Cryosurgery for Malignant Endobronchial Tumors*

Analysis of Outcome

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Study objectives: **More than 80% of patients with lung cancer are unsuitable for curative surgical treatment. Palliative relief of symptoms, often caused by airway obstruction, is very important. Endobronchial cryosurgery is used for destruction of intraluminal tumors. This study analyzes the effects of cryosurgery on patients with obstructive endobronchial carcinoma.**

Design: **Retrospective analysis of data extracted from a prospective computerized database.**

Setting: **Tertiary referral thoracic surgical center.**

Patients: **Data of the 172 patients who underwent at least two sessions of endobronchial cryosurgery (group A) were compared with 157 patients who underwent one session of cryosurgery (group B) for malignant primary or metastatic obstructive lung carcinoma over a 5-year period.**

Intervention: **Endobronchial cryosurgery is performed under general anesthesia. A nitrous oxide cryoprobe is inserted through a rigid bronchoscope. The probe achieves a temperature of − 70°C at its tip and is applied to the tumor for two 3-min periods. Statistical analysis assessed the effects of cryosurgery on symptoms, lung function, Karnofsky performance score, and survival.**

Results: **Symptoms of dyspnea, cough, and hemoptysis were significantly reduced in both groups after cryosurgery ($p < 0.001$), although group A benefited more than group B. Lung function test results improved significantly in group A. The mean Karnofsky performance score (± SD) increased from 67 ± 9 to 74 ± 10 (group A) and from 67 ± 10 to 73 ± 11 (group B). The mean survival was 15 months (median, 11 months) for group A and 8.3 months (median, 6 months) for group B ($p = 0.006$). Univariate regression analysis showed that no particular patient or tumor characteristic was associated with reduction of symptoms. Patients who had cryosurgery and external beam radiotherapy showed longer survival ($p < 0.01$). Females and patients with stage IIIa and IIIb tumors achieved significantly improved Karnofsky scores ($p < 0.02$). Female sex was also a factor for increase in FEV at 1 min ($p = 0.003$) and FVC ($p < 0.001$).**

Conclusions: **Cryosurgery is a safe method for palliation of endobronchial malignancies causing airway obstruction. Statistical analysis showed improvement of dyspnea, cough, and hemoptysis. Cryosurgery can be considered in patients with inoperable obstructive endobronchial carcinoma.**

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Key words: bronchial tumor; bronchoscopy; lung cancer; regression analysis

Abbreviations: NYHA = New York Health Association; PEF = peak expiratory flow

Lung cancer is the leading cause of death from malignant disease in the world and represents > 17% of all new cases of cancer and 28% of all cancer deaths worldwide.[1] At the time of diagnosis, > 80% of patients are inoperable, resulting in a 5-year survival rate of 14%.[2] Approximately 30% of patients present with a large carcinoma obstructing the trachea or main bronchi and causing dyspnea, cough, or hemoptysis. Palliative reopening of the affected airways often alleviates symptoms. Radiotherapy and chemotherapy are the standard treatment modalities available for palliation of lung cancer. Methods of endobronchial treatment include laser photoresection, photodynamic therapy, endobronchial stents, brachytherapy, and cryosurgery.[3]

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Cryosurgery is the controlled application of extreme cold for local destruction of abnormal living tissue. Attempts to treat malignant tumors with local application of cold were made in the mid-19th century, although manufacturing of reliable cryosurgery equipment was not achieved until a century later.[4] Cryosurgery for the palliative treatment of endobronchial tumors was first reported in Europe by our group in 1986[5] and has since been used in > 1,000 patients. Endobronchial cryosurgery is performed on patients under general anesthesia using a rigid bronchoscope. Temperature of − 70°C at the end of a cryoprobe causes destruction of the tumor. A course of cryosurgery usually consists of two sessions with a 2- to 6-week interval. Often, however, clinical condition of patients prevents them from undergoing more than one session. Patient-specific information and postcryosurgery clinical data have been placed prospectively in a computerized database since 1995. In this study, we analyzed the effects of palliative endobronchial cryosurgery on symptoms, performance status, lung function, and survival in patients with malignant lung tumors who underwent at least two cryosurgery sessions. We compared these findings with a group of patients who underwent only one session of cryosurgery. Furthermore, we analyzed patient-specific and specific-specific characteristics in relation to outcome.

Materials and Methods

Data Collection

Prospective data of all patients receiving endobronchial cryosurgery are collected on the Cryosurgery Research Data Base at Harefield Hospital (Harefield, UK). Data are collected by a nurse with > 10 years of experience in thoracic surgery and processed by a database manager. Patients are assessed clinically and radiologically in the outpatient clinic before and 2 weeks after each treatment session. Patients are followed up indefinitely, provided that their clinical condition allows them to attend the outpatient clinic. Patient identification and endobronchial pathology are recorded, and clinical examination, a chest radiograph, and respiratory function tests are carried out. Symptoms, objective lung function tests (peak expiratory flow [PEF], FEV_1, and FVC), site and stage of the tumor, histologic type, adjuvant therapy, and survival are also recorded. The New York Health Association (NYHA) classification was used for assessment of dyspnea, and estimation of life quality was performed using the Karnofsky score.[6] Hemoptysis was classified as follows: 0, none; 1, previous episodes but not for 1 month; 2, previous episodes but not for 1 week; and 3, hemoptysis over previous week. Cough was classified as follows: 0, none; 1, mild; 2, persistent, does not disturb sleep; and 3, persistent, disturbs sleep. Tumor staging was carried out based on radiologic information and followed the latest published guidelines.[7]

Patient Groups

Three hundred twenty-nine new patients underwent cryosurgery for obstructive, symptomatic, malignant endobronchial tumors by the senior author of this article (M.O.M.) from January 1996 to December 2000. Patients were classified into two groups for the purpose of this study. Group A included the 172 patients who underwent at least two sessions of cryotherapy. The common feature of these patients was that their selection was based on completion of the standardized cryosurgery protocol, including the two sessions. Group B included 157 patients who underwent only one session of cryosurgery. Group B included a more diverse patient group, most of which were presented in a condition that did not allow them to undergo a second session of cryosurgery. All patients included in the analysis had 100% completion of data collection during the study period. Analyzed outcome variables were measured at follow-up appointments at 2 weeks and 8 weeks after the second session of cryosurgery.

Technical Aspects of Endobronchial Cryosurgery

The technical aspects of endobronchial cryosurgery have been described previously.[5,8] Indications for endobronchial cryosurgery include endobronchial, obstructive tumors that cause symptoms or that are likely to result in the immediate development of symptoms. The majority of these tumors are regarded as inoperable based on the advanced stage of the disease or the lung function and performance status of the patient. Before endobronchial cryosurgery, the procedure, benefits, and risks are explained to the patient, and informed consent is obtained. The procedure is performed under short-acting IV general anesthesia, using a large rigid (9.2 mm) and a flexible bronchoscope (2.4 mm). Oxygenation is maintained with Venturi positive pressure ventilation. A Joule-Thomson-type probe (Spembly Medical; Hampshire, United Kingdom) with nitrous oxide as the cryogen is used. A temperature of approximately − 70°C is achieved at the probe tip. The distal tip of the bronchoscope is placed about 5 mm above the lesion, and the cryoprobe is inserted through the bronchoscope and applied to the tumor. Tissue samples for histologic examination are obtained before each cryosurgery. Bleeding from the site of a biopsy or cryosurgery is contained by the local application of epinephrine (adrenaline) 1:1,000. The tumor is frozen for 3 min and then allowed to thaw until the probe separated from the tissue. If the tumor covered wider areas of the bronchial tree, multiple cryoapplications of epinephrine are made during the same treatment session. Necrotic tumor material, when present, was removed after each cryoapplication of epinephrine using a biopsy-type clamp. Patients often report that additional necrotic-appearing material is coughed out 24 to 48 h after cryosurgery. More than 95% of patients are discharged to home on the same day. Patients are reviewed in the outpatient clinic 2 weeks after each cryosurgery session and every 6 weeks thereafter. In view of the nature of the disease, regrowth of the endobronchial portion of the tumor is often rapid. Although quantification of tumor recurrence is difficult, medium-term outcome is reflected by survival reported in this study. Contraindications of cryosurgery include inability of the patient to undergo general anesthesia or previously observed poor tumor response to the procedure.

Statistical Analysis

Age, sex, site of tumor, histologic type, stage, and adjuvant treatment were used as explanatory variables of interest. These were related to outcome variables such as dyspnea class, severity of cough, hemoptysis, Karnofsky score, lung function tests (FEV_1 and FVC), and survival (time between cryosurgery and death). A Wilcoxon-matched pairs signed-rank sum test was carried out for each outcome variable to determine whether there was a difference between before and after cryosurgery measurements. Categorical data were compared between groups using Fisher Exact Test or the χ^2 test. Distributions of continuous data were observed, and *t* tests or Mann-Whitney *U* tests were performed accordingly for comparisons of groups. Univariate Cox regression analysis, with calculation of hazard ratio, was performed for each variable of interest to assess their association with survival. Ordered logistic regression analysis, with calculation of odds ratio, was used to assess the association of variables of interest with all other outcome variables. Univariate regression analysis was followed by multivariate analysis. Actuarial survival curves were calculated by the Kaplan-Meier method and compared with the log-rank test. Results are expressed as mean ± SD or as the appropriate ratio at 95% confidence interval. A p value of < 0.05 was considered significant.

Results

Patient characteristics, disease characteristics, survival times, and complications after cryosurgery in the two patient groups are shown in Table 1. Overall, the two groups were similar with regard to sex, age, histologic type, and stage of the tumor. Group B included more small cell carcinomas and fewer patients at stage II and IIIa, although these differences did not reach statistical significance. Significantly more patients received radiotherapy in group A. Early and late survival were also significantly better in group A, although immediate postoperative complication rates were similar between groups. There were no cases of bronchial perforation. Follow-up attendance was significantly lower in group B. Figure 1 displays the actuarial survival curves of the patients, showing significantly better survival for group A (p = 0.006).

The histologic type of the tumors was predominantly squamous in both groups, although there was a variety of other tumors that were mainly metastatic. With regards to the stage of the tumors at the time of presentation for cryosurgery, 67% of the lesions in group A and 77% in group B were stage IIIb or IV. Patients with lung cancer at stage II or IIIa underwent cryosurgery for immediate alleviation of symptoms before surgery or because they were too clinically unwell to withstand lung resection.

All patients were discussed at multidisciplinary meetings. Palliative or adjuvant treatment was decided according to stage of the tumor, histologic type, performance score of the patient, and wish of the patient. Of the 172 patients in group A, 101 patients underwent adjuvant radiotherapy, and 20 patients underwent lung resection, whereas chemotherapy was administered to 12 patients. The 20 patients who underwent lung resection had their tumor stage revised after surgical assessment and lymph node sampling. The timing of applying adjuvant therapy varied considerably among the patients because radiotherapy, surgery, or chemotherapy may have been applied before or after cryosurgery. Furthermore, a small number of patients underwent more than one mode of adjuvant treatment. Rates of palliative or adjuvant radiotherapy were significantly lower in group B. The relatively low number of patients undergoing radiotherapy in both groups (101 of 172 patients [59%] in group A, and 45 of 157 patients [29%] in group B) is explained by the fact that some of the patients were referred for cryosurgery with acute dyspnea but despite symptom relief, did not survive long enough.

Table 1—*Patient Characteristics, Disease Characteristics, and Complications After Endobronchial Cryosurgery in the Two Patient Groups**

Characteristics	Group A	Group B	p Value
Patients, No.	172	157	
Male gender	112 (65)	97 (62)	0.8
Age, yr	68 ± 9	67 ± 2	
Histologic type			
Squamous cell carcinoma	114 (66.2)	99 (63)	0.1
Adenocarcinoma	29 (16.8)	18 (11.5)	
Small cell carcinoma	11 (6.5)	21 (13.4)	
Other	18 (10.5)	19 (12.1)	
Stage at presentation			
II	13 (7.5)	6 (3.8)	0.08
IIIa	43 (35)	30 (19.1)	
IIIb	34 (19.7)	35 (22.3)	
IV	68 (39.6)	60 (38.2)	
Undefined (IIIb or IV)	14 (8.2)	26 (16.6)	
Other treatment			
Palliative radiotherapy	101 (57.7)	45 (28.6)	0.0001
Palliative chemotherapy	20 (11.6)	17 (10.8)	0.8
Lung resection	12 (7)	8 (5)	0.5
Complications after cryosurgery			
Bleeding	6 (3.5)	8 (5.0)	
New onset of atrial fibrillation	3 (1.7)	6 (3.8)	
Respiratory distress	4 (2.3)	8 (5.0)	
30 d after cryosurgery	2 (1.1)	17 (10.8)	0.0002
Survival after cryosurgery, mo			
Mean	15	8.3	
Median	11	6	
Range	0–60	0–60	
Interquartile range	6–19	2–13	
Outpatient follow-up appointments attended			
1st	172 (100)	117 (74.5)	0.0001
2nd	126 (73.2)	32 (20.3)	
3rd	71 (41.2)	17 (10.8)	
4th	50 (29.0)	9 (5.7)	
5th	34 (19.7)	5 (3.1)	
6th	24 (13.9)	4 (2.5)	

*Data are presented as No. (%) or mean ± SD unless otherwise indicated.

Effects of Cryosurgery on Outcome Measures

Dyspnea: Of the 172 patients in group A (Table 2), dyspnea improved by at least one NYHA class in 87

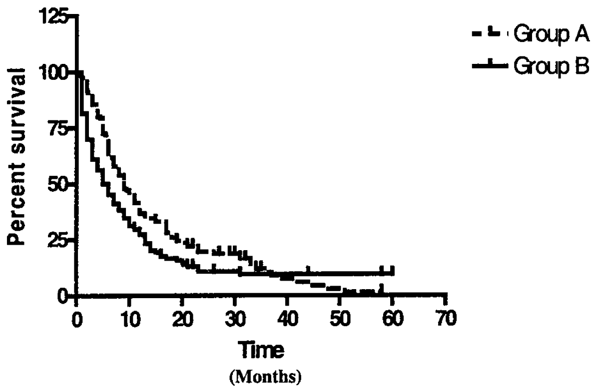

FIGURE 1. The Kaplan-Meier actuarial survival curve for patients undergoing palliative endobronchial cryosurgery. Patients undergoing at least two cryosurgery sessions (group A) achieved significantly longer survival than patients undergoing one cryosurgery session (group B) [p = 0.006].

patients (50.5%) and remained unchanged in 50 patients (29.0%), whereas 25 patients (14.5%) experienced deterioration by at least one NYHA class at their first follow-up after cryosurgery. These figures were lower after the second follow-up. Patients referred to as "not applicable" were not able to attend follow-up after cryosurgery or did not experience dyspnea. Overall, there was a statistically significant chance ($p < 0.001$) that dyspnea would improve by at least one NYHA class at 2 weeks after the second session of cryosurgery. Patients in group B benefited to a lesser degree from cryosurgery.

Cough: Cough (Table 2) improved subjectively by at least one class in 88 patients (51.1%), remained unchanged in 50 patients (29.0%), and deteriorated by at least one class in 18 patients (10.4%) in group A. The chance of a patient experiencing improvement in cough by at least one class after two sessions of cryosurgery was statistically significant ($p < 0.001$). Similar to the effects on dyspnea, group B patients benefited less with regards to improvement in cough.

Hemoptysis: This was an infrequent symptom in this patient population (Table 2). Only 78 of the 172 patients (43.3%) in group A reported episodes of hemoptysis before or after treatment. Of these patients, however, 36 patients (20.9%) reported reduction in hemoptysis by at least one class, whereas 14 patients (22%) improved by two classes, and 12 patients (19%) improved by three hemoptysis classes. This reduction in hemoptysis was statistically significant ($p < 0.001$) overall. Figures in group B remained small due to limited follow-up attendance.

Table 2—*Effects of Cryosurgery on Dyspnea, Cough, and Hemoptysis**

Characteristics	Group A	Group B	p Value
Dyspnea			0.0001 for both first and second follow-ups
Improved First follow-up	87 (50.5)	39 (24.8)	
Second follow-up	63 (36.6)	17 (10.8)	
Unchanged First follow-up	50 (29.0)	18 (11.4)	
Second follow-up	28 (16.2)	6 (3.8)	
Deteriorated First follow-up	25 (14.5)	13 (8.2)	
Second follow-up	21 (12.2)	5 (3.1)	
Not applicable First follow-up	10 (6.0)	87 (55.4)	
Second follow-up	60 (36.0)	129 (83.3)	
Cough			0.0001 for both first and second follow-ups
Improved First follow-up	88 (51.1)	45 (28.6)	
Second follow-up	72 (41.9)	18 (11.4)	
Unchanged First follow-up	50 (29.0)	14 (8.9)	
Second follow-up	27 (15.7)	4 (2.5)	
Deteriorated First follow-up	18 (10.4)	11 (7.0)	
Second follow-up	19 (11.0)	6 (3.8)	
Not applicable First follow-up	16 (9.5)	87 (55.5)	
Second follow-up	54 (31.4)	129 (82.3)	
Hemoptysis			0.0001 for both first and second follow-ups
Improved First follow-up	36 (20.9)	17 (10.8)	
Second follow-up	35 (20.3)	6 (3.8)	
Unchanged First follow-up	20 (11.6)	2 (1.2)	
Second follow-up	16 (9.3)	1 (0.6)	
Deteriorated First follow-up	22 (12.8)	8 (5.1)	
Second follow-up	9 (5.2)	2 (1.2)	
Not applicable First follow-up	94 (54.7)	130 (82.9)	
Second follow-up	112 (65.2)	148 (94.4)	

*Data are presented as No. (%), distinguishing between patients who improved by at least one class, remained unchanged, or deteriorated by at least one class of symptoms, as assessed at their first and second follow-up appointments. Not applicable refers to patients who were not assessed because they were unable to attend or they never had the symptom.

Lung Function Tests: A significant increase in mean PEF from 170 ± 79 to 181 ± 73 L ($p = 0.03$) at first follow-up was recorded in group A patients (Table 3). This benefit was lost by the second follow-up appointment. Patients attending follow-up clinics in group B did not show improved PEF rates. FEV_1 increased from 1.36 ± 0.63 to 1.43 ± 0.47 L and was recorded following cryosurgery in group A patients, although the difference did not reach statistical significance. There was also a small but statistically significant increase in FVC from 1.89 ± 0.63 to 2.02 ± 0.72 L at first follow-up

Table 3—*Lung Function Tests and Karnofsky Performance Scores**

Characteristics	Group A	Group B
PEF, L		
Before cryosurgery	170 ± 79	186 ± 81
First follow-up	181 ± 73	189 ± 82
Second follow-up	174 ± 73	173 ± 86
p Value		
Before first follow-up	0.03	0.49
Before second follow-up	0.72	0.76
FEV at 1 min, L		
Before cryosurgery	1.36 ± 0.53	1.45 ± 0.56
First follow-up	1.43 ± 0.47	1.49 ± 0.54
Second follow-up	1.41 ± 0.49	1.42 ± 0.50
p Value		
Before first follow-up	0.13	0.43
Before second follow-up	0.54	0.39
FVC, L		
Before cryosurgery	1.89 ± 0.63	2.07 ± 0.64
First follow-up	2.02 ± 0.72	2.11 ± 0.74
Second follow-up	1.98 ± 0.63	1.90 ± 0.58
p Value		
Before first follow-up	0.001	0.86
Before second follow-up	0.06	0.19
Karnofsky performance score		
Before cryosurgery	67.7 ± 9	67.5 ± 10
First follow-up	72.2 ± 9	74.6 ± 11
Second follow-up	74.6 ± 10	73.6 ± 11
p Value		
Before first follow-up	0.001	0.001
Before second follow-up	0.001	0.001

*Data are presented as mean ± SD unless otherwise indicated. Only patients who attended at least two follow-up appointments were included in the analysis.

($p = 0.001$). Patients in group B attending follow-up did not show improved performance in lung function tests after cryosurgery.

Karnofsky Score: The mean Karnofsky score (Table 3) increased from 67.7 ± 9 before cryosurgery to 74.6 ± 10 [$p < 0.001$] at the second follow-up appointment in group A and from 67.5 ± 10 to 73.6 ± 11 in group B ($p < 0.001$). Of the 172 patients in group A, 90 (52.3%) showed at least a 10% increase in Karnofsky score after two cryosurgery sessions, whereas in 63 patients (36.7%), the score remained unchanged, and in 19 patients (11%), it deteriorated by at least 10%. In total, cryosurgery was associated with at least 10% improvement in the Karnofsky score in a significant number of patients ($p < 0.001$). Similarly to group A, Karnofsky performance score also improved in group B patients attending follow-up appointments.

Univariate Regression Analysis

Univariate regression analysis was performed only in group A patients (Table 4).

Survival: Univariate Cox regression analysis was used to relate one or more explanatory variables to survival (time from the first session of cryosurgery until death). The hazard ratio gives an estimate of the relative risk of death in subjects with different characteristics. For each variable, the different categories are compared with an arbitrarily selected baseline category. The only variable related to prolonged survival is the performance of adjuvant treatment procedure and, among such procedures, in particular, radiotherapy.

Dyspnea: Ordered logistic regression was used for analysis of data related to the effect of explanatory (patient) variables to dyspnea, cough, hemoptysis, and Karnofsky score. Ordered logistic regression analysis is an extension of logistic regression analysis and allows modeling of ordered categorical response variables. It is used when more than two different outcomes are analyzed. With regard to the present study, we used the model to compare "improvement" to "no change" or "deterioration" after cryosurgery. The model assumes that the odds ratio comparing improvement and no change is the same as that comparing no change and deterioration. There is borderline evidence that advanced age ($p = 0.08$) and stage IIIa ($p = 0.06$) are associated with alleviation of dyspnea.

Cough: Regression analysis correlating variables to improvement of cough was performed similarly to the analysis of dyspnea. There was also borderline evidence that cough is more likely to be reduced by cryosurgery in advanced age ($p = 0.07$).

Hemoptysis: There is borderline association between advanced age and clinical improvement of hemoptysis ($p = 0.07$). There is also weak evidence that hemoptysis related to adenocarcinoma or other histologic type of lung malignancy is more likely to improve compared with squamous cell or small cell carcinoma ($p = 0.08$).

Karnofsky Performance Score: Results displayed in Table 4 show that the Karnofsky performance score is particularly likely to improve by at least 10% in female patients ($p = 0.05$) and in patients with cancer at stage IIIa and IIIb ($p = 0.02$).

Lung Function Tests: Ordinary, least squares regression analysis was used to examine the relationship between FEV_1 or FVC and each variable. Female patients benefit significantly more than male patients from cryosurgery with regards to FEV_1 ($p = 0.003$) and FVC ($p < 0.001$).

Table 4—*Univariate Regression Analysis Relating Patient and Disease Variables**

Variable	Outcome Measure	Category	Hazard Ratio (95% CI)	Overall p Value
Radiotherapy	Survival	No (baseline)		
		Yes	0.63 (0.44–0.95)	0.03
Stage	Dyspnea	II (baseline)		
		IIIa	0.42 (0.13–1.42)	0.06
		IIIb	1.32 (0.36–4.80)	
		IV	0.96 (0.29–3.13)	
Sex	Karnofsky score	Male (baseline)	1.83 (1.00–3.38)	0.05
		Female		
Stage	Karnofsky score	II (baseline)	0.58 (0.17–1.94)	0.02
		IIIa	0.65 (0.18–2.28)	
		IIIb	1.66 (0.51–5.41)	
		IV		
Sex	FEV_1	Male (baseline)		
		Female	1.14 (1.04–1.23)	0.003
Sex	FVC	Male (baseline)		
		Female	1.19 (1.09–1.30)	0.001

*Only correlations that achieved at least borderline statistical significance are presented in this table. CI = confidence interval.

Multivariate Regression Analysis

In view of the small number of patient variables that are associated with significantly positive results, as shown in the univariate analysis, multivariate analysis is of relatively minor relevance. Stepwise regression was used to find the best multivariate model for each outcome variable. A cutoff point of $p = 0.05$ was used for adding variables and of $p = 0.1$ for removing variables. The only multivariate models of significance were the following: (1) age ($p = 0.003$) and site ($p = 0.08$) for hemoptysis; (2) sex (0.04), site (0.009), and stage ($p < 0.001$) for Karnofsky score; and (3) age ($p = 0.04$), sex ($p < 0.01$), and stage ($p = 0.04$) for FVC.

Discussion

Since the first report on endobronchial cryosurgery in 1986,[5] we have published results that the technique provides effective symptom relief, improved respiratory function, and improved performance status.[9,10] This study adds to our knowledge by demonstrating the benefits of endobronchial cryosurgery for malignant tumors through a comprehensive statistical analysis of standardized clinical data. Group A consists of patients who completed a course of cryosurgery, as defined by two sessions of the procedure performed over a period of 2 to 6 weeks, followed by review in the outpatient clinic. We compared these patients to the less standardized group B. The distinction between groups is somewhat arbitrary but serves the purpose of clinically meaningful standardization of information. Data were collected prospectively with a 100% completion rate. The main outcome point of our analysis was to examine the effects of cryosurgery on symptoms, lung function, and performance score. A further aim was to correlate patient- and specific-specific characteristics with survival time and with changes in symptoms, lung function, and performance score. We applied a matched-pairs test and logistic regression in our analysis to demonstrate the clinical effects of endobronchial cryosurgery.

Cryosurgery was shown to be associated with significant reduction in dyspnea, cough, and hemoptysis. It was also shown to be associated with improvement in the Karnofsky performance score, whereas the effect on PEF, FEV_1, and FVC was moderate. Univariate Cox regression analysis demonstrated correlation between the use of external beam radiotherapy and prolonged survival. Although difficult to quantify, application of radiotherapy has undoubtedly contributed to patients' survival. Because the opening of the airways by cryosurgery may allow many patients to undergo radiotherapy or other procedures, it may serve as a mechanism of prolonging survival. No particular patient or tumor characteristic, however, was shown to strongly affect symptoms such as dyspnea, cough, or hemoptysis. Karnofsky performance score, however, improved significantly more in patients with stage III carcinoma. Female sex was the only variable associated with improvement in lung function tests. Expectedly, the benefits of endobronchial destruction of tumor were more significant in group A. Patients in group B did not complete two cryosurgery sessions and displayed significantly shorter survival.

Cryosurgery achieves destruction of the endobronchial element of the tumor and recanalization of tracheobronchial obstruction. The effect on dyspnea and lung function tests can therefore be explained by the mechanical removal of the tumor. These findings are in agreement with previously reported results. In a small study, Mathur et al[11] demonstrated dyspnea improvement in 12 of 17 patients treated with endobronchial cryosurgery, whereas similar results were produced in a larger trial.[12] The related improvement in the Karnofsky performance score, an indicator of quality of life, may be attributable to the reduction of symptoms. Indeed, cough and hemoptysis were also reduced after two sessions of cryosurgery. It was inevitable that most patients' symptoms deteriorated at a later stage in view of the very advanced nature of the disease.

Univariate regression analysis revealed only a weak correlation between demographic characteristics of the patients or characteristics of the tumors and outcome measures. Karnofsky score showed the most significant improvement in patients with stage IIIa or IIIb tumors. One can only postulate that patients with stage IV tumors were too unwell to benefit from endobronchial cryosurgery. The reason for the significantly better improvement on lung function tests results in female patients remains unclear.

Fewer than 25% of patients who received diagnoses of lung cancer have localized disease amenable to surgical treatment. Even patients that are operable have <50% chance to be cured.[1] Because prognosis is poor, it is important to ensure alleviation of symptoms and improved quality of life. In cases in which the possibility of surgery has been eliminated, other palliative measures should be considered. These treatments include, apart from cryosurgery, laser therapy, photodynamic therapy, argon plasma coagulation, and brachytherapy. The aim of these treatments is to relieve the distressing symptoms of breathlessness, cough, and obstructive pneumonia and to improve respiratory function, general health, and performance status. Because the clinical benefit of cryosurgery is mainly attributable to tumor debulking, other modalities of endobronchial palliation should be expected to produce comparable results.

Nd-YAG or carbon dioxide laser has become a well-established method of treating endobronchial malignancies, particularly in the United States. Cavaliere et al[13] reported a series of nearly 2,000 patients treated with Nd-YAG. Quality of their results depended strongly on the site of the tumor, with tracheal tumors responding to treatment more favorably than more peripheral lesions. Postoperative complication rate was low, and there were 12 in-hospital deaths. Cumulative survival at 6 months was 50%. Other studies[14–16] on patients treated with endobronchial Nd-YAG laser have shown a median survival of 5 months. Indications for laser therapy are similar to cryosurgery. Although laser treatment may be more effective for emergency treatment due to its presumed greater short-term effects, it is significantly more expensive and carries a higher risk of bronchial perforation.[12]

Photodynamic therapy has been shown to achieve a median survival of 5 to 7 months.[17,18] It is most effective on tumors of small size but has considerable cost. Tumors are photoradiated by argon dye laser. Indications are similar to cryosurgery, whereas tumors are often not resectable surgically. When photoradiation is followed by surgical resection, long-term survival is satisfactory.[19]

Endobronchial argon plasma coagulation is also used for palliation of endobronchial neoplasms. It is particularly effective in the treatment of hemoptysis.[20] Bronchoscopic electrocautery is effective and inexpensive and for symptomatic palliation of patients with intraluminal airway obstruction. In a small study,[21] mean survival was 11.5 months after electrocautery.

The mechanisms involved in tissue destruction by cryosurgery can be divided into immediate and delayed. Immediate mechanisms include the physical effect of intracellular ice crystal formation, the biochemical effect of cell dehydration and shrinkage, and thawing effects.[22] The delayed effect involves vascular stasis and apoptosis.[22] Cell destruction is influenced by the freezing regime, the distance from the probe, tissue vascularity, and the type of cell being frozen. Areas close to the probe, with high cooling rates, are more likely to undergo intracellular ice crystal formation.[23] During the cooling process, an osmotic potential across the cell membrane is created, leading to withdrawal of water from within the cell into the extracellular spaces and cell shrinkage.[24] Further cell damage occurs during thawing as smaller ice crystals recrystallize to form larger, more damaging crystals, with lower surface energy. As the ice crystals thaw, the extracellular spaces will become hypotonic for a brief period of time, and water will move into the cell causing expansion and rupture.[22] The delayed effect of freezing involves vascular damage, which can lead to cell schema. The mechanism involves detachment of damaged endothelial cells from inside the vessel, increased permeability of the vessel walls, platelet aggregation, and microthrombus formation.[25] There is evidence to suggest that some cells undergo apoptosis (gene-regulated cell death) when exposed to temperatures approximately $-6°C$ to $-10°C$.[26]

The main weakness of our analysis of results is the absence of a control group of patients with comparable malignancies who did not undergo cryosurgery. A randomized trial comparing patients undergoing external beam radiotherapy and endobronchial cryosurgery vs patients undergoing only radiotherapy is in progress and will address this question. A further weakness is the objective nature of classifying symptoms such as dyspnea, cough, and hemoptysis. Care was taken to use a nominal scale of symptom severity that was marked by the patient to minimize investigator bias.

In conclusion, endobronchial cryosurgery for malignant tumors is associated with significant improvement in dyspnea class, cough, hemoptysis, Karnofsky score, and lung function tests. These effects were achieved after two sessions of cryosurgery. The mean survival time after application of two sessions of cryosurgery was 15 months. Endobronchial cryosurgery is a palliative technique, with the aim of alleviating symptoms and improving the patient's performance status. Future randomized trials, comparing the results of endobronchial cryosurgery with other forms of palliative treatment for lung cancer, will be needed in support of the above findings.

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