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The value of endobronchial cryotherapy in the management of malignant endobronchial obstruction in patients with inoperable NSCLC: a prospective analysis of clinical and survival outcomes

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Abstract

Background: Malignant endobronchial obstruction (MEBO) is the most debilitating complication in non-small cell lung cancer (NSCLC). The therapeutic role of cryotherapy and its impact on survival has not been well addressed. This is to clarify whether the combination of endobronchial cryotherapy (EBCT) and chemoradiotherapy (CRT) improved symptoms, respiratory functions, performance status, and survival outcomes in inoperable NSCLC with symptomatic MEBO compared to that obtained by CRT alone.

Results: A prospective cohort study included 60 cases presented to Qena University Hospital, Egypt, between December 2016 and May 2019. They were divided into two groups. Group A included 30 patients who were managed with EBCT plus CRT. Group B included 30 patients who were managed with CRT alone. The outcomes assessed were symptoms relief, respiratory function tests (RFT), performance status, and survival outcomes at baseline and 4 weeks of follow-up. Group A patients showed a highly significant improvement in symptoms (cough, dyspnea, and hemoptysis), RFT, 6MWD test, and arterial blood gases, compared to group B. The mean Karnofsky score increased from $57.33 \pm 5.67\%$ at baseline to $60.67 \pm 6.39\%$ post-EBCT ($P=0.036$); group A was significantly improved compared to group B ($P=0.04$). The Kaplan-Meier median survival for all patients was 9.7 ± 0.4 months (95% CI= 8.86–10.54), and group A cases (10.77 ± 0.44 months, 95% CI= 9.9–11.6) was significantly longer than that of group B cases (8.6 ± 0.68 months, 95% CI= 7.3–9.97; T test = 2.631, $P=0.011$).

Conclusion: The use of EBCT with CRT for the management of MEBO in symptomatic patients with inoperable NSCLC is an efficient and safe procedure. EBCT improves clinical outcomes, RFT, performance status, and median survival.

Trial registration: ClinTrial.Gov registration: [NCT04710459](https://clinicaltrials.gov/ct2/show/study/NCT04710459) on 4/3/2021.

Keyword: Non-small-cell lung carcinoma, Cryotherapy, Malignant endobronchial obstruction, Median survival

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Background

Globally, bronchogenic carcinoma is the leading cause of cancer-related mortality worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers [2]. Malignant endobronchial obstruction (MEBO) refers to any malignant, mechanical, obstructive process that impedes the airflow within the central airways (trachea, main-stem bronchi, and right bronchus intermedius), and it complicates one third of these cases. This may occur via bronchial edema, invasion, or endoluminal growth. In advanced bronchogenic carcinoma with malignant obstruction, airway compromise occurs as cancer continues to progress [3, 4]. This will lead to atelectasis, pneumonia, and decrease response to chemoradiotherapy (CRT). Also, it affects patients' survival and responsible for 40% mortality. Moreover, inoperable NSCLC cases without MEBO have better survival than those with MEBO [5, 6]. Recently, due to the difficulty of NSCLC management, it is recommended to utilize a multidisciplinary team, including chest physicians, surgeons, oncologists, and interventional radiologists, to provide optimal, multimodality therapy options for these patients [7, 8].

Many interventional procedures have been evolved for MEBO ablation to relieve bronchial obstruction and alleviate symptoms. The basis of these procedures includes endobronchial tumor debulking, tumorectomy (laser, electrocautery, argon plasma coagulation, and cryotherapy), stents insertion, photodynamic therapy, or chemotherapy injection. The rationale for each procedure choice depends on tumor characteristics, degree of obstruction, patient clinical presentation, practitioner expertise, and equipment availability [9, 10].

The principle of endobronchial cryotherapy (EBCT) is the local tumor cell apoptosis and destruction by extreme cold application to tissues. EBCT is a cheap, safe, and reproducible method for MEBO palliation in patients with inoperable bronchogenic carcinoma; its therapeutic role and its impact on survival outcomes have not been well addressed, and a few studies about the impact of post-EBCT on performance status [11, 12]. Therefore, our study aimed to clarify whether the combination of EBCT and CRT improved the clinical outcomes, respiratory functions, performance status, and survival outcomes compared to those obtained by CRT alone in patients with inoperable NSCLC with symptomatic MEBO.

Methods

Study design

This is a single-center, random, prospective cohort study that included 60 inoperable NSCLC cases presented with symptomatic MEBO, between December 2016 and May 2019. The study conformed to the ethical standards of

the Helsinki Declaration, and approval was obtained from the IRB. Signed consent was taken from all cases. The outcomes assessed were symptoms relief, performance status, and survival outcomes.

Subjects

The study cases were randomly divided into two groups. Group A included 30 patients who were managed with EBCT plus CRT. However, group B included include 30 patients who were managed with CRT alone. The cases were considered inoperable for the following reasons: advanced unresectable bronchogenic carcinoma (stages III and IV), multiple metastases, advanced age, or refusal of surgery. All cases were evaluated clinically, radiologically, and for performance status at baseline before the procedure and 4 weeks after the procedure. All cases with pathologically proven, inoperable NSCLC cases with symptomatic MEBO obstructing >50% of the airways lumen in the proximal main bronchi or intermediate bronchus were included in the study. Cases with severe respiratory distress, uncorrectable impaired coagulation profile, and without MEBO were excluded from the study. All patients had CT chest and chest X-ray performed in their initial evaluation and 4 weeks post-procedure. All patients underwent clinical evaluation for dyspnea, hemoptysis, cough, and chest pain. The Medical Research Council (MRC) scale was used for clinical dyspnea evaluation. Six-minute walking distance (6MWD) test and spirometry for the assessment of forced expiratory volume 1 (FEV1) and forced vital capacity (FVC) were done at baseline before the procedure and 4 weeks after the procedure. The performance status was assessed using the Karnofsky score.

Methods

Chemoradiotherapy

It was 5000 CGY in conventional fractionation on the lung mass only, along with a concurrent gemcitabine short infusion of 600 mg per square meter weekly.

Endobronchial cryotherapy

A cryoprobe (Erbe, Germany, Flexible, 80 cm, 2.2 mm in diameter) with nitrous oxide as a cryogen was used. The procedure was done via flexible bronchoscopy (PENT AX EB-1970K, 2.8 mm channel) under intravenous midazolam sedation and local anesthesia with 2% xylocaine solution or gel. Routine monitoring was done for all cases during bronchoscopy [13]. The patient lay comfortably in a semirecumbent position. The bronchoscope was introduced transnasally into the tracheal and bronchial lumen. The distal end of the bronchoscope is placed approximately 5 mm above the proximal end of the lesion, and the appropriate cryoprobe is inserted

through the biopsy channel of the bronchoscope and applied to the tumor.

EBCT was started with -80°C at the probe tip from 20 to 60 s at the lesion site and then allowed to thaw until the probe separated from the tissue. The probe was then moved 5–6 mm and another one to three freeze-thaw cycles carried out in the adjoining area. The procedure was continued until the entire visible part of the tumor had been frozen. Necrotic tumor material was removed after each cryo-application using a biopsy-type clamp. After complete removal of the mass, the bronchoscope was reintroduced to check for airway patency. The procedure was considered successful if airway patency of at least 80% of the normal was achieved post-EBCT. The procedure took approximately 20 min, and most patients recovered well enough to be discharged on the same day.

Statistical analysis

The Statistical Package for Social Sciences (IBM-SPSS), version 25 (IBM-Corporation, Chicago, USA; August 2017) was used for statistical data analysis. Data are expressed as mean, standard deviation (SD), number, and percentage. Student *t* test was used to compare the means between two groups, and the Pearson chi-square test was used to compare percentages of qualitative variables. The paired *t* test was used to compare means of the same variable at different periods, and the McNemar chi-square test was used to compare percentages of the same variables at different periods also. Survival outcomes were assessed using the Kaplan-Meier curve analysis. For all these tests, the level of significance (*P* value) was explained as non-significant $P > 0.05$, significant $P < 0.05$, and highly significant $P < 0.001$.

Results

Baseline clinical data

Group A included 30 patients; their mean age was 56.73 ± 8.5 years and 18 (60%) patients were males. Group B included 30 patients with a mean age of $59.4 \pm$

12 years and 14 (47 %) patients were males (Table 1). Both groups were comparable regarding the baseline clinical data (cough, dyspnea, hemoptysis, and chest pain). The most distressing complaint was hemoptysis, which was present in all cases (100%) in group A and group B in 28 (93%) cases. Also, dyspnea was presented in 26 (87%) cases in group A and 28 (93%) cases in group B. In each group, 24 (80%) cases presented with cough.

Respiratory function tests (RFT) showed obstructive values in both groups, and they were comparable regarding the baseline RFT ($P=0.6$). The 6MWD and arterial blood gases (ABG) were comparable ($P>0.05$). Also, both groups were comparable regarding the performance status ($P= 0.8$) (Table 2).

Group A patients were subdivided into two subgroups, 21 patients with main bronchial obstruction (group A1) and 9 patients with lobar obstruction (group A2). They were comparable regarding the baseline clinical data, baseline RFT, 6MWD, ABG, and performance status (Table 3).

Post procedures clinical outcomes

EBCT was performed successfully in all group A cases. Also, it resulted in a highly significant improvement in hemoptysis, dyspnea, and cough ($P<0.001$) and a non-significant improvement in chest pain ($P = 0.09$) at 4 weeks follow-up. However, group B cases showed a non-significant improvement in hemoptysis, cough, dyspnea, or chest pain ($P > 0.05$) at 4 weeks follow-up.

Meanwhile, group A patients showed a highly significant improvement in cough, dyspnea, and hemoptysis than group B ($P<0.001$). There was a non-significant improvement in chest pain among both groups ($P = 0.5$). There was no mortality, bleeding, or any other life-threatening complications in group A. Also, none of group B patients experienced severe side effects (Table 2).

In group A1, there was a highly significant improvement in hemoptysis, dyspnea, and cough ($P<0.001$) and

Table 1 Preoperative demographic data

Variable	Group A (n=30)	Group B (n=30)	P value	
Age	56.73±8.5	59.4±12	0.5	
Gender (male)	18 (60%)	14 (46.7%)	0.5	
Comorbidities	Hypertension	21 (70%)	19 (63.3%)	0.6
	Diabetes mellitus	7 (23.3%)	8 (26.7%)	
	COPD	9 (30%)	6 (20%)	
Special habits	Current smoker	8 (27%)	10(33%)	
	Ex-smoker	10 (33%)	10 (33%)	
	Bird breeder	8 (27%)	8 (27%)	
	No special habits	4 (13%)	2 (7%)	

Table 2 Comparison of the clinical presentation outcomes, respiratory function tests, arterial blood gases, and the mean Karnofsky performance score for group A (EBCT+CRT) and group B (CRT) at baseline and follow-up after the procedure

Variable		Group A		Group B		P values I & II	P values I & III	P values II & IV	P values III & IV
		Pre-cryotherapy (I) (n=30)	Post-cryotherapy (II) (n=30)	Pre-therapy (III) (n=30)	Post therapy (IV) (n=30)				
Clinical presentation	Cough	24 (80%)	6(20%)	24 (80%)	22(73%)	<0.001	1.000	<0.001	0.592
	Dyspnea	26 (87%)	6(20%)	28 (93%)	24(80%)	<0.001	0.667	<0.001	0.254
	Hemoptysis	30 (100%)	0	28 (93%)	26(87%)	<0.001	0.472	<0.001	0.667
	Chest pain	12 (40%)	6(20%)	10 (32%)	8(27%)	0.090	0.592	0.541	0.573
Respiratory function tests	Mean FVC %	62.13±2.8	65±3.65	62.47±1.8	62.53±1.7	0.001	0.578	0.001	0.895
	Mean FEV1 %	64.53±3.8	69.87±4.0	65±2.9	65±2.6	<0.001	0.592	<0.001	1.000
	Mean 6MWT (m)	262±56	330±76	287±78	292±48	<0.001	0.159	0.024	0.766
Arterial blood gases	Mean PH	7.382±0.2	7.385±0.1	7.381±0.1	7.39±0.03	0.465	0.807	0.390	0.124
	Mean So2	87.07±1.8	90.4±1.5	86.7±1.9	87±1.7	<0.001	0.442	<0.001	0.522
	Mean PaO2	77.07±1.8	82.9±1.8	76.9±2.4	77.3±2.6	<0.001	0.757	<0.001	0.538
	Mean PaCo2	36.9±1.6	41±1.1	37.7±1.8	38.2±1.9	<0.001	0.074	<0.001	0.300
Mean Karnofsky performance score %	57.33±5.67	60.67±6.39	56.87±9.19	56.32±9.63	0.036	0.816	0.044	0.822	

a non-significant improvement in chest pain ($P = 0.079$) at 4 weeks follow-up. However, in group A2 cases, there was a non-significant improvement in cough, dyspnea, or chest pain ($P = 0.5$), and there was a highly significant improvement in hemoptysis ($P < 0.001$). Group A1 cases compared to group A2 cases showed a significant improvement in cough and dyspnea ($P < 0.028$ and 0.001). Hemoptysis improved in both subgroups ($P = 1$) (Table 3).

Impact on RFT, 6MWD test, and ABG

The EBCT modality proved to be an efficient procedure during this study in achieving a highly significant improvement in the mean FVC and mean FEV1; they were $62.13 \pm 2.8\%$ and $64.53 \pm 3.8\%$ pre-EBCT and increased to $65 \pm 3.65\%$ and $69.87 \pm 4.0\%$ post-EBCT, respectively ($P < 0.001$). Moreover, this resulted in a highly significant improvement in the mean 6MWD test in group A, which increased from 262 ± 56 m at baseline to 330 ± 76 m after the 4 weeks follow-up ($P < 0.001$). On the contrary, group B showed a non-significant improvement in the mean FVC, FEV1, or 6MWD test post-therapy ($P > 0.05$). However, group A post-EBCT showed a highly significant improvement in the mean FVC and FEV1 ($P < 0.001$) and a significant improvement in the mean 6 MWD test ($P < 0.02$) in comparison to group B post therapy at 4 weeks follow-up.

Regarding ABG, there was a highly significant improvement in the mean ABG parameters (SaO_2 , PaO_2 , and PaCO_2) in group A cases post-EBCT ($P < 0.001$). On the other hand, group B cases showed a non-significant

improvement in the mean ABG parameters post-therapy ($P > 0.05$). However, group A cases post-EBCT showed a highly significant improvement in the mean ABG parameters in comparison to group B post therapy at 4 weeks follow-up ($P < 0.001$) (Table 2).

Regarding group A subgroups, group A1 post-EBCT showed a significant improvement in the mean FVC and FEV1 compared to group A2 ($P = 0.049$ and 0.015). However, 6MWD showed a non-significant improvement among both subgroups. There was a highly significant improvement in the mean ABG parameters (SaO_2 , PaO_2 , and PaCO_2) in group A1 cases compared to group A2 post-EBCT ($P < 0.001$) (Table 3).

Impact on performance status and median survival

There was a significant improvement in the mean Karnofsky performance score in group A ($P = 0.036$), and it increased from $57.33 \pm 5.67\%$ at baseline to $60.67 \pm 6.39\%$ after 4 weeks of follow-up. On the contrary, group B cases showed a non-significant improvement in the performance status during follow-up in comparison to the pre-CRT value ($P = 0.8$). However, group A showed a significant improvement in performance status in comparison to group B at 4 weeks follow-up ($P = 0.04$) (Table 2).

Regarding group A subgroups, there was a significant improvement in the mean Karnofsky performance score in group A1 ($P = 0.014$), and it increased from $57.30 \pm 5.52\%$ at baseline to $62.04 \pm 6.46\%$ after 4 weeks of follow-up. However, there was a non-significant improvement in the mean Karnofsky performance score among both group A1 and A2 ($P = 0.177$) (Table 3).

Table 3 Comparison of the clinical presentation outcomes, respiratory function tests, arterial blood gases, and the mean Karnofsky performance score for group A subgroups (main bronchi and lobar bronchi obstruction)

Variable		Main bronchi (Group A1)		Lobar bronchi (Group A2)		P values I & II	P values I & III	P values II & IV	P values III & IV
		Pre-cryotherapy (I) (n=21)	Post-cryotherapy (II) (n=21)	Pre-therapy (III) (n=9)	Post therapy (IV) (n=9)				
		Clinical presentation	Cough	18(85.7%)	2(9.5%)				
	Dyspnea	20(95.2%)	1(4.8%)	6(66.7%)	5(55.6%)	<0.001	0.128	0.001	0.629
	Hemoptysis	21(100%)	0	9(100%)	0	<0.001	1.000	1.000	<0.001
	Chest pain	8(38.1%)	3(14.3%)	4(44.4%)	3(33.3%)	0.079	0.745	0.232	0.629
Respiratory function tests	Mean FVC %	62.21±1.9	66.81±2.8	62.11±2.2	64.2±3.34	<0.001	0.906	0.049	0.137
	Mean FEV1 %	64.33±3.5	71.11±3.8	64.69±3.8	67.34±3.6	<0.001	0.809	0.015	0.148
	Mean 6MWT (m)	259±55	341±71	268±62	301±59	<0.001	0.709	0.121	0.264
Arterial blood gases	Mean PH	7.382±0.01	7.386±0.01	7.381±0.02	7.383±0.01	0.202	0.888	0.458	0.792
	Mean So2	87.11±1.9	91.1±1.9	86.99±1.6	89.1±1.8	<0.001	0.860	0.011	0.018
	Mean PaO2	77.12±1.9	84.2±2.2	76.97±2.1	80.4±1.9	<0.001	0.855	<0.001	0.002
	Mean PaCo2	37.01±1.9	42.81±0.9	37.72±1.8	38.72±1.9	<0.001	0.339	<0.001	0.269
Mean Karnofsky performance score %		57.30±5.52	62.04±6.46	57.39±5.76	58.28±6.97	0.014	0.969	0.177	0.772

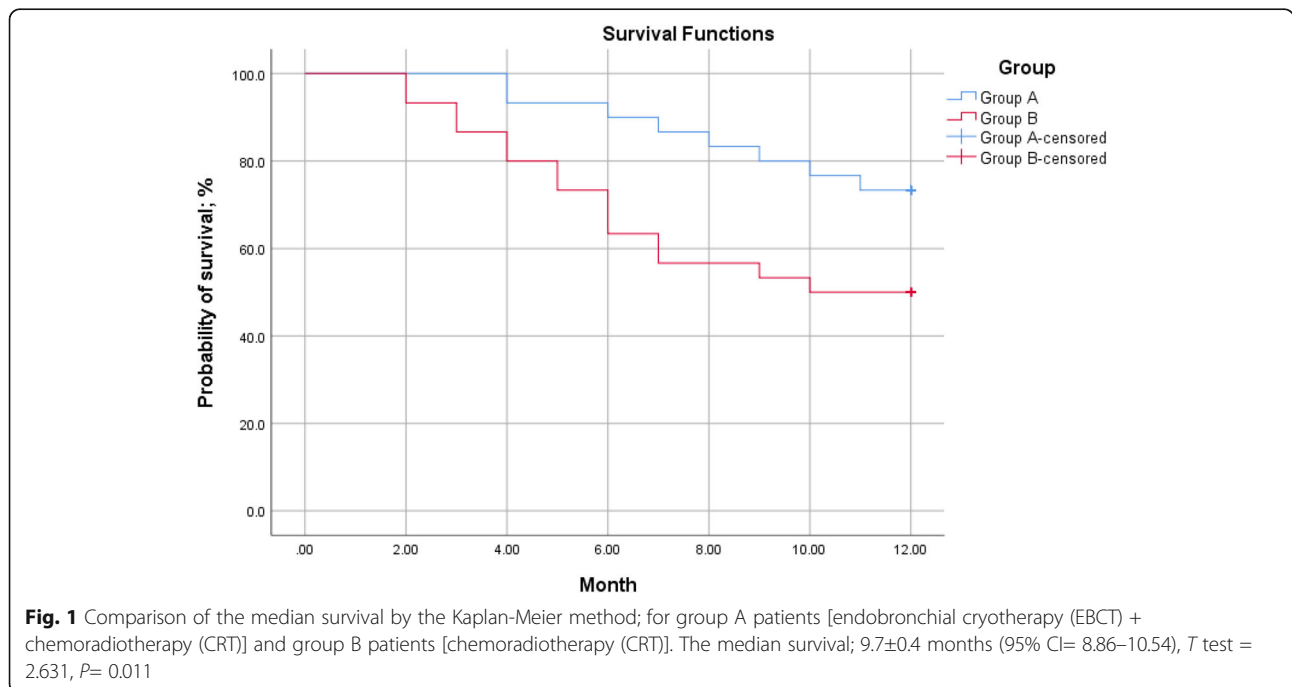
The median survival for all 60 patients by the Kaplan-Meier method was 9.7±0.4 months (95% CI= 8.86–10.54). The median survival of group A patients (10.77±0.44 months, 95% CI= 9.9–11.6) was significantly longer than that of group B cases (8.6±0.68 months, 95% CI= 7.3–9.97; *T* test = 2.631, *P*= 0.011) (Fig.1).

There was a non-significant change in the median survival among group A1 and group A2 (the median

survival; 10.77±0.44 months (95% CI= 9.90–11.63), *T* test = 0.629, *P*= 0.535.) (Fig.2).

Discussion

MEBO is the most debilitating complication that may occur in inoperable NSCLC; especially, about 75% of cases are not amenable for surgery at the time of diagnosis. Also, in association with hemoptysis and dyspnea,



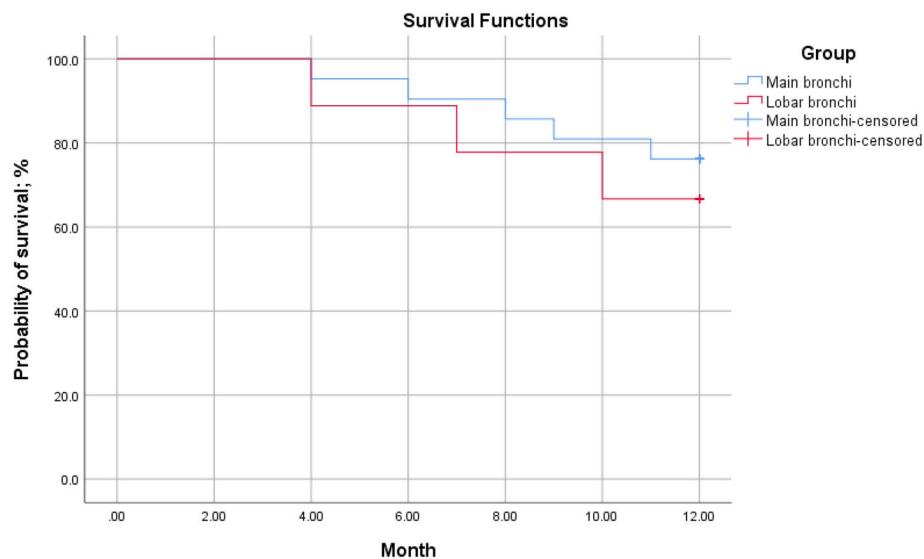


Fig. 2 Comparison of the median survival by the Kaplan-Meier method; for main bronchi patients and lobar bronchi patients in group A patients. The median survival; 10.77 ± 0.44 months (95% CI = 9.90–11.63), T test = 0.629, P = 0.535

MEBO may cause physical and psychological distress. Cryotherapy was used in the beginning to diagnose MEBO; however, the therapeutic role of cryotherapy and its impact on survival has not been well addressed [14]. In this prospective study, we found that EBCT with CRT improves the symptoms, RFT, ABG, performance status, and median survival in patients with inoperable NSCLC with MEBO.

EBCT was performed successfully in all of our cases. It was effective in relieving cough and dyspnea in all group A cases. Interestingly, hemoptysis was the most distressing complaint, and it was successfully controlled in all group A cases. However, a non-significant improvement in chest pain at 4 weeks follow-up. Similarly, Asimakopoulos et al. reported that EBCT significantly improved the symptoms of dyspnea, cough, and hemoptysis in 329 patients ($P < 0.001$) [15].

Moreover, Maiwand et al. reported that EBCT provided an improvement in hemoptysis (76.4%), cough (69%), and dyspnea (59.25%), in their study including 512 patients with MEBO [16]. Additionally, relief of symptoms in 86% of cases was reported in a study by Fang et al. [17]. In accordance with previous studies, the symptoms improved post-EBCT in bronchogenic carcinoma patients with MEBO [18–20]. On the contrary, the improvement of the symptoms was seen in 37% of cases in a study by Walsh et al. [21]. The relatively higher rate of dyspnea improvement could be explained by that we do not have many chronic obstructive pulmonary diseases (COPD) cases, and their mean age was lower than other studies.

During this study, EBCT modality proved itself as an efficient procedure in achieving a significant

improvement in the RFT, 6MWD test and the mean ABG parameters in group A compared to group B at 4 weeks follow-up post-therapy. In accordance, there was a significant improvement in FEV1 and FVC post-EBCT in a study by Maiwand et al. (FEV1 from 1.80 ± 0.6 l to 1.95 ± 0.8 (8.3%) l; FVC from 2.50 ± 0.8 to 2.68 ± 0.8 l (7.2%) ($P < 0.05$) [16]. Similarly, Mohamed et al. reported a significant improvement in mean FVC and mean FEV1 from 1.43 and 1.21 at baseline to 2.41 and 2.94 6 weeks post-EBCT, respectively [19]. Also, Asimakopoulos et al. found that the RFT improved significantly post-EBCT [15]. Oppositely, there was a low percentage of RFT improvement in 24% of cases in a study by Walsh et al. This could be clarified by that most of their patients were generally old (mean value of age 71 ± 9.3 years) with severe limitation of breath and many had the pre-existing COPD (82%) [21].

In our study, the mean Karnofsky performance score showed a significant improvement post-EBCT compared to the baseline score as well compared to group B cases post therapy at follow-up. On the contrary, group B cases showed a non-significant improvement in the performance score compared to the pre-therapy score. In accordance with Fang et al. and Chung F et al., they declared a significant improvement in the performance status post-EBCT in patients with MEBO; furthermore, they were candidates to receive chemotherapy [17, 20]. Additionally, previous studies reported a similar performance score improvement post cryotherapy [16, 19]. Nevertheless, Asimakopoulos et al. and Tag-El-din et al. reported a lower incidence of performance score improvement than our results; in 8.5% and 7%, respectively, [15, 22].

Using the Kaplan-Meier method, the median survival for group A cases was significantly longer than that of group B cases. Our results were comparable with previous studies, which declared that the overall survival was significantly improved in bronchogenic carcinoma patients with MEBO for whom EBCT was done in conjunction with systemic treatment, and it was longer than those who did not receive EBCT [17, 20, 23]. Beeson on here study on 645 patients and about 72% of them with advanced bronchogenic carcinoma; she declared that cryotherapy could increase the survival rate [24]. Moreover, Asimakopoulos et al. reported that EBCT improved overall survival in patients with advanced lung cancer; also, when performed more than twice (15 months) was better than one session (8.3 months) [15]. Also, Maiwand et al. performed two sessions of cryotherapy for 521 inoperable bronchogenic carcinoma patients and improved survival [16]. Oppositely, Zoganas et al. in their study on inoperable cancer patients and found a non-significant difference in the survival rate over 2 years between the EBCT group compared to anticancer treatment [25]. Limitations of our study include non-randomization, small sample size, and a short follow-up period.

Conclusion

The use of EBCT with CRT for the management of MEBO in symptomatic patients with inoperable NSCLC is an efficient and safe procedure. EBCT improves clinical outcomes, RFT, performance status, and median survival.

Abbreviations

NSCLC: Non-small cell lung cancer; MEBO: Malignant endobronchial obstruction; CRT: Chemoradiotherapy; EBCT: Endobronchial cryotherapy; MRC: Medical Research Council; 6 MWD: Six-minute walking distance; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; RFT: Respiratory function tests; ABG: Arterial blood gases; COPD: Chronic obstructive pulmonary disease

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Authors' contributions

AR: Conceptualization, methodology, writing - review & editing. MB: Investigation, supervision. MMA: Data curation, writing - original draft. HM: Software, validation, investigation, resources. MA: Writing - review & editing, visualization, project administration. The authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study conformed to the ethical standards of the Helsinki Declaration, and approval was obtained from the institutional ethics committee of Qena Faculty of Medicine (no. 84), South Valley University (10/12/2016). A written consent was obtained from the study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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