Technology in Cancer Research & Treatment
ISSN 1533-0346
Volume 3, Number 2, April (2004)
Adenine Press

Cryosurgery for Lung Cancer: Clinical Results and Technical Aspects

M. O. Maiwand, M.D.*
G. Asimakopoulos, M.D.

Department of Thoracic Surgery
Harefield Hospital
Harefield, Middlesex
England UB9 6JH

www.tcrt.org

Lung carcinoma is the most frequently diagnosed malignancy in the world, with the incidence increasing through the 20th century. Presentation may be as a tumor mass primarily obstructing the central bronchial lumen, or a mass infiltrating lung tissue. Cryosurgery can be used as a method of palliative treatment for both these endobronchial and extrabronchial presentations. The aim of this study is two-fold: to present data relating to our extensive experience in treating obstructing endobronchial tumors and to present our initial results of direct cryosurgery to infiltrating lung tumor masses.

During a nine-year period, 521 consecutive patients (male:female ratio 1.8:1) with a mean age of 67.9 years who had advanced obstructive tracheobronchial malignant tumors underwent cryosurgery with a mean of 2.4 treatments per patient. Hemoptysis, cough, dyspnoea and chest pain improved by at least one class in 76.4%, 69.0%, 59.25% and 42.6% ($p<0.01$) of symptomatic patients respectively. Quality of life studies showed that the mean Karnofsky score improved from 60 ± 7 to 75 ± 8 and the mean WHO score from 3.04 ± 0.7 to 2.20 ± 0.56. There were 7 (1.2%) in-hospital deaths, and 2-year survival was 15.9%.

Direct cryosurgery to carcinoma of the lung was performed on 15 patients at exploratory thoracotomy. Results showed an increase in FEV1 from 1.80 ± 0.6 liters to 1.95 ± 0.8 (8.3%) liters and in FVC from 2.50 ± 0.8 to 2.68 ± 0.8 liters (7.2%). The Karnofsky score improved from 68 ± 9 to 78 ± 10 and the WHO score from 2.63 ± 0.81 to 2.38 ± 0.78 (9.6%). Major symptoms including cough, dyspnoea, and hemoptysis were assessed and showed improvement in 77.8%, 66.7%, and 100% ($p<0.01$) of symptomatic patients respectively.

Patients were followed for a mean period of 18 months (range 4-84 months). Median survival from the date of surgery (Kaplan-Meier, 95%Cl) was 11.6 (6.8 to 18.2) months, range 1 to 84 months.

Cryosurgery provides a safe and effective method for the palliation of advanced central bronchial obstructive tumors, and compares favorably with other methods in terms of safety, cost, and complications. Initial experience suggests that similar palliation may be achieved by cryosurgery applied to advanced parenchymal tumor masses.

Key words: Cryosurgery, Lung cancer, Palliation.

Introduction

Carcinoma of the lung is the most common cause of death from malignant disease in humans. At diagnosis, about 85% of patients are in an advanced stage of the disease. Due to this late presentation, overall 5-year survival is only 15%. For patients with stage IIIa, IIIb and IV disease, the 5-year survival rate falls to 13%, 5% and 1% (1) respectively. These figures have changed little over recent

* Corresponding Author:
M. O. Maiwand, M.D.
Email: cryotherapy@rbh.nthames.nhs.uk

years, in spite of advances in radiotherapy and chemotherapy. Surgical resection offers the best possibility of improved survival, but only around 20% of the 30,000 patients diagnosed with lung cancer in the UK each year are considered suitable for surgery. Of patients with operable tumors, about 20% are unable to undergo curative surgical treatment because of poor respiratory function or other major organ dysfunction. A further 2-11% of these patients who are considered to be operable are found to have unresectable malignancies at thoracotomy (2). Symptoms such as cough, breathlessness, and hemoptysis are often caused by obstruction of central airways or by tumor infiltrating the lung parenchyma. Approximately 30% of inoperable patients with carcinoma of the lung present with obstruction of the central airway, which can cause distressing symptoms of cough, breathlessness, hemoptysis and recurrent infections, and may lead to gradual asphyxiation (3).

The first successful documented use of low temperature for treatment of a tumor was reported by James Arnott for the treatment of an advanced uterine carcinoma more than 150 years ago (4). There had been little technological advance in this area until the 1970's. Understanding the biological effects freezing has on living cells, advances in technology related to the safe use of coolants, and improved equipment has made the treatment of carcinomas at different body sites possible over the last 15 years. Neel *et al*. reported the first successful endobronchial cryosurgery in the 1970's (5) while a series of 75 patients was published by us in 1986 (6). To date, over 2000 patients have received cryosurgery in our hospital.

Endobronchial cryosurgery is used primarily to treat patients with inoperable obstructive central bronchial lung tumors and involves the application of a cryoprobe through the channel of a bronchoscope. Radiotherapy and chemotherapy are the standard palliative treatments but have limited effectiveness in reopening obstructed airways (7). Cryosurgery is one of several techniques that can be used to reopen an obstructed tracheobronchial lumen. Other techniques are laser treatment, diathermy, photodynamic therapy, and stent placement. All these local therapies recanalize the airways and so relieve symptoms. In addition, cryosurgery has recently been used for palliation in a small number of patients initially considered to be operable, but who were found to have unresectable tumors at thoracotomy with subsequent direct application of the probe to the lung tumor.

The advantages of endobronchial cryosurgery are that it has proven effectiveness with minimal complications. It is relatively easy to use and economical in comparison with other techniques. Patients tolerate the procedure very well and show a significant improvement in symptoms at the end of the procedure. The use of a general anaesthetic has the advantage that it allows greater head and neck mobility and provides a more relaxed patient. General anaesthetic may, however, carry some risk in frail patients.

In this article, we present our extensive experience in treating the endobronchial element of lung carcinoma with cryosurgery. We also report our initial experience with cryodestruction of parenchymal lung carcinoma at exploratory thoracotomy. Cell pathophysiology and technical aspects of cryosurgical techniques are also discussed.

Materials and Methods

Endobronchial Cryosurgery

From January 1995 to December 2003, 521 consecutive patients with obstructive, malignant endobronchial tumors underwent endobronchial cryosurgery at our institution. The mean age was 67.9 years (range 22-88, median 70.0 years) and the male to female ratio 1.8:1. These patients were not considered for lung resection because of the advanced stage of the disease or the patient's general condition. Patients were assessed clinically, radiologically, and for performance status before and after each cryosurgery. Symptom evaluation was carried out for dyspnoea, hemoptysis, cough and chest pain as described previously (8). Chest radiographs were taken before and after treatment. Respiratory function tests, forced expiratory volume in one second (FEV1), and forced vital capacity (FVC) were measured using a Microlab 3000 turbine spirometer before and on average 10 weeks after cryosurgery. Performance status was assessed using the Karnofsky and WHO scale. Bronchoscopy was performed in all cases, computed tomography in 38% and mediastinoscopy in 14% of patients. All patients had confirmed pathology: 97.2% histologically and 2.8% on sputum cytology. The majority of the patients were stage IIIb or IV (72%).

Prior to endobronchial cryosurgery, the procedure, benefits, and risks were explained to the patient, and informed consent was obtained. The procedure was performed under short-acting intravenous general anaesthesia, using a large rigid (9.2mm) and a flexible bronchoscope (2.4mm). Oxygenation was maintained with Venturi positive-pressure ventilation. The distal tip of the bronchoscope was placed about 5mm above the lesion and the appropriate cryoprobe (straight, right angled or flexible) inserted through the bronchoscope and applied to the tumor. The tumor was frozen for 3 minutes and then allowed to thaw until the probe separated from the tissue. If the tumor covered wider areas of the bronchial tree, multiple cryo-applications were made during the same treatment session. Necrotic tumor material, when present, was removed after each cryo-application using a biopsy-type clamp. Patients often reported that further necrotic-appearing material was coughed out 24 to 48 hours after cryosurgery.

A Joule-Thomson type probe with nitrous oxide as the cryogen was used. A temperature of around -70º C was achieved at the probe tip. Probe temperature was determined potentiometrically with a needle placed about 2mm from the tip while tissue temperature was not measured directly. Careful monitoring of temperature during cryosurgery was carried out, as tissue destruction is directly related to a temperature drop achieved at the treatment site. The selection of probe diameter, 2.2mm or 5mm, was based on the size and position of the tumor. The 2.2mm probe was used for peripheral, smaller tumors through the fiber optic bronchoscope. The 5mm probe was used for larger, central tumors. The large rigid bronchoscope allowed a small suction catheter to be placed to remove blood and secretions throughout the procedure. Tissue samples for histological examination were taken before each cryosurgery. Bleeding from the site of a biopsy or cryosurgery was not a major problem, and moderate bleeding was contained by the local application of epinephrine (adrenaline) 1:1,000. Each procedure took about 20 minutes, and the majority of patients recovered well enough to be discharged home the same day. A repeat treatment was carried out two weeks later. The procedure was repeated if symptoms recurred.

Direct Intrathoracic Cryosurgery

This study involved a retrospective analysis of 15 patients who underwent direct cryosurgery for inoperable pulmonary tumors, by a single thoracic surgeon (M.O.M.) between January 1992 and December 2002. There were 13 males and 2 females with a mean age 64.0 years (range 49 to 71 years). Pre-operatively, the TNM staging was: stage IIa (1 patient), stage IIb (12 patients) and stage IIIa (2 patients). Pre-operative histology was confirmed as squamous cell carcinoma (12 patients), adenocarcinoma (1 patient) and large cell carcinoma (2 patients). Patients had been assessed for operability on the basis of their general clinical condition and the following investigations: Chest radiograph; CT scan of the thorax and abdomen; respiratory function tests (RFT's), including diffusion factors and spirometry; routine biochemistry, including renal and hepatic function; and a bone scan where indicated. Mediastinoscopy was performed when at least one mediastinal node of over 0.5cm was seen on CT scan.

All patients had been scheduled to undergo thoracotomy and planned lung resection but were found to be inoperable at the time of operation. Due to the possibility that the patients may be found to be inoperable, the planned procedure and the potential use of cryosurgery along with its risks and benefits were explained, and informed consent was obtained. At the time of thoracotomy, the tumor was found to be more advanced than expected, and the patient was deemed unresectable (surgical stage IIIb in 9 patients, stage IV in 4 and 2 tumors crossing the fissure in patients with poor respiratory function not fit for pneumonectomy or bilobectomy). The tumor was precisely located, its size measured, and its relation to vital structures documented. Prior to cryoprobe insertion, needle aspiration was performed to confirm the position of major blood vessels. The patients were treated with a short, straight, nitrous oxide cooled cryoprobe (5mm in diameter and 150mm in length, Spembly Medical, Andover, UK). The probe was introduced into the tumor mass and the freezing continued until the ice-ball was large enough to cover it. For larger tumors, multiple applications were made with the aim to destroy all macroscopically visible tumor. A 5mm margin of normal lung tissue was included in the freezing process and necrotic tissue that formed intra-operatively was remove mechanically. Removal was usually performed easily with a biopsy instrument. A layer of necrotic material covering the free margin of healthy-appearing lung tissue was left *in situ* in order to minimize the risk of air-leak.

Symptoms including cough, dyspnoea, and hemoptysis were quantified by means of a linear scale before and after the procedure, while their performance status was measured using both the WHO performance scale and Karnofsky index. FEV1 and FVC were determined spirometrically before the procedure and at follow up.

Statistical Analysis: A Wilcoxon matched pairs signed rank sum test was carried out for each outcome variable to determine whether there was a difference between pre- and post-cryosurgery measurements. Results are calculated as mean ± the appropriate ratio at 95% Confidence Interval. A P value of less than 0.05 was considered significant.

Results

Endobronchial Cryosurgery

The 521 patients received a mean of 2.4 cryosurgical treatments. Pathological were: squamous cell carcinoma 68.3%, adenocarcinoma 15.2%, large cell 2.6%, unclassified NSC carcinoma 5.2% and small cell 8.7%. The TNM staging (1) for NSC patients at the time of treatment was: stage IIB 6.7%, stage IIIa 21.0%, stage IIIb 23.9% and stage IV 48.4%. Of these patients, 39% had previously received radiotherapy and 9% chemotherapy. All patients were symptomatic prior to cryosurgery. The results of respiratory function tests, performance status and symptom quantification are given in Table I. Improvement in one or more symptoms was demonstrated in 86.0% of patients. Hemoptysis, cough, dyspnoea and chest pain improved in 76.4%, 69.0%, 59.25% and 42.6% of symptomatic patients respectively. The Karnofsky score improved from 60 to 75 and the WHO score from 3.04 to 2.20 ($P<0.05$).

Post-operative complications were 9%, including 21 cases of hemoptysis (4%), 12 cases of post-operative atrial fibrillation (2%) and 16 patients developed respiratory distress

Table I
Clinical findings in patients undergoing endobronchial cryosurgery for malignant tumours. Measurements were made before cryosurgery and after the first cryosurgery session.

	Before cryosurgery (Mean ± SD)	After cryosurgery (Mean ± SD)	P value
FEV1 (litres)	1.39 + 0.61	1.51 + 0.57	<0.05
FVC (litres)	1.93 + 0.76	2.13 + 0.72	<0.05
Karnofsky performance status	60 + 7	75 + 8	<0.05
WHO performance status	3.04 + 0.7	2.20 + 0.56	<0.05
	% of all patients	% of symptomatic patients improved	
Cough	88.4	69.0	<0.01
Dyspnoea	97.4	59.2	<0.01
Haemoptysis	38.8	76.4	<0.01
Chest pain	32.0	42.6	<0.01

and poor gas exchange that eventually resolved (3%). There were 7 (1.2%) in-hospital deaths. Cause of death was respiratory failure in all of these patients. The Kaplan-Meier median survival was 8.2 months (Figure 1) while one-year survival was 38.4% and 2-year survival was 15.9%. The median survival (95% confidence limits) by stage was as follows: Stage IIb 15.1 months (9.1-22.7), Stage IIIa 8.5 months (5.6-11.7), Stage IIIb 9.0 months (6.4-11.4), and Stage IV 6.6 months (5.4-7.7). Examples of radiological and bronchoscopic findings before and after cryosurgery are shown in Figures 2 and 3.

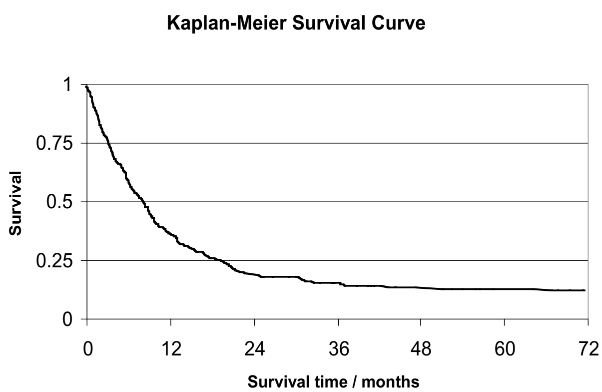

Figure 1: Kaplan-Meier actuarial survival curve of 521 patients undergoing cryosurgery for obstructive endobronchial malignancies between January 1995 and December 2003.

Direct Intrathoracic Cryosurgery

The intraoperative findings which led to the decision not to perform lung resection are shown in Table II. Instead, these patients went on to receive direct cryosurgery. There were no post-operative complications attributable to the application of direct cryosurgery. In particular, there were no cases of prolonged air-leak or pneumothorax post-operatively. Results after direct cryosurgery showed an increase in mean FEV1 from 1.80 liters to 1.95 liters (8.3%) and an increase in mean FVC from 2.50 to 2.68 liters (7.2%) over an average follow-up period of 9 months. Performance indices improved from 68 to 78 (14%) for Karnofsky Performance Status and from 2.63 to 2.38 (9.6%) for the WHO scale. Symptoms such as cough, dyspnoea and hemoptysis were assessed and showed improvement in 77.8%, 66.7%, and 100% of symptomatic patients respectively. Tumor size and progression were compared before and after cryosurgery by examining pre-procedure and 3 month post procedure CT scans. Measurable reduction in tumor mass was recorded in three of the fifteen patients (Figure 4).

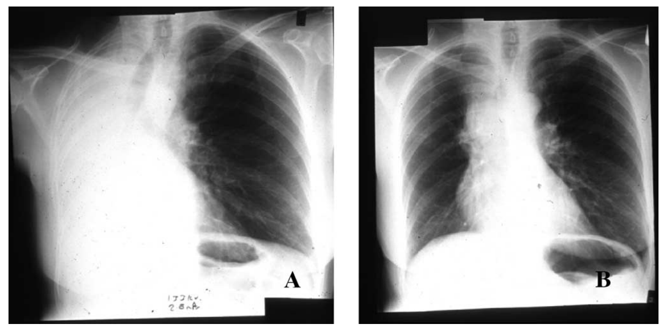

Figure 2: Chest radiograph of a patient presenting with endobronchial malignancy causing obstruction of the right main bronchus and atelectasis of the right lung (**A**). Cheats radiograph of the same patient one day after endobronchial cryosurgery. Destruction of the endobronchial part of the tumor resulted in re-expansion of the lung within 24 hours (**B**). Necrotic tumor material is usually removed mechanically after each cryosurgery application. Most patients also report that further necrotic material is coughed up at 24 to 48 hours after cryosurgery.

Patients were followed for a mean period of 18 months (range 4-84 months). Of the fifteen patients in this study, seven went

Table II
Reasons for inoperability in patients receiving direct cryosurgery.

Reason for Inoperability	Number
Physically unable to survive pneumonectomy	3
Invasion of proximal pulmonary artery	2
Invasion of proximal pulmonary vein	5
Chest wall invasion	4
Sub aortic nodes	1

on to receive palliative radiotherapy and one chemo-radiotherapy. Median survival from the date of surgery (Kaplan-Meier, 95%Cl) was 11.6 (6.8 to 18.2) months, range 1 to 84 months. One-year survival was 50% with 25% and 6% surviving 2 and 5 years respectively. Actuarial survival is shown in Figure 5. There were no major complications as a result of the operative procedure or the use of direct cryosurgery and there was no in-hospital mortality as a direct result of the procedure.

Discussion

Endobronchial Cryosurgery

Little progress has been made in the last 20 years in improving the survival of patients with advanced lung cancer. This has added to the importance of alleviating their symptoms and improving quality of life. Once the possibility of surgery has been eliminated, palliative measures must be considered. Radiotherapy is the most common palliative treatment and aims to reduce tumor size and prolong life expectancy. This is, however, unlikely to reopen a blocked tracheobronchial lumen, which often causes the onset of severe symptoms. Palliative treatments of such lesions include laser therapy, photodynamic therapy, brachyotherapy, electrocautery and cryosurgery; which relieve the distressing symptoms of breathlessness, cough, and obstructive pneumonia and improve respiratory function and performance status.

Endobronchial cryosurgery requires good anatomical knowledge and the ability to perform rigid and flexible bronchoscopy. It is performed under direct vision by use of a bronchoscope with a rigid or flexible cryoprobe. It has been used in our institution for over 15 years and has been shown to provide effective symptom relief, improved respiratory function, and performance status (8, 9). Results of this study (Table I), relating predominantly to an elderly group of patients (69% over 65 years) with advanced stage lung cancer (73% stage IIIb or IV), showed improvement in symptom quantification with 86% of patients showing an improved score for one or more symptoms. Results for performance status showed that 63% of patients achieved an increased Karnofsky score. Respiratory function tests showed small but significant improvement. The median survival of 8.2 months compares well with other methods of palliation of endobronchial obstruction. A number of studies on patients treated with endobronchial Nd-YAG laser have shown a median survival of 5 months (10-12), and photodynamic therapy achieves a median survival of 5-7 months for patients with advanced endobronchial carcinoma (13). The complication rate of 9% is relatively low for this high-risk group of patients. Patients treated with endobronchial cryosurgery are generally elderly with advanced stage disease and frequently have other coexisting conditions. These patients may only be able to withstand a short general anaesthetic, and therefore the procedure should be as quick as possible. This places some limitations on the cryosurgeon in terms of holding time and repeat freeze thaw cycles. The use of a flexible cryoprobe with a fiber optic bronchoscope under local anaesthesia is ideal for patients who are unable to tolerate general anaesthetic. However, in our experience, it is often unpleasant, and patients can only tolerate a short procedure. It must be remembered, however, that endobronchial cryosurgery is a palliative technique, with the aim of alleviating symptoms and improving the patient's performance status, and so complete cell destruction, although desirable, is not imperative. Additional advantages of cryosurgery to obstructive endobronchial tumors are that it can open bronchi to allow drainage of infected secretions, and lead to re-aeration of a collapsed lung. The effect of this improved oxygenation and general enhancement of well-being can be seen very rapidly allowing the patient to be discharged on the day of cryosurgery.

In our experience, endobronchial cryosurgery with a large 5mm probe provides macroscopically satisfactory tumor destruction by the end of the procedure in the majority of cases. When an extra luminal tumor element causes more than 75% lumen obstruction, recanalization of the bronchial tubes may not occur. In these cases, stenting, radiotherapy or chemotherapy are the options for further palliation.

From our experience, we based the selection of patients for endobronchial cryosurgery on:

- Histologically proven carcinoma of the trachea and bronchi.
- Inoperability based on the position of the tumor, performance status or poor respiratory function.
- Predominantly intraluminal tumors.
- Extra luminal elements of tumors should not cause occlusion from external pressure of more than 75% of the normal diameter.
- Tumor recurrence following radiotherapy, chemotherapy or lung resection.

Direct Cryosurgery

Of patients considered for lung resection, approximately 10% (ranging from 5-50%) (14, 15) are found to be unresectable at thoracotomy. In the past, our institution had a similar 'open and close' rate, but this has fallen considerably in recent years to about 10% due to strict staging and, most importantly, due to the use of Pet Scanning. There are few options available to the surgeon when a tumor is considered unresectable at thoracoctomy. Treatment should aim to alleviate symptoms and prolong life, if possible. In view of our experience with endobronchial cryosurgery and the successful results of cryosurgery of liver and prostate carcinoma (16, 17), we decided to extend the use of direct freezing to lung tumor masses before closing the chest. To our knowledge, this has

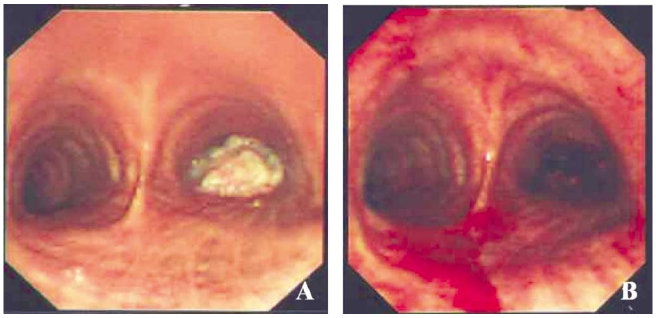

Figure 3: Photograph obtained at bronchoscopy demonstrating a carcinoma obstructing the right main bronchus (**A**). Cryosurgery resulted in almost complete clearance of the endobronchial part of the tumor (**B**). Both photographs were obtained during the same cryosurgery session.

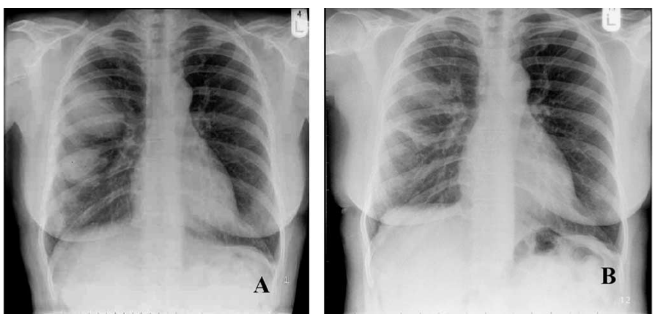

Figure 4: Pre-operative chest radiograph of a patient with lung carcinoma regarded inoperable at thoracotomy (**A**). Chest radiograph of the same patient six months after direct cryosurgery to the lung carcinoma (**B**).

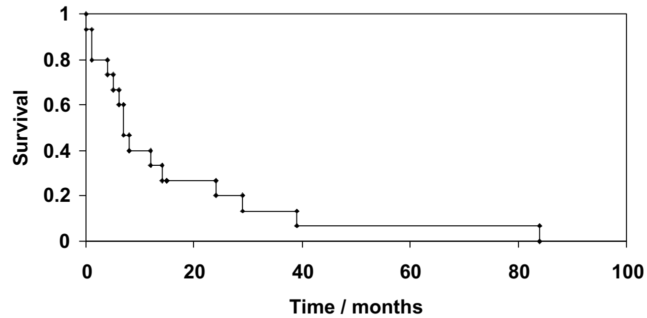

Figure 5: Kaplan-Meier actuarial survival curve of 15 patients undergoing direct cryosurgery to lung carcinomas found to be inoperable at exploratory thoracotomy between January 1992 and December 2002.

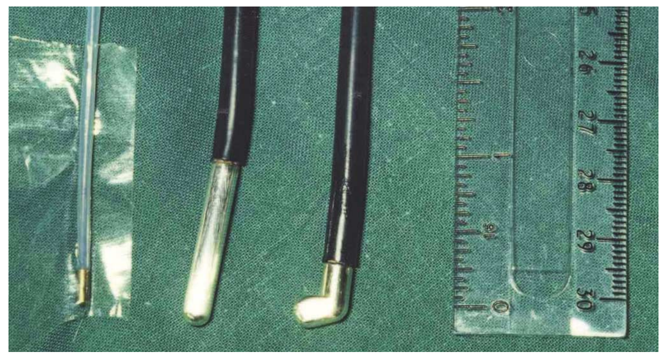

Figure 6: Probes used in endobronchial cryosurgery.

not been previously reported. The results of this pilot study, involving a limited number of patients, shows a one-year survival of 50%, comparing favorably with other studies of patients found to be inoperable at thoracotomy. For example, a study by Coy *et al*. (18) reported a survival rate of 22% at one year and a median survival of 24 weeks for a group of 1839 patients with unresectable lung cancer. In their study, patients received a variety of palliative treatments, involving radiotherapy and chemotherapy, or no treatment at all. Another study by Ratto *et al*. (19) reported two-year survival rates of 7% for a group of stage III patients after exploratory thoracotomy. They also reported a complication rate of 12% and mortality of 8%. There was no difference in survival after exploratory thoracotomy compared to conservative treatment.

While the aim of the surgeon must be to continue to reduce the number of patients found unresectable at thoracotomy, the use of direct cryosurgery presents another option for this group of patients. Our initial findings suggest that direct cryosurgery may be beneficial by improving objective performance status and respiratory function and importantly, subjective symptoms. It is difficult to interpret the effect of direct cryosurgery for a relatively small group of patients who had also undergone other palliative treatments for tumor control. Improvement of symptoms, in particular of cough and dyspnoea, may be attributable to the temporary airway decompression resulting from tumor de-bulking. Combination of direct cryosurgery with palliative radiotherapy may have also influenced symptoms. We feel, however, that the results are encouraging, and that cryosurgery may help in symptom control. It also enhances performance status and provides patients with improved quality of life while awaiting further palliative treatment. Direct cryosurgery at the time of thoracotomy is a simple, easily used method of treatment that is relatively inexpensive. Further studies are required to clarify the role of direct cryosurgery in patients undergoing thoracotomy whose tumors are found to be unresectable.

Equipment used in Endobronchial Cryosurgery

In general, cryosurgical equipment has three components: The console, the cryogen and the cryoprobe (Figure 6). While there are little differences in consoles made by different companies, it is important that they provide monitoring of cryogen pressure. It is advantageous if the probe tip temperature and the length of treatment application are displayed.

Although nitrous oxide is the most commonly used cryogen for endobronchial cryosurgery, carbon dioxide can also be used to achieve a theoretical temperature of -70º C at the end of the probe. Utilization of the Joule-Thompson effect dictates that a highly compressed gas that exits at high flow expands rapidly and creates low temperature. Rapid control of variations in flow and, therefore, in temperature, allows the tip to be cooled or warmed. When a cryoprobe is connected to the console, the cryogen is supplied to the tip of the probe at high pressure which lowers the temperature. The cryogen subsequently exits the system through an exhaust port. Cessation of flow and pressure decrease is followed by release of heat and defrosting. Probe temperatures are determined potentiometrically with a needle placed about 2mm from the tip. In a previous study, these were found to achieve a mean minimum temperature of -30º C (standard deviation ± 5.6) over 100 applications (15).

Cryoprobes for endobronchial use are rigid, semi-rigid and flexible with tip diameters of 2.2mm for flexible probes and 5.5mm for rigid probes, with a length of 500-600mm. Flexible probes used through the channel of fiber optic bronchoscopes offer an excellent view of the anatomy and the tumor. Using a video imaging system with fiber optic bronchoscope and flexible probe has proved invaluable for teaching purposes. Rigid or semi-rigid cryoprobes are utilized through the rigid bronchoscope lumen. Straight rigid probes are ideal for lesions in the trachea, main bronchi, and lower lobes. A right-angle probe has been designed to fit within the upper lobes. Rigid bronchoscopes are largely unaffected by the low temperatures maintained during the procedure, whereas flexible bronchoscopes may be damaged by ice droplets forming in the channel of the apparatus, such that distortional damage of the probe may occur. With the larger, rigid bronchoscopes, a fine suction catheter can be positioned adjacent to the tip of the cryoprobe in order that secretion and debris may be removed.

Based on our experience, a larger probe would be preferable in order to destroy the maximum amount of tumor. There is a limitation, however, in the size of probe that can be fitted through a rigid bronchoscope, which has a maximum internal diameter of 9.2 gauge. Ideally, the temperature delivered to the treatment site should be around -100º C. This would create a sufficiently low temperature in the tissue, taking into account the temperature drop away from the probe. The fact that the wall of the trachea and bronchial tree are largely composed of cartilage renders them resistant to freezing and minimizes the danger of wall damage. In our experience of treating around 2000 patients, we have encountered only one case of bronchopleural fistula.

Cryotechnology using a cryogen with a lower freezing point would allow lower tissue temperatures to be achieved for enhanced deep tumor destruction. Liquid nitrogen could be one such alternative, although its use may cause tissue damage if used inappropriately. We have recently acquired the Cryotech LCS2000 device (Spembly Medical Ltd, Hampshire, UK), for the use of direct intrathoracic cryo-surgery with liquid nitrogen. A disadvantage of this device, however, is its large size and weight.

Shortcomings of Current Technology

A challenge for the future of cryotechnology is the development of more practical and user-friendly equipment. This requires close cooperation of clinicians, scientists and cryotechnology in order to improve the current systems and ensure the well-merited position of cryosurgery in the treatment of malignancies. In view of this, we feel that the following comments would be useful.

Machines: The current machines work well. However, recording of the probe tip temperature is temperamental and not always accurate. The Spembly 142 machine can only be used for a rigid probe and has no appropriate connection for the use of flexible probes. Flexible probes are made by Erbe, but can only be used with an Erbe machine. A further drawback of current cryotechnology is that the machine valve needs to be opened gradually or the probe may become blocked if the nitrous oxide supply is opened too rapidly and fluid droplets accumulate. This may take a considerable amount of time to clear; therefore, spare probes are essential. Additionally, when the pressure in a cylinder falls during a procedure, the temperature at the probe tip increases to -20 to -30º C; therefore, a sufficiently low temperature cannot be achieved. The other limitation of current cryotechnology is the small capacity of gas cylinders that only last for the treatment of 2-3 patients.

Probes: Large probes are robust and can be used repeatedly for numerous applications. However, this will obstruct most of the bronchoscope lumen; therefore, the positioning of the tip may require care and expertise. Large probes can easily be blocked when they are connected to the console and cryogen source rapidly, because the coolant gas expands within the lumen of the probe and causes bubbles.

Small probes can easily be positioned under direct vision to the tumor site and have very good freezing power. However, the connection of a probe to the handle is very delicate; and in our experience, the probe can easily be broken close to the handle and is not easily replaced by the manufacturers.

Flexible probes of 2.2mm are important to treat small tumors or tumors located within the segmental division of the bronchial tree. Access to the distal areas of the tracheobronchial tree is limited. This problem particularly affects the upper lobes of the lung, as using a small probe and fiber optic bronchoscope would not allow enough angulations to position the probe in the apical segments. The smaller flexible probe can also be used without general anaesthetic; however, it can only be used to treat a small area of tumor and so is usually unsuitable for reopening a major blocked lumen.

Cryogen: Current technology for endobronchial cryosurgery only allows use of Joule-Thompson cryoprobe, which uses nitrous oxide or CO_2 as the cryogen. The theoretical freezing temperature at the probe tip is around -60º to -70º C.

In our experience, there is temperature drop of 15 to 20º C every millimeter away from the probe. As a result, bronchial probes only destroy 1.5-2mm of tumor tissue. Repeated procedures would, therefore, be required to achieve lumen patency. However, the possibility of damage to the bronchial walls has been minimized by the use of Joule-Thomson type probes with nitrous oxide coolant. There were no cases of bronchial perforation in our series. Although this fact highlights the low complication rate of endobronchial cryosurgery, it also suggests that cryosurgery with nitrous oxide does not achieve low temperatures throughout the tumor mass. Possible damage to the bronchial walls is also limited by the fact that the trachea and larger bronchi are mainly composed of cartilage, which is resistant to the effects of freezing.

Scope for Future Improvement

Cryosurgery delivery systems for the treatment of the bronchial lumen pathology requires a temperature of around -100º C at the tip of the probe to ensure tumor destruction to 2-3mm depth. Probes should be available in a variety of sizes. Small flexible probes of 2-3mm diameter are necessary to reach distal areas within the bronchial tree while probes of 5 to 9mm are used for central endobronchial tumors. Direct cryosurgery will require large probes (5 to 10mm) able to deliver low temperature in order to maximize the destruction of large lesions. Consoles should be portable and of relatively small size and should be compatible with all types of probes and useable within the complex equipment settings of an operating room. Cryogen sources should last for at least three cryosurgery sessions. There is also a need to produce temperature probes that can achieve temperatures lower than -70º C, which will still fit the internal anatomy of the tracheobronchial tree and pass through the channel of the bronchoscope. Probes must be safe to use, portable, and easy to use and handle. The probes must be robust and easy to sterilize.

Conclusion

Cryosurgery offers an effective therapy in the alleviation of distressing symptoms caused by obstructing tracheobronchial carcinoma. This method rapidly restores the patency of blocked lumina; therefore, post-procedure recovery is rapid. As a result, cryosurgery restores pulmonary reserve and respiratory function to a stage that further treatment such as radiotherapy and chemotherapy can be tolerated, thus providing improvement in quality of life and survival. This procedure takes about 20 minutes, is well tolerated, and has little or no side effects for either patients or operators.

We have shown cryosurgery for inoperable lung tumors to be effective in terms of survival and improvement in quality of life. This, coupled with its cost-effectiveness, means cryosurgery has great potential for wider application in the treatment of a variety of malignant and benign conditions.

References

1. Mountain, C. F. Revisions in the International System for Staging Lung Cancer. *Chest 111*, 1710-7 (1997).
2. De Perrot, M., Licker, M., Robert, J., Spiliopoulos, A. Time Trend in the Surgical Management of Patients with Lung Carcinoma. *Eur. J. Cardiothorac. Surg. 15*, 433-437 (1999).
3. Bolliger, C. T., Solèr, M., Tamm, M., Perruchoud, A. P. Kombinierte Endobronchiale und Konventionelle Therapie-möglichkeiten bei Inoperablen Zentralen Lungentumoren. *Schweiz. Med. Wochenschr. 125*, 1052-1059 (1995).
4. Arnott, J. *On the Treatment of Cancer by Regulated Application of an Anesthetic Temperature*. J Churchill, London (1851).
5. Neel, H. B. 3rd, Farrell, K. H., DeSanto, L. W., Payne, W. S., Sanderson, D. R. Cryosurgery of Respiratory Structures. I. Cryonecrosis of Trachea and Bronchus. *Laryngoscope 83*, 1062-71 (1973).
6. Maiwand, M. O. Cryotherapy for Advanced Carcinoma of the Trachea and Bronchi. *BMJ 293*, 181-182 (1986).
7. Murren, J. R., Buzaid, A. C. Chemotherapy and Radiation for the Treatment of Non-small Cell Lung Cancer. *Lung Cancer 14*, 161-171 (1993).
8. Maiwand, M. O. The Role of Cryosurgery in the Palliation of Tracheo-bronchial Carcinoma. *Eur. J. Cardio-Thoracic. Surg. 15*, 764-768 (1999).
9. Walsh, D. A., Maiwand, M. O., Nath, A. R., Lockwood, P., Lloyd, M. H., Saab, M. Bronchoscopic Cryotherapy for Advanced Bronchial Carcinoma. *Thorax 45*, 509-13 (1990).
10. Brutinel, W. M., Cortese, D. A., McDougall, J. C., Gillio, R. G., Bergstralh, E. J. A Two-year Experience with the Neodymium-YAG Laser in Endobronchial Obstruction. *Chest 91*, 159-165 (1987).
11. Desai, S. J., Mehta, A. C., Medendorp, S. V., Golish, J. A., Ahmad, M. Survival Experience Following Nd-YAG Laser Photoresection for Primary Bronchogenic Carcinoma. *Chest 94*, 939-944 (1988).
12. Quin, J. A., Letsou, G. V., Tanoue, L. T., Matthay, R. A., Higgins, R. S., Baldwin, J. C. Use of Neodymium Yttrium Aluminum Garnet Laser in Long Term Palliation of Airway Obstruction. *Connecticut Medicine 59*, 407-412 (1995).
13. McCaughan, J. S., Williams, T. E. Photodynamic Therapy for Endobronchial Malignant Disease: A Prospective Fourteen Year Study. *J. Thoracic Cardiovascular Surgery 114*, 940-947 (1997).
14. Steinbaum, S. S., Uretzky, I. D., McAdams, H. P., Torrington, K. G., Cohen, A. J. Exploratory Thoracotomy for Nonresectable Lung Cancer. *Chest 107*, 1058-1061 (1995).
15. Ferguson, M. K., MacMahon, H., Little, A. G., Golomb, H. M., Hoffman, P. C., Skinner, D. B. Regional Accuracy of Computed Tomography of the Mediastinum in Staging of Lung Cancer. *J Thorac Cardiovasc Surg 91*, 498-504 (1986).
16. Rues, T. J. M., Joosten, J., Jager, G. J., Wobbles, T. Long-term Results of Treating Hepatic Colorectal Metastases with Cryosurgery. *Br. J. Surg. 88*, 844-9 (2001).
17. Long, J. P., Bahn, D., Lee, F., Shinohara, K., Chinn, D. O., Macaluso, J. N, Jr. Five-year Retrospective, Multi-institutional Pooled Analysis of Cancer-related Outcomes after Cryosurgical Ablation of the Prostate. *Urology 57*, 518-23 (2001).
18. Coy, P., Elwood, J. M., Coldman, A. J. Clinical Indicators of Prognosis in Unresected Lung Cancer. *Chest 80*, 453-8 (1981).
19. Ratto, G. B., Fabiano, F., Rovida, S., Baracco, F., De Palma, M. Survival After Incomplete Resection or Exploratory Thoracotomy in Patients with Advanced Non Small Cell Lung Cancer. *Ital. J. Surg. Sci. 18*, 377-83 (1988).

Date Received: February 13, 2004