Role of Cryotherapy in Obstructive endobronchial Neoplasms

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Abstract

Background: A common manifestation of lung cancer is central involvement of the airway. Bronchoscopic electrocautery, laser, argon plasma coagulation (APC), cryotherapy, photodynamic therapy, brachytherapy, intra-tumoral chemotherapy, mechanical debridement, and rotational micro-debrider are common treatments for patients with endobronchial neoplasms with the goals of debulking and palliation. Cryotherapy causes local tissue destruction by the application of extremely low temperatures (below -15 to -40°C). The profound cooling that occurs at the tip from the rapid expansion of gas results in intracellular and extracellular cryogenesis with coagulation necrosis

Aim: to evaluate the Safety, feasibility, and usefulness of Bronchoscopic Cryotherapy in the management of endobronchial neoplasms.

Methods: This study was conducted in Chest department, Kasr Al Ainy hospital, Cairo University; we enrolled Thirty-Three patients diagnosed with Endobronchial neoplasms, all patients were subjected to medical history and clinical examination, blood tests (CBC, KFT, LFT, coagulation profile, and ABG), and Radiology (Chest x-ray and CT chest). All Patients underwent the Cryotherapy ablation technique.

Results: We found that males represented (20 (60.6%), and non-smokers were (28 (84.8%) of the included patients. Cryotherapy ablation techniques showed significant improvement in the degree of obstruction and relief of clinical symptoms (Cough, Dyspnea, and hemoptysis) after the procedure. The duration of the procedure was 45.83±5.9 min. Bleeding was most reported with cryotherapy.

Conclusion: The bronchoscopic cryotherapy ablation technique is used for treating endobronchial lesions and plays a part in the palliative care of malignant central airway lesions.

Keywords: Endobronchial neoplasms, cryotherapy, Lung cancer.

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Introduction

Pure endobronchial neoplasm, defined as the tumor involving the bronchial lumen mainly, is rare and presents as diverse pathological distributions(1).A significant proportion of lung cancer patients will develop obstruction of the central airways at some point in the course of disease and as many as 40% of lung cancer related deaths are a direct result of loco-regional disease (2).Although most commonly a result of primary lung cancer, malignant central airway obstruction (CAO) can result from any primary or metastatic intrathoracic malignancy. Malignancies adjacent to the airways such as esophageal carcinoma, thyroid cancer and primary mediastinal tumors can cause airway obstruction either by external compression or direct tumor growth into the airways, while extra thoracic cancers can metastasize to the airways with the commonest culprits being breast, colorectal and renal malignancies (3). Although much less common, malignant CAO can also occur as a result of primary airway malignancies (4).

Cryotherapy causes local tissue destruction by the application of extremely low temperatures (below -15 to -40°C). The profound cooling that occurs at the tip from rapid expansion of gas results in intracellular and extracellular cryogenesis with coagulation necrosis. The area of necrosis is generally limited to the immediate area of the probe application and the ice ball formation. The cartilage is cryo-resistant, which adds to the safety of the procedure (5).

The term "cryotherapy" refers to the use of a liquid gas (such as nitrogen or carbon dioxide) to freeze the lesion tissues, causing structural damage and necrosis at low temperatures, making lesions simple to remove (6).

we conducted a cross section study to evaluate Safety, feasibility, and usefulness of bronchoscopic Cryotherapy ablation technique in the management of endobronchial neoplasms.

Patients and methods

We conducted a cross section study and enrolled Thirty-three patients diagnosed with Endobronchial neoplasms in the Chest department, Kasr Al Ainy hospital, Cairo University in the period from November 2020 to October 2022. Histopathology assessment prior intervention showed that twenty-three patients had malignant endobronchial neoplasms and ten patients had benign endobronchial neoplasms.

Any adult patient with endobronchial lesion and fit for bronchoscopy Cryotherapy ablation was eligible for inclusion in our study. Patients who reported coagulopathy (INR>1.5), Severe refractory hypoxemia, Hypoventilation with hypercapnia (type 2 respiratory failure), Severe

pulmonary hypertension > 55 mmHg by echocardiography, or Hemodynamic instability were excluded from the current study.

All patients were subjected to detailed history taking, history of present illness, thorough physical examination, Evaluation of dyspnea according to the modified Medical Research Council (mMRC) scale, evaluation of cough, evaluation of hemoptysis, Laboratory investigations including complete blood picture, liver and kidney function tests, coagulation profile, fasting blood glucose, and Arterial blood gases. All patients underwent plain Chest X-ray (PA view) and CT chest imaging.

Fiberoptic Bronchoscopic Procedures:

Bronchoscope with a flexible tip: Pentax EB-1970 TK Cryotherapy was performed using a 3.2 mm working channel. Prior to fiberoptic bronchoscopy, patients were required to fast for 6 to 8 hours. Premedication was administered in the form of intramuscular atropine (0.5 mg). Atropine's anti-cholinergic effects may lower airway secretions and the likelihood of reflex vasovagal symptoms such bronchoconstriction and bradycardia. The Freitag scheme was used to determine the location and level of impediment (7)

Technique of Bronchoscopy: The bronchoscope shaft is placed into an endotracheal tube size 8 after being thoroughly lubricated with 2% lidocaine gel following general anesthesia and intubation.

Bronchoscopic cryotherapy: Transbronchial cryoablation requires a well-equipped room with equipment for monitoring blood pressure, oxygen saturation, heart rate, and respiratory rate.

EB-1970 TK Pentax working channel of 3.2 mm. Cryo machines work in accordance with the Joule-Thompson effect, which indicates that when a compressed gas is released at a high flow, it will soon expand and generate very low temperatures. Cryo machines are made up of the console, cryogen, and cryoprobe (Diameter 2.4 mm / length 900 mm, ERBE, Germany). The cooling agent is applied through the core canal of the probe at high pressure (60 bar). For cooling, we used carbon dioxide (CO_2). The gas at the probe's tip expands quickly due to the pressure difference from atmospheric pressure, which results in a reduction in temperature (to -78°C). (8).

All procedures were carried out during flexible bronchoscopy, which was performed under general anesthesia over the course of 1 or 2 sessions lasting between 30 and 71 minutes. The bronchoscope's biopsy channel was used to insert the proper cryoprobe into the tumor, which was roughly 10 mm above the lesion. In this work, carbon dioxide is the cryogen. The flexible bronchoscope and cryoprobe are removed together with adherent tissue after being brought into touch with the target lesion, frozen for 20 to 30 seconds, and then frozen three more times to devascularize the tumor mass.

After bronchoscopy: Within 2 h after the procedure, a chest X-ray was done to exclude pneumothorax. Any complications observed were recorded, particularly bleeding and pneumothorax.

Ethical considerations: study protocol, and written informed consent were submitted for approval from the local ethical committee of Cairo university, and approval was granted with code: (MD-291-2020).

Statistical analysis: Results were presented numerically as mean ± SD, percentages, and median (interquartile range). The difference between groups were assessed using One way ANOVA followed by LSD post-hoc. Chi-square and Mann-Whitney tests were used for nominal data. Comparing means before and after interventions was measured by paired t-test for the same group. All statistical analyses were carried out by Statistical Package for the Social Sciences (SPSS) v.25 (IBM Corp. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

We enrolled 33 patients, Demographic data of patients who were included in this study, where the mean age of studied patients (44.97 ± 15.69) years and the percentage of male and female patients were 60.6% and 39.4% respectively. Smokers represented 84.8%. The most common site for airway obstruction in the studied patients was the right main bronchus (13 patients, 39.39%) followed by the left main bronchus (12 patients 36.36%) the lobar bronchi (2 patients, 6.06%) and the tracheal lesions were in 1 patient (3/03%) bronchus intermedius (5 patients, 15.15%). 69.7% of the obstructions were due to malignant lesions while 30.3% were caused by benign lesions. According to Freitag et al (7) classification, 66.66% of the studied patients showed a complete CAO, 24.24% were 90% obstructed, 6.06% were 75% obstructed, 3.03% were 50% obstructed, while 0% of patients showed 25% obstruction (**Table** 1). The symptoms assessment 1 month after the Cryotherapy ablation procedure showed significant improvements in cough, dyspnea, hemoptysis and the oxygen saturation improved (**Table** 2). Bronchogenic carcinoma and carcinoid tumor 78.3% were the most common malignant lesions while fibro lipoma and mucous gland adenoma 50% were the most common benign lesions. The mean procedure duration in the study was 45.83±5.9 min. 26 patients (78.78%) underwent one ablation session, 7 patients (21.21%) underwent 2 ablation sessions. Complete airway canalization was achievable in 72.72% of the study patients. While 24.24% of patients showed partial canalization and failed canalization was present in 3.03% of patients. Complications were reported in 4 (12.12%) patients. complications included bleeding in 4 patients, 1 case of peri-procedure mortality because of massive uncontrolled bleeding (**Table** 3).

Discussion

Endobronchial lesions can be managed with a variety of Bronchoscopic techniques, particularly when they are malignant neoplasms, which account for more than 50% of central airway lesions (10). Central airway neoplasms are frequently treated with one of the following methods. For debulking and palliative purposes, mechanical debridement methods include laser, argon plasma coagulation (APC), cryotherapy, photodynamic therapy, brachytherapy, intra-tumoral chemotherapy, and rigid bronchoscopy and rotational micro-debrider(11).

This study included 33 patients all of them were diagnosed as having lung neoplasm (malignant and Benign) via fibrooptic bronchoscopy and pathological reports. The included subject were underwent Cryotherapy ablation . In this study, there were significant improvement in cough, dyspnea and hemoptysis scores after Cryotherapy ablation where there is a highly significant improvement ($p<0.001$) in cough severity of dyspnea and hemoptysis in the studied patients. Amjadi et al (12), also reported 17 of 20 patients with an improvement in dyspnea and this is also present in the study of Oviatt et al (13).

respectively. According to Mohamed and Alm El-Din. (14), 30/38 patients (78.94%) who had cryotherapy experienced at least a one class improvement in their dyspnea symptoms. Following cryotherapy, the cough was relieved in 24/38 patients (63.15%) and the hemoptysis was improved in 12/14 patients (85.71%). According to Abd El Hafez et al. (15), cryotherapy resulted in a significant reduction in cough score (P: 0.002), a significant improvement in hemoptysis compared to baseline (p: 0.008), and a significant improvement in symptoms overall.

In the current study the Bronchoscopic Cryotherapy success rate in complete recanalization of bronchial tree accounting for 72.72% while partial recanalization was achieved in 24.24% and failed canalization in 3.03%.

According to Reichle et al. and Amjadi et al., the degree of recanalization of the airways can be utilized to assess the success of a surgery. Partial success is defined as more than 50% re-opening, failure as less than 50% patent after the treatment, and complete success as complete ablation of the endobronchial lesion (16,12). Mohammad et al. found that 85% of patients had more than 50% of their lumen recanalized after having Bronchoscopic cryosurgery for malignant endobronchial lesions, 15% had partial success, and there were no unsuccessful instances (14). Also in trial done by Hetzel et al. palliatively recanalized 60 patients with a cryoprobe utilizing a flexible bronchoscope, and they reported that 61% and 22% of the patients had complete and partial responses, respectively (17).

According to Lyu et al., 37% of patients experienced airway canalization, and 50% of lesions had a partial response to cryosurgery(18).

In the study by Dang and Zhang (19), complete clearance of the lesion and instantaneous airway patency was obtained in every instance (100%); Hisham E. Abdel-Aaty et al. found a highly significant improvement in the degree of obstruction in both EC and CRYO groups (P 0.01) (20).

In the present study, the rate of complications was relatively low affecting 4 cases (12.12%) complicated by bleeding 1 case of peri-procedure mortality because of massive uncontrolled bleeding.

Our results were in line with those of the study by Mohamed et al., who noted a few moderate and manageable adverse effects with cryotherapy, including mild hemoptysis, blood-tinged sputum (7.8%), respiratory discomfort (5.2%), mild fever (5.2%), and post-operative atrial fibrillation (2.6%). There was never any evidence of infection, cardiorespiratory arrest, or airway perforation (14).

According to Elkolaly et al. Hemoptysis, fever, and one case of airway perforation were among the manageable and infrequent non-lethal effects that occurred in both groups, 33.33% in group A and 33.33% in group B (9).

Cryotherapy results in tissue damage in these lesions by causing extracellular ice crystal formation, hypertonicity, and intracellular water loss. The increase in intracellular solute concentration and pH shift to around 4 cause damage to cellular proteins, lipoproteins, and enzymes (21).

The amount of free water in tissues directly affects how susceptible they are to freezing. Bronchial wall perforation is less frequent when lesions arising from the bronchial tree are treated with cryosurgery because the bronchial cartilage has a low free water content and is thus cryo-resistant. In response to freezing, the respiratory mucosa experiences necrosis, which is then followed by gradual epithelial regrowth. After 30 days, the respiratory mucosa regenerates as normal respiratory pseudo-stratified ciliated columnar epithelium after initially regenerating as cuboidal epithelium (22).

The healing process occurs without leading to the creation of fibrosis or strictures. This was supported by the Moorjani et al. investigation, which found no bronchial wall perforation-related pneumothorax, pneumomediastinum, or bronchoscopy-detected stricture formation (21).

The prognosis of patients, the frequency of side effects, and the degree of central airway stenosis brought on by lung cancer can all be dramatically improved by cryotherapy with argon plasma coagulation (23).

Conclusion

Bronchoscopic cryotherapy ablation for endobronchial tumors is a safe and effective treatment method that will improve the symptoms, degree of obstruction, and performance in patients with endobronchial obstruction also play a part in the palliative care of malignant central airway lesions.

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Table (1): Demographic data and Characteristics of central airway obstructing neoplasms among the studied population (N=33):

Variable		N=33
Age	(Mean ±SD)	44.97±15.69
Gender	Male Female	20 (60.60%) 13 (39.39)
Smoking history	Smoker Non smoker	28 (84.84) 5 (15.15)
Location of the lesion radiologically by CT Chest	Trachea Right main bronchus left main bronchus Bronchus intermedius Lobar Others	1 (3.03%) 13 (39.39%) 12 (36.36%) 5 (15.15%) 2 (6.06%)
Etiology of central airway obstruction	Malignant Benign	23 (69.69%) 10 (30.30%)
Degree of central airway obstruction	25% 50% 75% 90% 100 % (Complete)	0 1 (3.03%) 2 (6.06%) 8 (24.24%) 22 (66.66%)

Table (2): Symptoms and degree of obstruction improvements after Cryotherapy ablation technique among the studied population (N=33):

Symptoms		Pre	Post	P value
Cough	No	1 (3.03%)	23	P<0.001
	Cough does not disturb sleep	13	(69.69%)	
		(39.39%)	10	
	Cough disturbs sleep	19	(30.30%)	
		(57.57%)	0	
Dyspnea	No	1 (3.03%)	17	P<0.001
	Class I	1 (3.03%)	(51.51%)	
	Class II	2 (6.06%)	6	
	Class III	12	(18.18%)	
	Class IV	(36.36%)	9	
		17(51.51%)	(27.27%)	
			1	
			(3.03%)	
			0	
Hemoptysis	No	17 (40.8%)	26	P<0.001
	Streaks of blood in the sputum	5 (16.3%)	(85.7%)	
			6	
	Clots of blood in 4 days or less during the next 2 weeks	5 (26.5%)	(12.3%)	
			1	
	Clots in 5 or more days during the next 2 weeks.	6 (16.3%)	(2%)	
			0	
	Hemoptysis requires blood transfusion.	0	0	
Degree of central airway obstruction	No	0	24	P<0.001
	25%	1 (3.03%)	(72.72)	
	50%	2 (6.06%)	5	
	75%	8 (24.24%)	(15.15%)	
	90%	22	3	
	100 % (Complete)	(66.66%)	(9.09%)	
			1	
			(3.03%)	
			0	
			0	
Oxygen saturation (	mean ± SD	94.18	96.76	P<0.001
		±2.95	±0.09	

* McNemar test

\# Paired T-test

Table (3): The characteristics & outcome of the Cryotherapy ablation procedure among the studied patients (N=33):

variable		Cryotherapy (n=33)
Number of sessions	1	26 (78.78%)
	2	7 (21.21%)
Duration of the procedure (min)	Mean ± SD	45.83±5.9
Type of outcome	Complete canalization	24 (72.72%)
	Partial canalization	8 (24.24%)
	Failure	1 (3.03%)

Complications	Yes	4 (12.12%)
	No	29 (87.87%)
Type of complications	Bleeding	4 (100%)
	Respiratory failure 1	0
	Respiratory failure 2	0
	Perforation	0
	Pneumomediastinum	0
	Collapse	0
	Mortality	1 (25%%)

chi square test * One-way-ANOVA