

## Effect of combined treatment with cryotherapy plus chemo- radiotherapy versus chemo- radiotherapy alone in a non-small-cell lung cancer

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**Background:**In end-stage patients when all management options have been used, will often develop compromise of their airways as the cancer continues to progress. Endobronchial therapy options may help to relieve some of their symptoms, allowing improvement in their shortness of breath as they go home in combination with other palliative therapies.

**Objective:** To compare the safety; efficacy; and clinical outcome of endobronchial cryotherapy combined with chemotherapy and/ or radiotherapy versus chemo-radiotherapy alone on patients with Non-small cell lung cancer.

**Patients and method(s):** A prospective randomized clinical trial was carried out on 60 patients, diagnosed as bronchogenic carcinoma non-small cell lung cancer type (NSCLC). The patients attended the hospital in the chest department, Qena Faculty of Medicine, South Valley University. Assessment of the patients was done and randomly assigned into two groups. Group1, Include 30 patients subjected to chemotherapy, radiotherapy and endobronchial cryotherapy. Group2, Include include 30 patients subjected to chemotherapy and radiotherapy alone.

**Result(s):** There was significant response meat in symptomatology in Group (1) cryotherapy with regard to cough (P value .000) , dyspnea (P value .000) and haemoptysis (P value .000) . Also, from the functional point of view, in group 1 there were significant improvement to cryotherapy was achieved in FVC(P value .000) , FEV1 (P value .000) , PEFr (P value .000) , and 6MWT (P value .000) . However, there were no significant difference in group 2 between the incidence of improvement in FVC , FEV1 , PEFr , and 6MWT.

**Conclusion:**There was beneficial effect of combination of endobronchial cryotherapy to patients with lung cancer plus chemo and/ or radiotherapy in the form of improved symptoms and lung functions.

**Keywords:** non-small cell lung cancer, cryotherapy, symptomatology, lung function.

### Introduction:

Cryotherapy defined as the therapeutic application of extreme cold to living tissue in order to obtain their local destruction, sometimes it used as adjuvant treatment of lung cancers. It can be used in the cases of inoperable tumours to relieve airway obstruction , and thus improve respiratory functions of the patients (Vergnon, 1999).

Spray cryotherapy allows the application of cryogen without direct contact with the tissue

mass, and therefore is not limited to the cryoprobe surface area (Browning et al., 2015).

The base of this method is the cytotoxic effects of extreme cold which is safe, efficient, inexpensive and easy to perform. In addition, this technique does not present any major side effect (Vergnon, 1999).

In end-stage patients when all management options have been used, will often develop compromise of their airways as the

cancer continues to progress. Endobronchial therapy options may help to relieve some of their symptoms, allowing improvement in their shortness of breath as they go home in combination with other palliative therapies (Edellet al., 1993).

### Subjects and Methods:

The study was done in the bronchoscopy unit, chest department, South Valley University hospitals during the period from ( December 2016) to (may 2019). 60 patients with ages range of both sexes were included in this study after taking their signed consent.

All patients with bronchogenic carcinoma non-small cell lung cancer type (NSCLC) who gave their signed consent were included in this study as long as they were matched with the protocol of the study.

The selection of patients is randomly assigned in each group .

They classified into into two equal groups:

Group 1:

Include 30 patients subjected to chemotherapy , radiotherapy and endobronchial cryotherapy.

Group 2 :

Include include 30 patients subjected to chemotherapy and radiotherapy alone.

Inclusion criteria: -

1. Histologically proven carcinoma of the main and subsegmental bronchi.
2. Inoperable carcinoma based on the position of the tumor.

Exclusion criteria

- 1- Severe respiratory distress and
- 2- Uncorrectable bleeding profile.
- 3- Previous chemotherapy.

All patients were submitted to: -

These patients were assessed before cryotherapy and 2–6 weeks after cryotherapy, as regards the:

- Symptoms: dyspnea, hemoptysis, cough and chest pain.
- Blood gas analysis :

Done by ABL 800 base (Mediacorporation , USA )

- Prothrombin time, concentration
- CBC.
- Urea and creatinin.
- ECG :

Done by electro-cardiograph , MODEL ECG -2150 ( NIHON KOHDEN CORPORATION) TOKYO , JAPAN.

- Chest radiography.

- Chest CT :

Done by TOCHIBA SCANNER Aquilion , 64 predictors JAPAN

- Respiratory function tests:

Done by ( VIASYS-Micro Medical Limited – PO Box 6. Rochester – Kent. ME 1 2AZ ENGLAND) for assessment of forced expiratory volume in one second (FEV1), and forced vital capacity (FVC), 6-min walk test (6 MWT).

### Methods:

Cryotherapy is performed in the bronchoscopic unit by a bronchoscope model (ERBE, Germany, Flexible cryoprobe 80 cm. 2.2 mm in diameter ). All patients were admitted to hospital. Patients were fasted for 8 hours prior to bronchoscopy. Occasionally it was necessary to give a supplementary dose of diazepam 5mg intramuscular during the procedure to keep patients calm.

The procedure was carried out under aseptic operating conditions with the operator wearing sterile gloves and masks. The fiberoptic bronchoscope was ready for use after complete sterilization in 2% activated glutaraldehyde disinfectant solution (Cidex) for twenty minutes. The shaft of the fiberoptic bronchoscope was lubricated with lignocaine gel 2% before insertion to give additional surface anaesthesia.

The patient lay comfortably, in a semirecumbent position facing the operator. Lignocaine 2% solution (2ml) was sprayed into

the nose and nasopharynx. After a few minutes the fiberoptic bronchoscope was introduced transnasally below the inferior turbinates and then passed gently through the nasopharynx, down passed the epiglottis to the vocal cords.

When the scope was positioned above the vocal cords, a surface anaesthesia was applied by two bolus injections of 2 ml of lignocaine 2% injected through the inner channel of the fiberoptic bronchoscope. Then bronchoscope was gently passed through the vocal cords and into the trachea. Further 2 ml of lignocaine 2% were injected through the central channel of the fibrescope into the trachea, right and left bronchi, upper and lower lobes.

Then, the bronchial tree was examined, usually starting with the right side. Detailed exploration of the right main bronchus, upper, middle, and lower lobe bronchi down to the subsegmental levels. The fiberoptic bronchoscope was then withdrawn back to the level of the main carina and examination of the left side was carried out. As with the right side, the left main bronchus followed by the upper lobe, lingula and lower lobe bronchi was examined down to subsegmental levels.

#### Statistical methods:

- Student T test was used to compare between two quantitative data.
- Chi square test was used compare between two qualitative data.
- Results are expressed as numeric values (%).
- A test with a P value of less than 0.05 was considered as statistically significant.
- Using SPSS version 20.

#### Results:

The study included 60 patients who were admitted to chest department, South Valley University hospitals during the period from (December 2016) to (may 2019), where it was proved as having carcinoma of the main and subsegmental bronchi.

The patients were randomly assigned into two equal groups:

Group 1: include 30 patients subjected to chemotherapy, radiotherapy and endobronchial cryotherapy with age range from 37 -69 years and their mean age was  $56.73 \pm 8.46$ .

Group 2 : include include 30 patients subjected to chemotherapy and/or radiotherapy alone alone age range from 45-90 years and their mean age was  $66.53 \pm 10.9$ .

Tables (1) showed the effectiveness of cryotherapy as a palliative modality for the symptomatology of patients with endobronchial tumors.

In group 1, hemoptysis, cough and dyspnea showed significant improvement after cryotherapy, while chest pain showed no significant improvement. In group 2, The incidence of improvement of hemoptysis, cough, dyspnea and chest pain showed no significant improvement.

**Table (1): The effect of cryotherapy on the presenting symptoms.**

Present ation	Post-cryotherapy Group1 (30)					Post-therapy Group 2 (30)				
	Compl ained		Impro ved		P val ue	Compl ained		Impro ved		P val ue
	N o	%	N o	%		N o	%	N o	%	
Cough	24	80	18	75	.000*	24	80	28	80	0.6
Dyspnea	26	87	20	77	.000*	28	93	46	16	0.3
Haemoptysis	30	100	30	100	.000*	28	93	28	80	0.5
Chest pain	12	40	60	50	0.2	10	33	28	80	0.7

**Table (2):**The presenting symptoms between two groups' pre cryo and chemo-rdiotherapy.

Presentation	Group 1		Group 2		P value
	Precryotherapy (30)		Pretherapy (30)		
	No	%	No	%	
Cough	24	80	24	80	-
Dyspnea	26	87	28	93	.4
Haemoptysis	30	100	28	93	.2
Chest pain	12	40	10	32	.6

**Table (3):**The presenting symptoms between two groups post cryo and chemo-rdiotherapy.

Presentation	Group 1		Group 2		P value
	Post-cryotherapy (30)		Post-therapy (30)		
	No	%	No	%	
Cough	6	20	22	73	.000
Dyspnea	6	20	24	80	.000
Haemoptysis	0	0	26	87	.000
Chest pain	6	20	8	27	.5

Tables (4):-showed that from the functional point of view, in group 1 there were significant improvement to cryotherapy was achieved in FVC,FEV1,PEFR , and 6MWT. However, there were no significant difference in group 2 between the incidence of improvement in FVC,FEV1 , PEFR , and 6MWT.

**Tables (4):-** The effect of cryotherapy on the respiratory function tests.

Variants	Group 1 Precryotherapy (30)	Group 2 Pretherapy (30)	P value
Mean FVC	62.13	62.47	.9
Mean FEV1	64.53	65±5.01	.8
Mean PEFR	62.33	60.9±6.5	.5
Mean 6MWT	262	187.33	.000

**Tables (5):**The respiratory function tests between two groups post cryo and chemo-rdiotherapy.

Variants	Group 1 Post- cryotherapy (30)	Group 2 Post- therapy (30)	P value
Mean FVC	65	62.53	.3
Mean FEV1	69.87	65±5.01	.01
Mean PEFR	67.6	60.9±6.5	.008
Mean 6MWT	330	192	.000

### Discussion:

Lung cancer has the highest incidence in the malignant tumor (Nishida et al., 2011). 30% of patients develop severe dyspnea due to tracheal or bronchial obstruction by the tumor and even die from the respiratory failure (Qiu et al., 2013).

In Egypt there are poor statistical data estimating the problem of lung cancer . However, reports show that the problem of lung cancer is increased and represent about 8% of all cancer types with a peak age above 50 years and predominance in males (Ernst et al., 2003).

In the course of our study cryotherapy is a therapeutic modality based on destruction of the biological materials through the cytotoxic effect of freezing (Vergnon and Mathur, 2000). Experience with cryotherapy interventions in the tracheobronchial tree has been started to occur in Europe and United States in the last two decades (Mathur et al., 1996).

Cryotherapy proved a new modality of choice in dealing with hemoptysis which is the most serious symptoms caused by endobronchial tumors as it was 100% successful in this regard during our study. The same experience was recorded in (Mathur et al., 1996). Other studies reported a success rate ranging between 76-92% (Maiwand et al., 2004). On the other hand, the Egyptian experience of 73% and 87.5% in control of hemoptysis in the studies reported by Yousef, (2001) and Tag- El-din et al., (2004) respectively.

Dyspnea as a distressing symptom for patients with endobronchial tumor was also successfully improved in 77% of patients with cryotherapy complaining dyspnea and the degree of improvement in the mean grade of dyspnea was statistically significant. (Walsh et al., 1990) reported only 37% improvement of dyspnea in their series treated with cryotherapy but most of other studies recorded improvement rate of dyspnea compared with our study being 59%- 65% in Maiwand studies (1999, 2001); Maiwand and Asimakopoulos, 2004) and 70% in (Mathur et al., 1996) study. The Egyptian experience was lower than our results in dyspnea improvement being 60% (Yousef, 2001 and Tag- El-din et al., 2004).

The explanation of our relatively higher rate of dyspnea improvement may be due to the fact that most of our patients had no pre-existing chronic obstructive pulmonary diseases.

The experience of cryotherapy showed successful management of endobronchial tumors and reflected on the improvement recorded in 75% and 50% of cases in cough and

chest pain respectively and the improvement in the grade of the symptoms was statistically significant. Our rates of improvement of these symptoms are comparable to both national and international results (Maiwand and Asimakopoulos, 2004; Yousef, 2001; Tag- El-din et al., 2004).

While other studies reported a much lower incidence of improvement than ours 8.5% (in Tag- El-din et al., 2004) and 7% (Asimakopoulos et al., 2005).

Cryotherapy modality proved itself as a significant procedure during the course of this study in achieving significant improvement in the mean FVC %, as it was 62.13% precryotherapy and became 65% postcryotherapy, also the mean FEV1% was 64.53% pre-cryotherapy and became 69.87% Postcryotherapy. The mean PEFr % was 62.33% precryotherapy and became 67.6% postcryotherapy and all these values were highly statistically significant. In group 2 there is no significant difference before and after therapy.

Maiwand et al. (2005), reported that the objective measurement of respiratory functions showed improvement of FEV1 in 63.4% of the patients and FVC in 55.7% of the patients while Walsh et al., 1990, reported improvement in FEV1 and FVC in 24% of their cases for each. The low percentage of improvement reported by Walsh et al might be related to the type of patients in their study who were generally old (mean value of age  $71 \pm 9.3$ ) with severe limitation of breath and many had pre-existing chronic obstructive pulmonary disease (82%).

### Conclusion:

The successful bronchoscopic cryo therapy in controlling of symptoms related to the non-small cell lung cancer especially cough and haemoptysis when we used it before the traditional treatment chemotherapy and /or radiotherapy

The beneficial effect of endobronchial cryotherapy was reflected on significant improvement in FEV1, FVC, and PEFr.

#### References:

- Asimakopoulos G, Beeson J, Evans J, Maiwand M. O., (2005).** Cryosurgery for malignant endobronchial tumors: analysis of outcome. *Chest*; 127:2007–2014.
- Baust J.G., Gage A.A., Clarke D, et al., (2004).** Cryosurgery—a putative to molecular-based optimization. *Cryobiology*; 48:190—204.
- Browning R, Turner J.F., (2015).** Jr, Parrish S. Spray cryotherapy (SCT): institutional evolution of techniques and clinical practice from early Figure 5. Histology of transbronchial cryobiopsy. Low power views (A) 34, (B) 310, and (C) 340 all demonstrating the well-expanded alveoli without significant diffuse hemorrhage and crush artifact. Reprinted by permission from Dr. Lonny Yarmus. experience in the treatment of malignant airway disease. *J Thorac Dis*; 7:S405–S414.
- Edell E, Cortese D, McDougall, (1993).** J: Ancillary therapies in the management of lung cancer: photodynamic therapy, laser therapy, and endobronchial prosthetic devices. *Mayo Clin Pro.*; 86:685-690.
- Ernst A, Silvestri GA, Johnstone D., (2003).** American College of Chest Physicians. Interventional pulmonary procedures: guidelines from the American College of Chest Physicians. *Chest*; 123: 1693–1717.
- Maiwand MO, Asimakopoulos G., (2004)** Cryosurgery for lung cancer: Clinical Results and technical aspects. *Technology of cancer research and treatment*; 3(2)93-928.
- Mathur PN, Wolf KM, Busk MF, Briete WM, Datzman M., (1996).** Fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. *Chest*; 110:718–723.
- Qiu M, Xu L, Yang X, Ding X, Hu J, Jiang F, Xu L, Yin R., (2013).** XRCC3 Thr241Met is associated with response to platinum-based chemotherapy but not survival in advanced non-small cell lung cancer. *PLoS One*; 8: e77005.
- Tag- El-din M, Ashmawi S, Abd El-sabour M, et al., (2004).** fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. *Egypt J Chest Dis and Tuberc.*; 53(2):200-208.
- Vergnon J.M., Cryoth´erapie endobronchique, (1999).** techniques et indications. *Rev Mal Respir*; 16:619-23.
- Walsh D.A, Maiwand M.O, Nath A.R, Lockwood P, Lloyd M.H, Saab M., (1990).** Bronchoscopic cryotherapy for advanced bronchial carcinoma. *Thorax*; 45:509–513.
- Yousef A., (2001).** bronchoscopic cryotherapy in the management of different tracheobronchial lesion. MD thesis, Faculty of medicine Alexandria university.