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The application of cryosurgery in the treatment of lung cancer☆

M.O. Maiwand,* J.M. Evans, and J.E. Beeson

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

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Abstract

Lung cancer is the commonest cause of cancer death, with a very poor survival rate. By the time of diagnosis, most cases are at an advanced stage and about 30% present with symptoms caused by central endobronchial obstruction. Endobronchial cryosurgery is an effective technique, which can be used to relieve tracheobronchial obstruction caused by lung cancer. This report describes the technique, using a nitrous oxide cooled cryoprobe, inserted through a bronchoscope, to remove the obstruction and reopen the airway. In this study, 476 consecutive patients (mean age 68.3 years, M:F ratio 1.9:1) with obstructive tracheobronchial tumours underwent a mean of 2.4 cryosurgical treatments. Their TNM staging was, stage II 6.7%, IIIa 21.0%, IIIb 23.9%, IV 48.4%. Improvement in symptom quantification was found with 76.4, 69.0, 59.2, and 42.6% of symptomatic patients for haemoptysis, cough, dyspnoea, and chest pain, respectively. Mean values for respiratory function improved from 1.38 to 1.41 litres for FEV1 and 1.91 to 2.04 litres for FVC ($p \leqslant 0.0001$). Mean performance status improved from 59.6 to 75.2 for Karnofsky scale and 3.04 to 2.20 for the WHO scale and the complication rate was 3.5% of treatments. The Kaplan–Meier median survival was 8.2 months and 1- and 2-year survival 38.4 and 15.9%, respectively. Survival analysis suggested a possible survival advantage over alternative palliative techniques. Endobronchial cryosurgery provides a safe and effective method for the palliation of otherwise inoperable lung cancer. It has advantages over other methods in terms of safety, cost, and a low complication rate. Cryosurgery can be repeated as often as required.

Keywords: Cryosurgery; Endobronchial obstruction; Lung cancer

Lung cancer is the commonest cause of cancer death in the world and affects about 900,000 people annually [1]. It is rapidly disabling and has a very poor survival rate of only 10–13% over 5 years [1], largely due to the fact that symptoms do not manifest themselves until the disease is well advanced. Surgical resection is the sole curative treatment, but only a small number of patients are considered operable and at least 80% will require palliative treatment. Around 30% of these inoperable patients present with obstruction of the central airway by a tumour, which can cause distressing symptoms of cough, breathlessness,

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* Corresponding author. Fax: +44-0-1895-828-528.
E-mail address: cryotherapy@rbh.nthames.nhs.uk (M.O. Maiwand).

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haemoptysis, and recurrent infections, and may lead to gradual asphyxiation [3]. Radiotherapy and chemotherapy are the standard palliative treatments but have limited effectiveness in reopening obstructed airways [18]. Cryosurgery is one of the techniques, which can be used for patients with symptoms caused by inoperable tumours, to reopen an obstructed tracheobronchial lumen. The alternatives include laser treatment, diathermy, photodynamic therapy, and stent placement. These local therapies recanalise the airways and relieve symptoms. This paper presents the results of a prospective study of 476 consecutive patients, treated for central malignant endobronchial obstruction, evaluates the safety and efficacy of the procedure, and also reviews the literature on the mechanisms of cell destruction in cryosurgery.

Patients and methods

From January 1995 to June 2002, 476 consecutive patients with obstructive, malignant endobronchial tumours underwent endobronchial cryosurgery in a single institution. These patients were all inoperable by conventional surgical resection because of the advanced stage of the disease, the site of the tumour, poor lung function or the patient's general health. The study involved recording patient's symptoms of dyspnoea, cough, haemoptysis, chest pain, dysphagia, anorexia, stridor and depression, respiratory function tests (forced expiratory volume in 1 s, FEV1, and forced vital capacity FVC), performance status (WHO and Karnofsky scales). Diagnostic tests comprised chest X-ray and bronchoscopy in all cases, computed tomography in 38% and mediastinoscopy in 14% of patients. All patients had confirmed pathology, 97.2% histologically and 2.8% by sputum cytology. The majority of the patients were stage IIIb or IV (72%). Patients with stage II or IIIa lung cancer, who were thought unfit for immediate surgical resection, underwent cryosurgery because they were (a) clinically unfit for surgery or (b) for palliation of symptoms, before or after oncological treatment.

Cryosurgery procedure

Endobronchial cryosurgery was performed under short-acting intravenous general anaesthesia, using a large rigid (9.2 mm) or flexible bronchoscope (2.4 mm). Oxygenation was maintained with Venturi positive-pressure ventilation. The distal tip of the bronchoscope was placed about 5 mm above the lesion and the appropriate cryoprobe (straight, right angled or flexible) inserted through the bronchoscope and applied to the tumour. The tumour was frozen for 3 min and then allowed to thaw until the probe separated from the tissue. One freeze–thaw cycle was used for superficial lesions and two cycles for lesions more than 3 mm deep. If the tumour covered wider areas of the bronchial tree, multiple cryo-applications were made during the same treatment session. Where a large mass of necrotic tumour was present after the cryo-application, the mass was removed, using large rigid biopsy forceps, before the second application.

The probe is a Joule–Thomson type with nitrous oxide as the cryogen and achieves temperatures of around −70 °C at the probe tip. The selection of probe diameter, 5 or 2.2 mm, was based on the size and position of the tumour. The 2.2 mm probe was used for peripheral, smaller tumours through the fibreoptic bronchoscope. The 5 mm probe was used for larger, central tumours so that a larger area could be treated. The use of a large rigid bronchoscope allowed a small suction catheter to be placed next to the treatment site to remove blood and secretions throughout the procedure.

Tissue samples for histological examination were taken before each cryotreatment. Monitoring and recording of temperature during cryotherapy is important as tissue destruction is directly related to the temperature drop achieved at the treatment site. Probe temperatures were determined potentiometrically with a needle placed about 2 mm from the tip. In a previous study these have been found to achieve a mean minimum temperature of −30 °C (standard deviation ± 5.6) over 100 applications [13]. In the author's experience, bleeding from the site of a biopsy or cryosurgery has not been a major difficulty and moderate bleeding can be contained by the local application of Epinephrine (adrenaline) 1:1000. The procedure generally takes about 20 min and the majority of patients recover well enough to be discharged home on the same day. A repeat treatment is carried out 2 weeks after the first treatment, large areas of tumour necrosis are often seen which can be removed using biopsy forceps. The procedure can be repeated when symptoms re-occur [11].

Results

Four hundred and seventy-six consecutive patients were treated between January 1995 and December 2002. The mean age was 68.3 years (range 22–88, median 70.0 years) and the male to female ratio 1.9:1. Each patient received a mean of 2.4 cryosurgical treatments. Pathological diagnoses were as follows: 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 [17] for NSC patients at the time of treatment was: stage II 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 improvements in respiratory function tests, performance status, and symptom quantification are given in Table 1 and 86.0% of patients showed improvement in one or more symptoms. Complications were bleeding 0.7%, pneumothorax 0.1%, respiratory distress 0.9%, anaesthetic related 0.2%, and cardiac 1.6% and the overall rate was 3.5% of

Table 1
Results of respiratory function tests, performance status, and symptom quantification

	Mean pre-cryosurgery	Mean post-cryosurgery
Fixed expiry volume in 1 s/litres	1.38	1.47 ($p \leqslant 0.0001$)
Forced vital capacity/litres	1.91	2.04 ($p \leqslant 0.0001$)
Karnofsky performance status	59.6	75.2
WHO performance status	3.04	2.20
	Pre-cryosurgery: percentage patients symptomatic	Post-cryosurgery: percentage of symptomatic patients improved
Cough	91.5	69.0
Dyspnoea	98.5	59.2
Haemoptysis	37.8	76.4
Chest pain	30.2	42.6
Dysphagia	10.7	28.6
Anorexia	41.7	47.8
Stridor	19.5	37.5
Depression	34.1	53.9

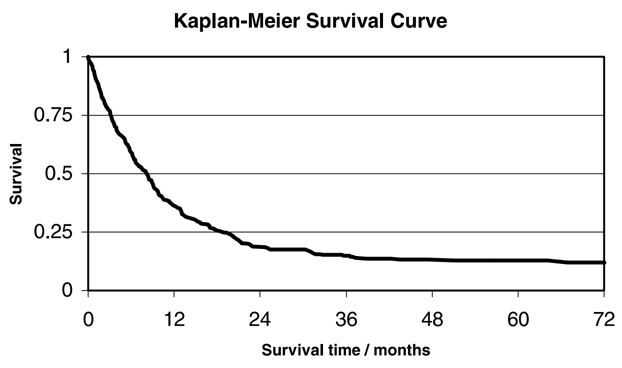

Fig. 1. Kaplan–Meier survival curves for 476 patients treated with cryosurgery.

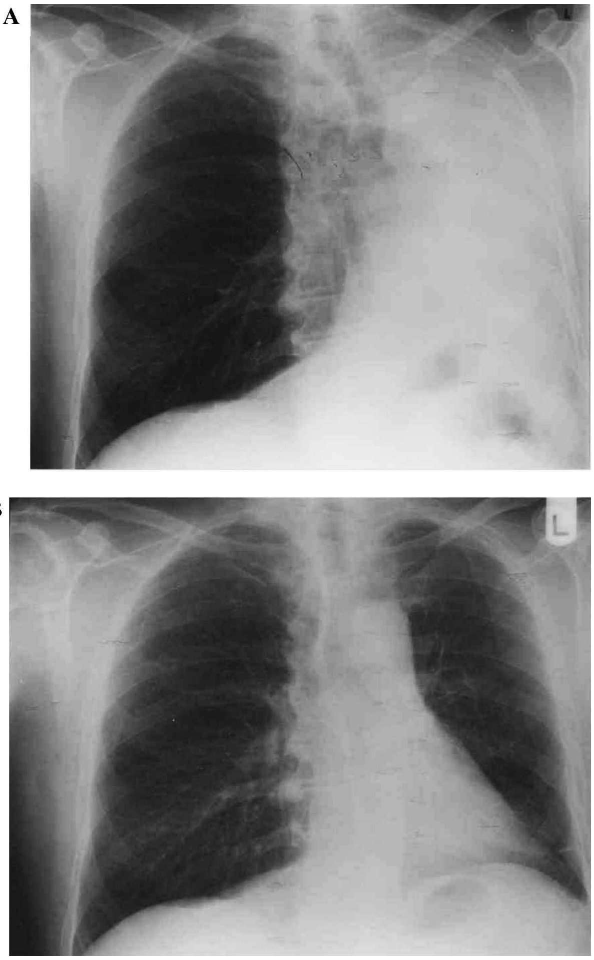

Fig. 2. Chest X-rays for a patient A with complete blockage of right lung and re-expansion following cryosurgery.

treatments. The Kaplan–Meier median survival was 8.2 months (Fig. 1), 1-year survival 38.4% and 2-year survival 15.9%. The median survival (95% confidence limits) by stage was as follows: stage II 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). Radiological and bronchoscopic findings before and after cryosurgery are shown in Figs. 2 and 3.

Discussion

In recent years, little progress has been made in improving the quality of life of patients with advanced lung cancer. This has added to the importance of alleviating symptoms and improving quality of life for patients with advanced stage, inoperable carcinoma. Where the possibility of surgery has been eliminated, other palliative measures must be considered. These treatments include laser therapy, photodynamic therapy, brachytherapy, and cryosurgery. 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.

Cryosurgery has some limitations when used endobronchially because of the difficulty in accessing the tracheobronchial tree. This has largely

A

B

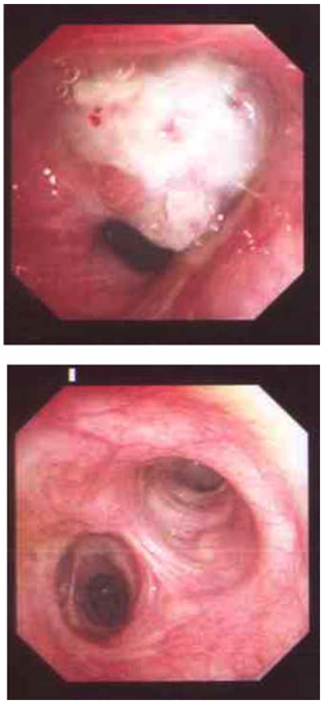

Fig. 3. Bronchoscopic images for a patient B before and after cryosurgery. Before image shows complete obstruction of right main bronchus. The patient received three sessions of cryosurgery, no radiotherapy or chemotherapy and 7 weeks later showed an unobstructed lumen. The patient remained symptom free for 6 months.

been overcome by the development of specially designed probes to fit the internal anatomy of the tracheobronchial tree. A further limitation is the possibility of damage to the bronchial walls, but this has been minimised by the use of Joule–Thomson type probes with nitrous oxide coolant. There would be advantages, in terms of cell destruction, in using a cryogen with a greater cooling capacity such as liquid nitrogen. Current technology, however, does not allow for probes sufficiently long and narrow ($0.5\,\mathrm{m} \times 5\,\mathrm{mm}$) to access the tracheobronchial tree, though such systems are being developed. 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 freezing damage. Probes used for endobronchial cryosurgery may be may be rigid, semi-rigid or flexible, and can be used through a rigid bronchoscope, or in the case of flexible probes, a fibreoptic bronchoscope. 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. In some cases, these extraneous materials may accumulate and freeze, thereby insulating the target tumour from the effects of the probe and decreasing the efficacy of the procedure.

Patients treated with endobronchial cryosurgery are generally elderly with advanced stage of the disease and frequently have other coexisting conditions. Such patients may be unsuitable for surgical resection because of the position of the tumour, the disease is in an advanced stage or poor lung function. 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. It must be remembered, however, that endobronchial cryosurgery is a palliative technique, with the aim of alleviation of symptoms and improving the patient's performance status, and so complete cell destruction is desirable but not imperative. Cryosurgical treatment of obstructive endobronchial tumours can open bronchi to allow drainage of infected secretions, and lead to re-aeration of collapsed lungs. The effect of this improved oxygenation and general improvement of well being can appear very rapidly.

Endobronchial cryosurgery has been used in this institution for over 10 years and has been shown to provide effective symptom relief, improved respiratory function, and performance status [12,24]. Results for this study (Table 1), which is comprised of an elderly group of patients (69% over 65 years) with advanced stage lung cancer (73% stage IIIb or IV), showed good improvement in symptom quantification with 86% of patients showing an improved score for one or more symptoms. Results for performance status showed 63% of patients with an increased Karnofsky score. Respiratory function tests showed 61% of patients improved and mean RFT values increased by 7%. Results for survival (median 8.2 months) compare 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 [4,5,19,23]. Photodynamic therapy has been shown to achieve a median survival of 5–7 months [15,16]. (The complication rate of 4% is relatively low for this high-risk group of patients with limited treatment options.)

It is important in the field of cryosurgery to maximise all the mechanisms by which tissue destruction occurs. These mechanisms can be divided into immediate effects and delayed effects. Immediate mechanisms include the physical effect of intracellular ice crystal formation (IIF), the biochemical effect of cell dehydration and shrinkage, and thawing effects [6,14,25]. The delayed effect involves vascular stasis and possibly apoptosis [2,7,9]. The effect of vascular stasis is greater in venules than arterioles [26] where blood velocity and heat transfer are much higher. The local ischaemia has a beneficial effect in clinical practice and cryosurgeons make use of the phenomena to control bleeding from the tumour surface [10]. The predominant mechanism of cell destruction is influenced by the freezing regime, the thermal history of the cell, distance from the probe, tissue vascularity, and the type of cell being frozen. These effects can be maximised by the cryosurgeon by using rapid cooling, low end temperature, slow thawing, and repeat freeze–thaw cycles [8,20–23,26].

Conclusions

Endobronchial cryosurgery is an important addition to the treatment of lung cancer and should be considered in the management of patients with advanced disease. For patients with respiratory symptoms it can provide symptom palliation and improved performance status. The use of cryosurgery in the tracheobronchial area has been established for some time and it has been shown to provide a safe, rapid, and effective method for the restoration of patency of a blocked tracheobronchial lumen. It improves symptoms, respiratory function, and also quality of life. The technique is easy to perform, economical, has minimal complications, and is well tolerated by the patient. Cryosurgery often leads to sufficient improvement in the patient's condition so that they can tolerate further treatments such as radiotherapy or chemotherapy, providing a better outcome and improved quality of life and survival.

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