The role of cryosurgery in palliation of tracheo-bronchial carcinoma

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Abstract

Objective: Carcinoma of the lung is the commonest cause of death from malignant disease in humans. At diagnosis, about 85% of patients are in an advanced stage of the disease and approximately 30% present with a tumour blocking a large bronchial lumen, causing distressing and life threatening symptoms. Early reopening and treatment of the blocked airways is required to improve symptoms and quality of life. There are a number of methods available to achieve this aim including cryotherapy, the controlled application of extreme cold. Methods: We present a prospective study of 153 consecutive patients, cryotreated between January 1995 and December 1997 with a mean age of 68.8 years and a male:female ratio of 1.59:1. The procedure can be performed under general or local anaesthetic using a rigid or flexible cryoprobe. A temperature of about −70°C is delivered to the tumour site for two 3-min periods causing destruction of the tumour mass. Patients were evaluated clinically and for performance status before and after treatment. Histological composition was: non-small cell 88.2%, small cell 11.1% and malignant melanoma 0.7%. The TNM staging for NSC patients, at the time of treatment was stage II 8.2%, IIIa 27.4%, IIIb 25.9%, IV 38.5%. Results: Subjective symptomatic improvement for cough was 68.3%, dyspnoea 63.9%, haemoptysis 92.7% and chest pain 55.5%. Respiratory function tests showed improvements in mean FEV1 from 1.34l to 1.45l (P = 0.001) and mean FVC from 1.93 to 2.02 l (P = 0.035). The Karnofsky performance status increased by 54.6%. Kaplan–Meier median survival time was 12.9 months. Complications were found with 11 patients (7.2%) and there was no operative mortality. Conclusions: Cryotherapy provides effective and rapid control of symptoms caused by tracheobronchial carcinoma and improves quality of life and survival. It is easy to perform, with minimum complications and the majority of patients are discharged the same day. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Cryotherapy; Tracheobronchial; Palliation; Lung cancer

1. Introduction

Carcinoma of the lung is the commonest cause of death from malignant disease in humans and causes almost 600 000 deaths world wide each year [1]. At the time of diagnosis over 85% of patients are at an advanced stage of the disease and only palliative treatment is possible [1]. About 30% of patients present with a tumour blocking the large bronchial lumen causing distressing symptoms of dyspnoea, cough, haemoptysis and chest pain [2]. To alleviate these symptoms requires physical reopening of the bronchial lumen. Although external beam radiotherapy and chemotherapy have been the commonest methods of palliation [3], they do not often achieve recanalisation of tracheobronchial obstruction and therefore a method of mechanical removal or destruction of tumour is also required. This can be achieved by cryotherapy, the controlled application of extreme cold. Over 700 patients have been treated for endobronchial lesions in this unit since 1980.

2. Patients and methods

The results of a prospective study of 153 consecutive patients treated at Harefield hospital between January 1995 and December 1997 are presented. The mean age of the cohort was 68.8 years (range 36–85, median 70.2 years) and the male to female ratio 1.59:1. Histological composition was as follows: squamous cell 68.0%, adenocarcinoma 15.0%, large cell 1.3%, undifferentiated 3.9%, small cell 11.1% and malignant melanoma 0.7%. The TNM staging [4] for NSC patients, at the time of treatment was, stage II 8.2%, IIIa 27.4%, IIIb 25.9%, IV 38.5%. Of these patients, 34% had previously received radiotherapy and 6% chemotherapy.

Endobronchial cryotherapy was performed as a palliation for obstructive, symptomatic, malignant endobronchial lesions. These patients were considered inoperable based...
on the advanced stage of the disease, the site of the tumour, poor lung function or general health. Patients were assessed clinically, radiologically and for performance status before and after each cryotreatment. Symptom evaluation was carried out for dyspnoea, haemoptysis, cough and chest pain as described previously [5]. Chest radiographs were carried out before and after treatment. Respiratory function tests, forced expired volume in one second (FEV1) and forced vital capacity (FVC) were measured using a Microlab 3000 turbine spirometer, before cryotherapy and after an average of 10 weeks. Performance status was assessed using the Karnofsky scale [6] and weight was determined before and after treatment.

Cryotherapy was performed under general anaesthesia (propofol) using a large 9.2 mm rigid bronchoscope. Oxygenation was maintained with Venturi positive-pressure ventilation. The distal tip of the bronchoscope was placed about 0.5 cm above the lesion and the appropriate cryoprobe (straight, right angled or flexible) inserted through the bronchoscope and applied to the tumour, which was frozen for two 3-min periods and then allowed to thaw. The probe (Joule-Thomson type, involving adiabatic expansion of compressed gas [7]) uses nitrous oxide as the cooling agent and achieves temperatures of about $-70^\circ C$ at the probe tip. The selection of probe diameter, 5 mm 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 a fibreoptic bronchoscope. The 5 mm probe was used for larger, central tumours so that a larger area was treated. If the tumour covered wider areas of the bronchial tree, multiple cryoapplications were made during the same treatment session. Where a large mass of necrotic tumour was present after the cryoapplication, the mass was removed before the second application. It was essential that all areas involved or infiltrated by the tumour were frozen to achieve adequate tumour destruction. The use of a large rigid bronchoscope allowed a small suction catheter to be placed next to the site of treatment 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 was important as tissue destruction is directly related to the temperature drop achieved to the treatment site. Probe temperatures were determined potentiometrically with a needle placed about 2 mm from the tip. These have been found to achieve a mean minimum temperature of $-30^\circ C$ (SD $\pm 5.6$) over 100 applications [8]. 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 majority of patients recover well enough to be discharged home on the same day. By the time of re-bronchoscopy, typically performed 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 the symptoms reoccur and then if necessary after a further six weeks [9].

Cryodestruction and removal of a tumour blocking a major bronchial lumen followed by drainage of secretions from behind the blockages and re-ventilation of a collapsed lung, not surprisingly, leads to patients reporting symptomatic relief soon after the procedure.

3. Results

Results are presented for 153 consecutive cryotreated patients which show good symptomatic improvement for dyspnoea, cough, haemoptysis and chest pain and improvements in Karnofsky performance status (Table 1). Respiratory function tests showed significant improvements after cryosurgery (paired Student’s $t$ test) (Table 2). Overall 71.9% of patients reported a subjective improvement in their condition (cough, dyspnoea, haemoptysis or chest pain). In a study of the last 100 patients, the mean weight loss was only 0.93 kg over an average time period of 21 weeks. It should be noted that this is an elderly group of patients with 54% being 70 years old or more. They were also in an advanced stage of the disease with 64% of NSC patients stage IIIb or IV. The median survival time (Kaplan–Meier) was 12.9 months and a survival curve is shown in Fig. 1. There were no operative deaths and complications were found in 11 patients (see Table 3).

Bronchoscopic and radiographic findings before and after cryotherapy are shown in Figs. 2 and 3.

4. Discussion

Cryotherapy is one of a number of palliative treatments which can be used in the management of endobronchial

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>Patients improved</th>
<th>Percentage improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>133</td>
<td>85</td>
</tr>
<tr>
<td>Cough</td>
<td>120</td>
<td>82</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>Chest pain</td>
<td>45</td>
<td>25</td>
</tr>
<tr>
<td>Karnofsky</td>
<td></td>
<td></td>
</tr>
<tr>
<td>performance status</td>
<td></td>
<td>76</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>RFT</th>
<th>Pre cryo mean</th>
<th>Post cryo mean</th>
<th>$P$-value</th>
<th>Percentage improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1/l</td>
<td>1.34</td>
<td>1.45</td>
<td>0.001</td>
<td>65.2</td>
</tr>
<tr>
<td>FVC/l</td>
<td>1.93</td>
<td>2.02</td>
<td>0.035</td>
<td>57.8</td>
</tr>
</tbody>
</table>
obstruction, including laser therapy, photodynamic therapy, brachytherapy, diathermy and stent insertion. The method used depends on the site and type of obstruction (intra or extra-luminal), the extent of the disease, the condition of the patient, the availability of techniques and the expertise of the clinician.

The application of cold for therapeutic purposes was first reported by James Arnott in 1851 [10,11], who used the direct application of ice and salt to treat advanced uterine tumour resulting in the regression of tumour size and effective symptom control. The use of cryotherapy was facilitated by the development of a number of different types of cryoprobe in the early 1960’s. The most important of these used the Joule-Thomson effect (adiabatic expansion of compressed gas) [7] and was first used for the treatment of Parkinson’s disease [12]. The use of cryotherapy in the tracheobronchial tree occurred later in Europe, in the mid 1980’s, after the development of specially shaped probes [9,13].

In general, the extent and permanence of a freeze injury is determined by the rate of cooling and thawing [14–16], the lowest temperature achieved [17], the number of freeze-thaw cycles performed [18,19] and the type of tissue being frozen [20]. The cryosensitivity of tissues is directly related to their free water content and it has also been suggested that tumour cells may be more cryosensitive than the normal cells of the host tissue [20].

The destructive effect of freezing involves physical, biochemical and vascular effects. The freezing of living tissues produces ice crystals, from pure water, in the extracellular spaces, at about $-10^\circ C$, causing hypertonicity and withdrawal of water from inside the cell. The increase in solute concentration and rise in pH to 4 causes damage to proteins, lipoproteins and enzymes. As the temperature falls further, the eutectic point is reached and complete internal solidification occurs resulting in complete cellular destruction [21,22].

The effect of extreme cold on blood vessels is to cause the propagation of large ice crystals inside the vessels leading to water entering the vessel which expands. At around $-20^\circ C$ showers of micro-cryoemboli appear and are gradually deposited on the vessel walls reducing blood flow and finally blockage causing local tissue ischaemia and eventual necrosis. These effects are more pronounced in the venules than arterioles and have a beneficial effect in controlling surface bleeding from the tumour [8].

Cryotherapy is also thought to enhance the responsiveness of bronchogenic tumours to radiotherapy and

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Table 3
Operative complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Respiratory</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>Anaesthetic</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>7.2</td>
</tr>
</tbody>
</table>

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Fig. 1. Kaplan–Meier survival curve.

Fig. 2. Chest radiographs before and after cryosurgery.
Chemotherapy and experimental studies have suggested that cryotreated cells acquire a greater affinity for trapping anticancer drugs than untreated cells [23]. It has also been shown that the combination of cryotherapy and radiotherapy gives a better survival rate than the combination of laser therapy and irradiation [24]. The results obtained for this group of patients, considered unresectable because of their general condition or RFT's, are in line with those obtained in previous studies [5,8].

Other palliative treatments for endobronchial obstruction include laser therapy, which is widely used and provides good symptomatic response, but is costly to establish and maintain and incidences of terminal haemorrhage have been reported [25] together with other complications of hypoxia, pneumothorax, perforation, bleeding and fire [26,27]. Photodynamic therapy offers good symptomatic relief [28] and is most effective on small tumours. It is also expensive and carries the risk of postoperative haemorrhage and the possibility of sunburn [29]. Endobronchial brachytherapy delivers intense local radiation directly to the tumour, thus sparing the healthy lung tissue. It is well suited to central tumours and patients with poor respiratory function, but may also have complications including massive fatal haemoptysis and radiation bronchitis [30,31]. Airway stents can be used successfully to palliate the effects of tracheobronchial obstruction caused by intra but mainly extra luminal pressure or loss of cartilaginous support with good results. Complications (Table 3) for endobronchial cryotherapy, in this study, were found to be 7.2% (11 patients). Three patients (2.0%) developed bleeding following cryotherapy, two moderately and one, who had received radiotherapy 10 weeks previously, severely. There was no mortality related to cryotherapy.

Cryotherapy also offers an effective method to restore the patency of blocked tracheobronchial lumen and therefore improve symptoms and quality of life. It is well tolerated by the patient who is discharged home the same day. Cryotherapy has the advantages of being easy to perform, not requiring expensive equipment, it does not have a risk of bronchial wall perforation, is safe for the operator and has minimal complications.

References