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ORIGINAL ARTICLE

DIAGNOSTIC YIELD OF CRYOBIOPSY AND FORCEPS BIOPSY IN VISIBLE ENDOBRONCHIAL LUNG TUMORS: A COMPARATIVE STUDY

Ismail S Mobarak,[1] Fatma Eel-Zahraa Salah El-Deen[2]

[1]Department of Chest Diseases, Qena Faculty of Medicine, South Valley University, [2]Department of Pathology, Sohag Faculty of Medicine, Sohag University, Egypt

Correspondence to: Ismail S Mobarak, Email: ismailsayed@yahoo.com

Background and objectives: ***Endobronchial biopsy by conventional forceps is a bronchoscopy procedure used to obtain tissue biopsy from endobronchial tumors. Small size samples lead to variable, and usually low, diagnostic yield. The use of cryoprobes may enable larger size and better quality biopsy samples to be obtained and hence a better results. The purpose of this study was to evaluate results of cryobiopsy in endobronchial lung tumors in comparison to the conventional biopsy forceps.***

Patients and Methods: ***During the period from June 2010 to February 2011, we selected 35 patients with endobronchial tumors who were suitable for endobronchial biopsy. This was taken by forceps biopsy and cryoprobe which were introduced through the video-bronchoscope work channel. The procedure was performed under sedation with local lidocaine instillation. Safety and histopathological findings has been evaluated.***

Results: ***The included 35 patients consisted of 29 (82.9%) males and 6 (17.1%) females; with a mean age of 58.7 ± 8.3 years (age range, 35 to 72 years). It was found that there was a significant statistical difference (p < 0.00) in mean diameter of the biopsy taken by the two modalities where it was 20.9 ± 4.1 mm and 6.8 ± 2.1 mm by cryoprobe and forceps biopsy respectively. Thirty three patients (94.3%) were diagnosed with cryoprobe biopsy and twenty six patients (74.3%) were diagnosed with forceps biopsy (p <0.04). No complications were recorded in both modalities other than mild to moderate post-biopsy bleeding (30%) which was controlled with standard bronchoscopy measures.***

Conclusion: ***Cryobiopsy is a novel technique which allows obtaining large biopsy samples of endobronchial tumors that exceed the size and quality of forceps biopsy samples and this improved the diagnostic yield of flexible bronchoscopy.***

Keywords: ***Biopsy, cryobiopsy, endobronchial tumor, bronchoscopy.***

INTRODUCTION

Cryotherapy was used as long ago as 1907 in dermatology[(1)] and first applied to the bronchial tree in the mid 1970s.[(2)] In Britain the technique has been pioneered by Maiwand[(3)] Cryotherapy was performed through a rigid bronchoscope with a liquid nitrogen probe to cool the tumors to - 70° C; it is allowed to destruct the tumors.

The action of cryotherapy on the tissue is based on the cytotoxic effect caused by the subsequent induction of intracellular ice crystals and the delayed formation of intravascular thrombosis with infarction.[(4)] So, cryosensitivity depends on the water content of cells and the microcirculation of the target tissue.

Cryotherapy has been used in interventional bronchoscopy for many years, and its main use is the treatment and excision of endobronchial lesions, particularly in cases of bronchial obstruction [5]. In studies assessing the histopathological material obtained using cryoprobes in cases of endobronchial tumors, the samples were found to be larger than those obtained with conventional forceps [6,7]. This has lead to considering the possibility of using cryoprobes for performing endobronchial lung biopsy as a new, improved alternative to the classic method. It could increase diagnostic yield without increasing risks, and avoid the added cost of surgery.

The new, flexible, and mechanically more stable cryoprobe with a larger surface at the tip allows the immediate extraction of tumor tissue from the bronchial wall by using the cryoadhesive effect.[8] The main difference from older probes is a firmer attachment of the central gas channel in the probe tip, resulting in greater stability to traction. The frozen tissue is attached to the probe's tip and removed by pulling the cryoprobe together with the bronchoscope.

Aim of the work: There is only a very limited amount of information about the use of cryoprobe biopsy technique and, to our knowledge; no centre in our country uses it. So this study was conducted to evaluate results of cryobiopsy in endobronchial lung tumors in comparison to the conventional forceps biopsy.

PATIENTS AND METHOD

A prospective study was conducted on 35 patients with endobronchial tumors indicated for biopsy. They were investigated in Chest Diseases Department, Qena University Hospital, Qena Faculty of Medicine, South Valley University, during the period from June 2010 to February 2011. The study protocol was approved by the local ethical committee prior to beginning and all the patients gave their informed consent. All patients were subjected to:

- A careful history taking.
- Chest and systematic clinical examination.
- Routine laboratory investigations especially a haemogram with coagulation study.
- Chest X-ray: postero-anterior and lateral views.
- Chest computed tomography scan.
- Flexible fibreoptic bronchoscopy.

Bronchoscoscopic procedure

The procedures were carried out in a conventional operating theatre. Patient monitoring and sedation were performed. All patients were monitored with electrocardiogram, automated blood pressure cuff and pulse oximetry. Patients were monitored post-procedure for a minimum period of 2 h. Midazolam was used for sedation and administered intramuscular half an hour before the procedure. Before the bronchoscope is inserted, local anesthesia with lidocaine is applied in the nares and the oropharynx to suppress sensation, cough, and the gag reflex. Endoscopic exploration of the bronchial tree was performed using a video bronchoscope (EB-1970 TK, Pentax, Japan). The following samples were taken:

- Cryobiopsy: The cryoprobe used was a flexible probe (Figure 1), 2.4 mm in diameter and 900 mm in length, which was connected to the cryotherapy equipment (Erbokryo® CA, Erbe, Germany). Contact of the probe with the tissue involves high power freezing (-89° C) which, due to the characteristics of the probe, has stability to traction. The cryoprobe was introduced through the flexible bronchoscope work channel. Cold was applied for 3 seconds and then the cryoprobe with the frozen sample attached to the tip was removed, along with the video-bronchoscope. We tried to obtain a minimum of 2 biopsies from each patient, although this number varied depending on the patient's tolerance.
- Endobronchial forceps biopsy: Biopsy forceps which is 2.4 mm in diameter and 900 mm in length was used. At least, 4 biopsies were taken from the site of the lesion prior to cryobiopsy. The samples were sent to the pathologist in a 10 % formalin solution.

Any complications such as bleeding, pneumothorax and others were recorded. Quantification of bleeding was carried out and recorded by the bronchoscopist after each biopsy according to a four-point scale (1: no bleeding; 2: minimal bleeding not requiring intervention; 3: mild-to-moderate bleeding requiring intervention, such as ice cold saline, topical adrenaline or electrocoagulation; 4: moderate-to-severe bleeding requiring termination of procedure, endotracheal intubation or other invasive treatment).[9]

Pathological examination

The cryoprobe and forceps biopsies were sent to the pathologist in separate containers. Each biopsy was measured, routinely processed, formalin fixed, paraffin embedded according to the usual schedule used in laboratory. Five micron serial tissue sections were cut, sections were de-paraffinized, rehydrated and stained with Hematoxylin and Eosin (H&E). All H&E sections were examined to assess artifact related to either cryoprobe or forceps biopsy application. Histopatholgical subtyping was done according to the World Health Organization histological classification of lung tumors.[10]

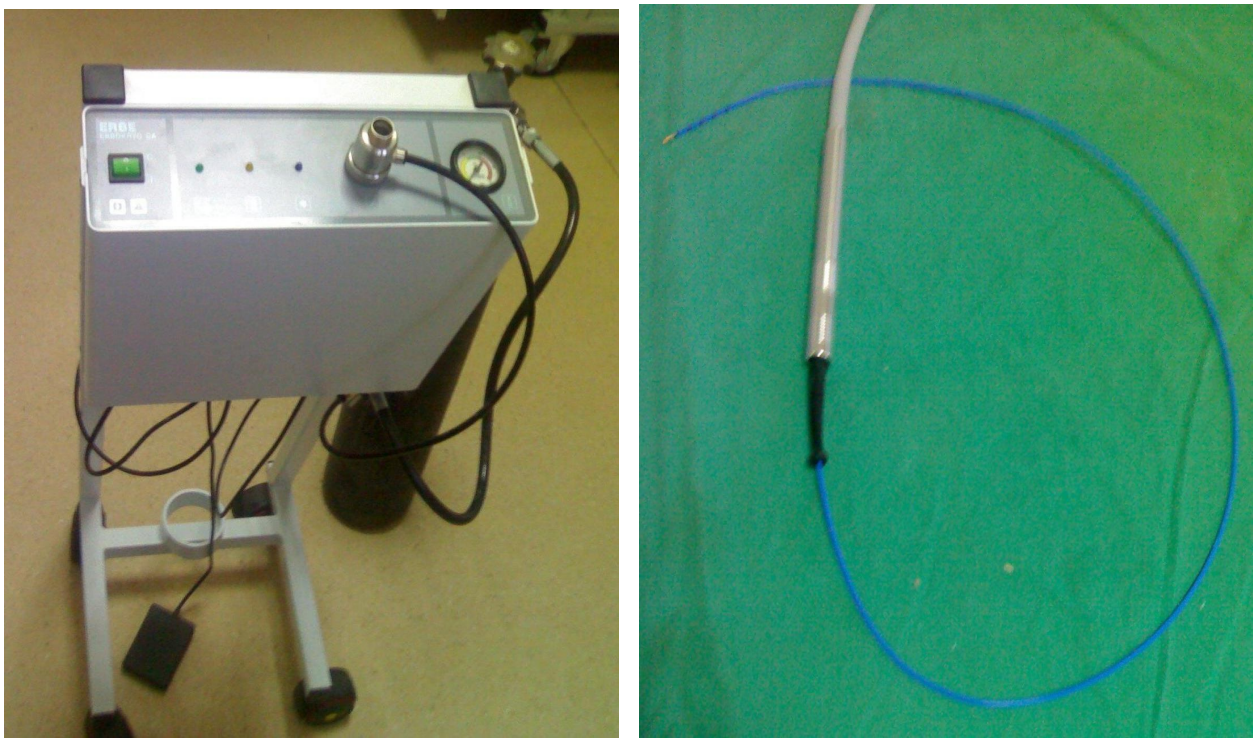

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Fig 1. a.) The cryotherapy equipment and b) Cryoprobe were used to perform endobronchial biopsies (Erbokryo® CA, Erbe, Germany).

Statistical analysis: Data were presented as mean and SD (or range) and were compared using the t-test, or Chi square test for data that were not normally distributed. Statistical analyses were performed using SPSS version 11 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was assessed at $p < 0.05$.

RESULTS

During the period of this study, 54 bronchoscopies were done in Chest Department; only 35 patients with visible endobronchial tumors were included in the study. They consisted of 29 (82.9 %) males and 6 (17.1%) females, with a mean age of 58.7±8.3 years (age range, 35 to 72 years) at the time of biopsy. More demographic and clinical data of the patients were demonstrated in Table 1.

Table 1. Demographic and clinical data of the studied patients (n=35)

Variables	No.	%
Sex		
Male	29	82.9
Female	6	17.1
Age	58.7± 8.3	
Occupation		
Worker	9	25.7
Miner	4	11.4
Farmer	7	20.0
Employer	6	17.1
Housewife	5	14.3
Others	4	11.4
Smoking habit		
Smoker	24	68.6
Non smoker	8	22.9
Ex-smoker	3	8.6

Most endobronchial lesions (17, 48.6 %) were located at main bronchi (10 in the right side and 7 in left). All these lesions were successfully diagnosed with both modalities except two were not diagnosed by forceps and these were located in the left main bronchus. One of 2 located at the right upper lobe bronchus, 4 of 5 at the right lower lobe bronchus, 2 of 3 at the left upper lobe bronchus, 4 of 6 at the lower lobe bronchus were successfully diagnosed with forceps biopsy. All lesions diagnosed by cryoprobe biopsy except one at lower end of the trachea and another at the right lower lobe bronchus. Detailed radiological findings and bronchoscopic localizations were demonstrated in Table 2.

Table 2. Radiological and bronchoscopic findings.

Variables	No.	%
X- ray findings		
Apparent normal	1	2.7
Rt upper lung zone opacity	8	22.9
Rt lower lung zone opacity	2	5.7
Pneumoconiosis with Rt upper zone opacity	3	8.6
Pneumoconiosis with Lt middle zone opacity	1	2.7
Rt middle lung zone opacity	3	8.6
Lt middle lung zone opacity	2	5.7
COPD without visible lung opacity	1	2.7
Lt upper lung zone opacity	5	14.3
Lt lower lung zone opacity	3	8.6
Rt pleural effusion	2	5.7
Lt pleural effusion	1	2.7
Rt hilar opacity	1	2.7
Lt hilar opacity	2	5.7
CT findings		
Rt upper lobe mass	12	34.3
Middle lobe mass	2	5.7
Rt lower lobe mass	3	8.6
Rt lower lobe mass with effusion	2	5.7
Lt upper lobe mass	8	22.9
Lt upper lobe mass with effusion	1	2.7
Lt lower lobe mass	5	14.3
Lt lower lobe mass with effusion	2	5.7
Bronchoscopic findings		
Lower part of the trachea	1	2.7
Rt upper lobe bronchus	2	5.7
Rt main bronchus	10	28.6
Middle lobe orifice	1	2.7
Rt lower lobe bronchus	5	14.3
Lt upper lobe bronchus	3	8.6
Lt main bronchus	7	20.0
Lt lower lobe bronchus	6	17.1

Comparing the mean diameter of biopsies taken with the 2.4 mm cryoprobe with that of 2.4 mm forceps biopsies (gold standard), it was found that mean diameter of the biopsies was 20.9 ±4.1 mm and 6.8 ± 2.1 mm respectively. So, cryobiopsies were significantly larger than forceps biopsies ($p < 0.00$).

Table 3 demonstrated the histo-pathological results and diagnostic rates for both cryoprobe and forceps biopsies. Thirty three patients (94.3%) were diagnosed with cryoprobe biopsy, on the other hand, twenty six patients (74.3 %) were diagnosed with forceps biopsy ($p < 0.04$). Furthermore, the histological quality of the cryobiopsy specimens was not impaired by the freezing process, whereas forceps biopsies showed typical crush artifacts. Two cases were not diagnosed by the two methods, these cases showed apparently healthy mucosa and diagnosed by CT-guided biopsy. The negative results in forceps biopsy were due to small samples or non-specific findings.

Table 3. Histopathological results and diagnostic rates for cryoprobe and forceps biopsies.

Biopsy / Histopathology	Cryoprobe biopsy	Forceps biopsy
Squamous cell carcinoma	26 (74.6 %)	23(65.7 %)
Adenocarcinoma	2 (5.7 %)	1 (2.9 %)
Small cell carcinoma	5 (14.3 %)	2 (5.7%)
Large cell carcinoma	0 (0 %)	0 (0 %)
Non diagnostic	2 (5.7 %)	9 (25.7 %)
Total	35 (100 %)	35 (100 %)

No complication related to anesthesia or bronchoscopic introduction were recorded. Only mild and moderate bleeding was noticed. Hemorrhage was found in 30 % of cases following cryoprobe and forceps biopsies. Adrenaline and cold saline was applied in 2 cases after cryobiopsy and one case after forceps biopsy. Severe hemorrhage with hemodynamic instability that would need to apply rigid bronchoscopy, surgery, or fluid replacement was not recorded.

DISCUSSION

Lung cancer is a significant public health problem and is of particular interest to primary care physicians because smoking, (the major attributable cause) is a modifiable risk factor. Despite the fact that the death rate from lung cancer has decreased modestly in recent years, the annual incidence of lung cancer, both in the United States and worldwide, continues to rise. As a result, lung cancer is the leading cause of cancer death in both men and women. According to estimates by the American Cancer Society, there were approximately 162,460 deaths owing to lung cancer in the United States in 2006.[11] At the time of diagnosis over 85% of patients are at an advanced stage of the disease and only palliative treatment is possible.[12] The ability to obtain a good biopsy without subjecting a patient to an open lung biopsy is a major advance in diagnostic bronchoscopy in the hopes of achieving useful pathologic information that would lead to appropriate clinical management and better survival.

Flexible fibreoptic bronchoscopy has revolutionized the practice of pulmonary medicine, enhanced our understanding of pulmonary disease, and has evolved into the most commonly used invasive diagnostic as well as therapeutic procedure. It is the most important investigation in lung malignancy with endobronchial lesions and is minimally invasive. The overall diagnostic yield of bronchoscopy is 88% in central tumours reported in a review by Schreiber and McCrory.[13] Reported overall diagnostic yields in endoscopically visible lung cancer range from 67 to 97%.[14,15] The average diagnostic yield for biopsies in endobronchial lung cancer was reported to be 74% based on the results of 20 studies.[13] Previous studies have shown that the tumour detection rate can be increased by complementary cytology-based sampling techniques such as endo-bronchial washings and brushings.[16-18] For endoscopically visible lesions, collection of cytology specimens is estimated to increase the sensitivity of bronchoscopy by 3-23%.[16,19-21] Average individual diagnostic yields for bronchial washings and brushings in endoscopically visible lung malignancy have been reported to be 59% (based on 18 studies) and 48% (based on 12 studies) respectively.[13] The diagnostic yield ranges from 29 to 78%[22,23] for bronchial washings and 23 to 79 % for bronchial brushings alone.[24,25] Other modalities such as cryobiopsy may increase the diagnostic yield of flexible bronchoscopy.

The possibility of tissue extraction from the bronchial system using a cryoprobe has led to the assumption that the extracted tissue could be valuable for histopathological examination since freezing does not appear to influence the histopathology of biopsy samples.[26] In addition, cryobiopsy samples have been shown to be large and with a high proportion of unaltered morphology and therefore are presumed to be of a higher diagnostic value.[7]

In this study, we used a cryoprobe with a wider diameter (2.4 mm). This can obtain biopsy specimens that are almost double the size of specimens obtained with standard biopsy forceps (2.4 mm diameter) after an activation time of 3 s. In their experimental study, Franke and colleagues concluded that the size of the biopsies depends on tissue type, probe diameter, application time, and pressure exerted by the probe on the tissue. Even the cryoprobe with the smallest diameter can provide larger biopsies than a forceps biopsy in the lung.[27]

In 2010, Aktas et al[28] investigated 41 patients with endobronchial tumors. Three forceps biopsy and one cryobiopsy with cryorecanalization probe were obtained from each patient. Thirty two patients (78%) were diagnosed with forceps biopsy and 38 patients (92.7%) were diagnosed with cryoprobe biopsies ($p < 0.031$). In

another study, Schumann and colleague[29] studied 55 patients and revealed a significantly higher diagnostic yield for cryobiopsy compared with forceps biopsy (89.1% vs 65.5%, $p < 0.05$). Quantitative image analysis showed significantly larger biopsies regarding size and artifact-free tissue sections for cryobiopsy compared with forceps biopsy ($p < 0.0001$). In our study, Thirty three patients (94.3%) were diagnosed with cryoprobe biopsy and twenty six patients (74.3%) were diagnosed with forceps biopsy ($p < 0.04$). So, our results were comparable with both studies as regard the cryoprobe biopsies but higher than the result of the forceps biopsies in the later study and this may be due to larger number (at least 4 biopsies) of biopsies were taken.

In the current study, It was found that the diameter of the biopsies were taken by cryoprobe were significantly larger than that taken by the forceps ($p < 0.00$) which consequently affect the histopathological findings. This result came in accordance with study of Schumann and colleague.[29] On the other hand, Dobler and Crawford found no significant differences in diagnostic yield in relation to number or size of the biopsies. Their result was attributed to the retrospective nature of the study, where the number and volume of diagnostic specimens was not standardized.[18]

Generally, bronchoscopy is nearly a safe tool and few complications were recorded in the course of the procedures. The most important complications are broncho-spasm, cardiac arrhythmia, hemorrhage, post-bronchoscopic fever, pneumothorax, pneumonia and very rarely death. Hemo-rrhage is the most common complication occurs during bronchoscopy and recorded more in transbronchial compared with endobronchial biopsies. Rate of hemorrhage was reported at 1-26 %. Susceptibility to hemorrhage was related to bleeding diathesis, thrombocytopenia, defect in thrombocytic functions (secondary to drugs or diseases as uremia), lymphoma and leukemia. Also, bronchial carcinoma may itself associate with bleeding tendency.[30] Haemogram with coagulation profile were done for all patients in our study. The rate of hemorrhage was 30 % and only mild and moderate grades were reported. This rate nearly matched the results of previous studies.[28,29]

CONCLUSION

In conclusion, we have compared the use of conventional biopsy forceps with larger cryoprobe biopsy. We found good improvement in sample size and consequently the histopathological diagnosis when using cryoprobe biopsy. An important future direction will be the possibility of extracting cryobiopsies through the working channel of the endoscope, thus making cryobiopsy a promising alternative technique in clinical bronchoscopy.

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