabetes	12 (25%)
Hypertension	10 (20.8%)
Ischemic heart disease	4 (8.3%)
HCV (N. %)	14 (29.2%)

Table 2: sites of the lesions in the studied patients

Site of the lesion	N	%
Left upper lobe bronchus	12	25 %
Right upper lobe bronchus	10	20.8%
Left main bronchus	10	20.8%
Right main bronchus	7	14.6%
Left lower lobe bronchus	5	10.4%
Right lower lobe bronchus	2	4.2%
Trachea	2	4.2%

Table 3: Comparison between the two studied methods as regards the biopsy characters and the diagnostic yield

Variable	Forceps biopsy	Cryoprobe biopsy	P value
Number of biopsies <i>median (IQR)</i> <i>Range</i>	3 (1) (3 – 4)	2.5 (1) (1 – 2)	<0.001
Biopsy size length (mm) <i>median (IQR)</i> <i>Range</i>	5 (0.8) (3 – 7.3)	9.1 (0.7) (6.1 – 11.1)	<0.001
Biopsy largest diameter (mm²) <i>median (IQR)</i> <i>Range</i>	17.3 (5.2) (13 – 24.6)	49.3 (4.18) (41 – 62.5)	<0.001
Bleeding: (N. %) Slight Mild Moderate Severe	14 (29.2%) 20 (41.7%) 12 (25%) 2 (4.2%)	18 (39.1%) 23 (50%) 5 (10.9%) 0 (0%)	0.14
Types for intervention Simultaneous clotting Ice cold saline application Diluted adrenaline application Electrocautery	14 (29.2%) 20 (41.7%) 12 (25%) 2 (4.2%)	18 (39.1%) 22 (47.8%) 6 (13.1%) 0 (0%)	0.21
Histopathological findings (N. %) Adenocarcinoma Squamous cell carcinoma Small cell carcinoma Spindle cell tumor Leiomyoma Chronic inflammation Non diagnostic	15 (31.3%) 19 (39.6%) 3 (6.2%) 2 (4.2%) 0 (0%) 0 (0%) 9 (18.7%)	15 (32.6%) 20 (43.5%) 5 (10.9%) 2 (4.3%) 1 (2.2%) 3 (6.5%) 0 (0%)	0.04
Diagnostic yield Non diagnostic	39 (81.3%) 9 (18.7%)	46 (100%) 0 (0%)	0.002
Crushed cells (artifacts) Absent < 5% 5% – 25% > 25%	3 (6.3%) 16 (33.3%) 21 (43.8%) 8 (16.7%)	13 (28.3%) 30 (65.2%) 3 (6.5%) 0 (0%)	<0.001

Mann Whitney test, Chi square test

DISCUSSION

Despite the promising outcomes associated with bronchoscopic cryobiopsy, its adoption into routine clinical practice necessitates careful consideration of safety and feasibility. While cryobiopsy is generally regarded as a safe and minimally invasive procedure, additional research is warranted further to elucidate its long-term safety profile and potential complications [13,14]

The study's primary aim was to compare the diagnostic value of bronchoscopic forceps biopsy and cryobiopsy for endobronchial lesions.

As shown in Table (2) regarding the sites of the lesions, the most common sites are the left upper & right upper lobe bronchus (25% & 20.8, respectively), followed by the left main & right main bronchus (20.8% & 14.6%, respectively), then the left lower & right lower lobe bronchus (10.4 & 4.2%, respectively), then trachea 4.2%. Our findings were in line with those of El-Assal et al. [11], who found that the right upper and

right lower bronchi, which accounted for 20.0% of the cases, were the most common locations for malignant tumors. After that, five cases (12.5%) were found in the right main bronchus and six cases (15.0%) in the right upper lobe bronchus. In addition, four (10.0%) masses were discovered in the left main bronchus; the remaining 7.5% of the masses were similarly distributed, with three cases each in the left upper lobar, left lower lobar, and left lingular bronchi.

Similarly, In Kinoshita et al. [15] study, the distribution of lesions by lobar location revealed that 55% were located in the upper lobe, 8% in the middle lobe, and 37% in the lower lobe.

Consistent with our findings, Shouhdy et al. [16] stated that their results indicated a disparity in the number of biopsies taken between cryoprobe and forceps techniques. Specifically, in cryoprobe biopsy, a single sample was obtained in 73.3% of instances, whereas two biopsies were performed in 26.7% of cases. In comparison, during forceps biopsy, three samples were collected in 56.7% of cases, and four biopsies were taken in 43.3% of cases. Additionally, they noted that cryoprobe biopsies tended to be larger compared to forceps biopsies. This difference in biopsy characteristics contributed to the enhanced diagnostic yield achieved by cryoprobe biopsies. Notably, this finding aligned with previous research by Schumman et al. [17], supporting the idea that cryoprobe biopsy may offer advantages over forceps biopsy in terms of sample size and diagnostic efficacy.

In this study, the results showed that the mean size of cryobiopsy was larger than forceps biopsy (5mm versus 9.1 mm for forceps biopsy & cryobiopsy, respectively), as shown in Table 3.

The sample size acquired by cryobiopsy was substantially larger than the sample size obtained by forceps biopsy in the study done by Chou et al. [4] ($13.8 \pm$ vs. 1.9 ± 0.6 mm, $p < 0.0001$).

In line with our findings, Kim et al [18] reported that biopsy size was larger with cryobiopsy versus forceps biopsy as the mean size of the specimen from the forceps biopsy was $2 \text{ minus } 1.2 \text{ mm}$ and $66.0 \text{ plus } 0 \pm 3.0$ mm for cryobiopsy.

Similarly, in the study conducted by Udagawa et al. [19], the cryoprobe sample size was larger than the forceps biopsy sample size (cryoprobe 15 mm^2 versus forceps 2 mm^2).

In this study, the results showed that the diagnostic yield was 81.3% versus 100% for

forceps biopsy and cryobiopsy, respectively as shown in table 3.

A total of 296 patients with apparent endobronchial tumors were studied by Schumann et al. [17]; of them, 55 patients underwent cryobiopsy and forceps biopsy on the same patient. Compared to forceps biopsy, cryobiopsy yielded a considerably greater diagnostic yield ($p < 0.05$).

Cryobiopsy had a considerably higher diagnostic value ($p < 0.0001$) than forceps biopsy in the study carried out by Chou et al. [4]

Additionally, Mohamed A. et al. [9] shown that cryobiopsy had a substantially higher diagnostic accuracy (95%) than forceps biopsy (80%) ($p < 0.001$).

According to Berame et al. [20], the diagnostic yield of cryobiopsy was substantially higher than that of cryobiopsy, with an odds ratio of 4.8 (95% CI 3.02-6.95), which is consistent with our findings.

However, in the study conducted by Udagawa et al. [19] there was no discernible difference between forceps biopsy and cryobiopsy as the diagnostic yield of cryobiopsy versus forceps biopsy was 84% and 83%, respectively (McNemar test; $p = 0.80$). The lower diagnostic rates were due to operator-dependant technical issues rather than mechanical-related issues.

The study's findings on bleeding at the biopsy bed did not reveal a statistically significant difference between the two procedures ($P > 0.05$). Additionally, there was no discernible difference between the two procedures in terms of the intervention employed to stop the bleeding ($P > 0.05$).

In agreement with our findings, Ehab et al. [13] observed mild to severe bleeding in both methods but no pneumothorax or pneumomediastinum, and there was no statistically significant difference between them. Following forceps biopsy and cryobiopsy, Aktas et al. [10] recorded 34.1% and 36.6% bleeding, respectively ($p > 0.05$). Two patients experienced moderate bleeding after cryobiopsy, which was managed with argon plasma coagulation.. Another study by Segmen et al. [12] showed a higher risk of hemorrhage when more than three cryo biopsies were taken (OR = 2.758).

In this study, both adenocarcinoma and squamous cell carcinoma were the most prevalent histopathological findings among the studied

patients. Notably, the prevalence of non-diagnostic results was significantly higher with forceps biopsy (18.7%, n=9) compared to cryoprobe biopsy (0%, n=0), with a statistically significant difference observed (P=0.04).

Furthermore, we found a statistically significant difference between the two methods as regards the diagnostic yield, as all the cryoprobe biopsies (100%) were diagnostic, while only (81.3%) of forceps biopsies were diagnostic (P value = 0.002). Essentially, our results suggest that using a cryoprobe for biopsy increases the likelihood of obtaining diagnostically useful tissue samples, leading to more accurate histopathological diagnoses.

This study revealed a highly statistically significant difference between the two biopsy methods regarding the presence of crushed cells, with forceps biopsies showing a higher prevalence of crushed cells compared to cryoprobe biopsies (P < 0.001), as shown in Table 3. This suggests that cryoprobe biopsies may offer advantages in preserving tissue integrity and reducing crush artifacts, indicating their potential as a reliable alternative for obtaining diagnostic tissue samples in patients with endobronchial tumors.

Consistent with our results, El-Dahdouh et al. [21] reported that no crushing was observed with cryobiopsy, whereas crushing was seen in 17 cases (68%) with forceps biopsy. It was determined that there was a statistically significant difference ($\chi^2 = 25.7$, p < 0.001).

Study limitations

One limitation of this study is the relatively small sample size, which may limit the generalizability of our findings to a broader population. Additionally, the study was conducted at a single center, which may introduce potential biases and limit the external validity of the results. Furthermore, the lack of long-term follow-up data prevents us from assessing the clinical outcomes associated with the diagnostic procedures.

Recommendations

We recommend further investigation into the long-term clinical outcomes associated with bronchoscopic cryobiopsy and conventional forceps biopsy in patients with endobronchial tumors. Longitudinal studies with extended follow-up periods would provide valuable insights into the efficacy and safety of these

diagnostic techniques over time. It's recommended to conduct multicenter studies to validate the findings of our study across diverse patient populations and clinical settings. This would help confirm the generalizability of the results and enhance the external validity of the conclusions drawn from our research. We recommend further research to identify factors associated with non-diagnostic results in forceps biopsy and explore strategies to mitigate these limitations. Understanding the determinants of diagnostic success or failure could guide the development of improved biopsy techniques and enhance overall diagnostic accuracy in endobronchial tumor evaluation.

CONCLUSIONS

Cryobiopsy yielded larger tissue specimens and demonstrated a lower incidence of crushed cells with a subsequent significantly higher diagnostic yield. These findings underscore the potential of cryobiopsy as a reliable and effective technique for histopathological analysis in patients with endobronchial tumors.

No potential conflict of interest was reported by the authors.

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