

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of cryosurgery for malignant endobronchial obstruction

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in February 2005.

Procedure name

- Cryosurgery, cryotherapy or cryoablation for malignant endobronchial obstruction.

Specialty societies

Specialist advice was sought from:

- Association of Cancer Physicians
- British Thoracic Society
- Society of Cardiothoracic Surgeons
- Association of British and Irish Cryosurgery.

Description

Indications

Malignant endobronchial obstruction.

Lung cancer is often at an advanced stage by the time it is diagnosed and survival rates are low. Patients can develop endobronchial lesions that obstruct the major airways, causing symptoms such as dyspnoea, cough, haemoptysis and postobstructive pneumonia. The obstruction may lead to gradual asphyxiation.

Current treatment and alternatives

The aim of treatment in patients with malignant endobronchial obstruction is mainly palliative. Current treatment options include a variety of endobronchial therapies such as resection, brachytherapy, laser ablation, photodynamic therapy and stenting. External beam radiotherapy and chemotherapy may also be used for palliative treatment.

What the procedure involves

Cryosurgery uses extreme cold to destroy tissue. General anaesthesia is usually used and a cryoprobe is inserted through a bronchoscope to reach the tumour. The selection of probe diameter depends on the size and position of the tumour. After a period of freezing, the tumour is allowed to thaw until the probe separates from the tissue. The freeze/thaw cycle may be repeated two to three times in the same place. The probe is then moved to an adjacent area and the process repeated until the whole tumour has been treated. Any resulting necrotic tumour material is then removed with forceps or the cryoprobe. Further necrotic-appearing material may be coughed out 24 to 48 hours later. The procedure can be repeated if necessary.

Cryotherapy has a delayed action and so it is not suitable for use as an emergency treatment for acute respiratory distress.

Efficacy

The main aim of the procedure in the studies was palliation of symptoms such as cough, dyspnoea and haemoptysis. In one case series of 521 patients, 86% (n = 448) had improvement in one or more symptoms and the quality of life scores were also significantly improved. Dyspnoea improved in 59% (300/507) of patients. In two further studies, dyspnoea improved in 71% (12/17) and 81% (87/107) of patients.

The Specialist Advisors did not express any major concerns about the efficacy of this procedure.

Safety

A large case series study reported in-hospital mortality of 1% (7/521), which was due to respiratory failure. This study also reported that 3% (16/521) of patients suffered from respiratory distress after the procedure.

A case series study of 27 patients reported one death due to myocardial ischaemia and another study of 22 patients reported one cardiopulmonary arrest. Two studies reported changes to the heart rhythm in 2% (12/521) and 11% (3/27) of patients.

The Specialist Advisors listed haemorrhage, fistula formation, cardiac arrhythmias, respiratory distress and infection as potential adverse effects.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to cryosurgery for malignant endobronchial obstruction. Searches were conducted via the following databases, covering the period from their commencement to December 2004: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory study or animal study.
Patient	Patients with malignant endobronchial obstruction.
Intervention/test	Cryosurgery.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on four case series reports.¹⁻⁴

Details of a randomised trial comparing external beam radiotherapy with endobronchial treatment were reported in 1999.⁵ The trial initially aimed to recruit 400 patients but it only randomised 75 patients (14 were randomised to cryotherapy) over 3.5 years and was abandoned prematurely. The main reasons for slow intake were: lack of referrals of untreated patients; patients being referred specifically for endobronchial treatment; patients having already received radiotherapy; emergency relief of obstruction being necessary; and radiotherapy and endobronchial treatments being considered as complementary to conventional treatment rather than as alternatives.

Table 1 Summary of key efficacy and safety findings on cryosurgery for malignant endobronchial obstruction

Abbreviations used: FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Maiwand MO (2004)¹</p> <p>Case series</p> <p>UK</p> <p>1995–2003</p> <p>521 patients</p> <p>Mean age = 67.9 years (range 22 to 88)</p> <p>Mean no. of treatments = 2.4</p> <p>Indications: symptomatic, obstructive, malignant endobronchial tumours. All patients had confirmed pathology (squamous cell carcinoma 68%, adenocarcinoma 15%, small cell 9%, unclassified non-small cell 5%, and large cell 3%). The majority of the patients were stage IIIb or IV</p> <p>39% of patients had previously had radiotherapy and 9% had chemotherapy</p> <p>Mean follow-up = 18 months (range 4 to 84)</p>	<p>Key outcome measures: results of respiratory function tests, performance status and symptom quantification</p> <p>Improvement in one or more symptoms = 86% (448/521)</p> <p>Improvement of cough = 69.0% (318/461)</p> <p>Improvement of dyspnoea = 59.2% (300/507)</p> <p>Improvement of haemoptysis = 76.4% (154/202)</p> <p>Improvement in chest pain = 42.6% (71/167)</p> <p>Mean FEV1 before cryosurgery = 1.39 litres</p> <p>Mean FEV1 after cryosurgery = 1.51 litres, $p < 0.05$</p> <p>Mean FVC before cryosurgery = 1.93 litres</p> <p>Mean FVC after cryosurgery = 2.13 litres, $p < 0.05$</p> <p>Mean Karnofsky performance status before cryosurgery = 60</p> <p>Mean Karnofsky performance status after cryosurgery = 75, $p < 0.05$</p> <p>Mean WHO performance status before cryosurgery = 3.04</p> <p>Mean WHO performance status after cryosurgery = 2.20, $p < 0.05$</p> <p>One-year survival = 38.4%</p> <p>Two-year survival = 15.9%</p> <p>Median survival (Kaplan-Meier) = 8.2 months</p>	<p>Complications</p> <ul style="list-style-type: none"> • In-hospital mortality (all due to respiratory failure) = 1.3% (7/521) • Haemoptysis = 4% (21/521) • Postoperative atrial fibrillation = 2% (12/521) • Respiratory distress and poor gas exchange = 3% (16/521) 	<p>Consecutive patients.</p> <p>The patients were not considered for lung resection because of the advanced stage of the disease or the patient's general condition.</p> <p>Patients were assessed clinically, radiologically and for performance status (Karnofsky and WHO scales) before and after each cryosurgery.</p> <p>A repeat treatment was carried out 2 weeks later.</p>

Abbreviations used: FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Mathur PN (1996)²</p> <p>Case series</p> <p>USA</p> <p>22 patients (20 with malignant obstruction)</p> <p>Mean age = 62 years (range 28 to 82)</p> <p>Indications: symptomatic endobronchial lesions unsuitable for surgery. Twenty patients had malignant lesions (non-small cell lung cancer or metastatic disease); two had benign strictures</p> <p>Exclusion criteria: acute respiratory distress, central obstructing lesion that was eminently causing respiratory distress, uncorrectable bleeding diathesis</p> <p>Previous treatments: external beam radiotherapy (14/20), brachytherapy (5/20), chemotherapy (2/20), Nd:YAG laser (1/20)</p> <p>No follow-up period was described</p>	<p>Key outcome measures: endoscopic appearance and symptom quantification</p> <p>All intrinsic tumour removed = 90% (18/20) Failure to remove tumour = 5% (1/20) Died before re-evaluation = 5% (1/20)</p> <p>Improvement in dyspnoea = 70.6% (12/17) Improvement in haemoptysis = 100% (5/5)</p>	<p>Complications</p> <ul style="list-style-type: none"> • Bronchospasm during bronchoscopy, necessitating premature abortion of procedure = 9.1% (2/22) (these patients were subsequently treated successfully after pre-treatment with bronchodilator or steroids) • Purulent drainage from obstructed lobe = 4.5% (1/22) • Cardiopulmonary arrest during procedure = 4.5% (1/22) 	<p>Patients were unsuitable for surgery.</p> <p>The study also included two patients with bronchial obstruction following lung transplantation.</p> <p>Bronchoscopic examination was repeated after 1 to 2 weeks, when either more cryotherapy was applied, and/or the slough was removed.</p>

Abbreviations used: FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Marasso A (1993)³</p> <p>Case series</p> <p>Italy</p> <p>1979–1988</p> <p>183 patients with malignant obstruction</p>	<p>Key outcome measures: respiratory function tests and symptom quantification</p> <p>Resolution of lung atelectasis = 57% (30/52) Resolution of lobe atelectasis = 76% (48/63) Resolution or reduction of haemoptysis = 93% (58/62) Dyspnoea improvement = 81% (87/107) PaO₂ improvement = 71% (120/168) Sepsis improvement = 40% (26/65)</p>	<p>Not reported</p>	<p>Results were not available for 7% (13/183) of patients.</p>
<p>Homasson JP (1986)⁴</p> <p>Case series</p> <p>France</p> <p>27 patients (22 with malignant obstruction)</p> <p>Mean age = 60 years (range 39 to 88)</p> <p>Indications: bronchogenic cancer and granulomas</p>	<p>Key outcome measures: local tumour control (biopsy and radiological results)</p> <p>Disappearance or regression of the tumour permitting renewed or improved ventilation of a lobe or lung and interruption of haemoptysis = 61.9% (13/21)</p> <p>Technical failures (probe was too short) = 18.5% (5/27)</p> <p>Residual tumour identified on biopsy = 4.5% (1/22)</p>	<p>Complications</p> <ul style="list-style-type: none"> • Death due to major myocardial ischaemia = 3.7% (1/27) • Change in heart rhythm during procedure = 11.1% (3/27) • Mild fever = 7.4% (2/27) 	<p>Patients were not candidates for other traditional therapies.</p>

Validity and generalisability of the studies

- Three studies specified that the patients were not suitable candidates for surgery.^{1,2,4}
- Two studies included a small proportion of patients with benign structures rather than malignant obstructions.^{2,4}
- Two of the four case series were small.^{2,4}
- Only one study reported results after a follow-up period.¹
- Two studies documented that patients were given repeat treatments.^{1,2}

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

- The procedure is established practice and no longer new.
- The key efficacy outcomes are improved respiratory function and quality of life.
- There are a number of alternative treatments available for this indication, including other endobronchial treatments such as resection, laser ablation, brachytherapy, photodynamic therapy and stenting.
- The likely speed of diffusion of this procedure is slow.

Issues for consideration by IPAC

NICE has recently produced guidance on the diagnosis and treatment of lung cancer (Clinical Guideline 24). The guideline states that patients with endobronchial symptoms that are not palliated by other means may be considered for endobronchial therapy. Level 3 evidence was identified for the use of cryotherapy as a palliative intervention in the management of dyspnoea, with three case-series reporting palliation of 65–68%.

No studies on cryotherapy for curative treatment of invasive non-small cell lung cancer were identified by the literature search. The guideline states that further randomised trials should be conducted on the effect on survival and quality of life of endobronchial techniques used as curative treatment in patients with early-stage non-small cell lung cancer not suitable for conventional treatment.

References

- 1 Maiwand MO, Asimakopoulos G. Cryosurgery for lung cancer: clinical results and technical aspects. *Technology in Cancer Research & Treatment* 2004;3:143–150.
- 2 Mathur PN, Wolf KM, Busk MF et al. Fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. *Chest* 1996;110:718–23.
- 3 Marasso A, Gallo E, Massaglia BM et al. Cryosurgery in bronchoscopic treatment of tracheobronchial stenosis. *Chest* 1993;103:472–474.
- 4 Homasson JP, Renault P, Angebault M et al. Bronchoscopic cryotherapy for airway strictures caused by tumors. *Chest* 1986;90:159–164.
- 5 Moghissi K, Bond MG, Sambrook RJ et al. Treatment of endotracheal or endobronchial obstruction by non-small cell lung cancer: lack of patients in an MRC randomized trial leaves key questions unanswered. *Clinical Oncology* 1999;11:179–183.

Appendix A: Additional papers on cryosurgery for malignant endobronchial obstruction not included in the summary tables

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Gorenstein A, Neel HB III, Sanderson DR. Transbronchoscopic cryosurgery of respiratory structures: experimental and clinical studies. <i>Annals of Oncology, Rhinology & Laryngology</i> 1976;85:670–678.	6 patients.	Case series.	Palliation = 83% (5/6).
Maiwand MO, Evans JM, Beeson JE. The application of cryosurgery in the treatment of lung cancer. <i>Cryobiology</i> 2004;48:55–61.	476 patients.	Case series. Same centre as Maiwand et al, 2004. ¹	Improved performance status. 1-year survival = 38% 2-year survival = 16% 3.5% complication rate.
Maiwand MO. The role of cryosurgery in palliation of tracheo-bronchial carcinoma. <i>European Journal of Cardio-thoracic Surgery</i> 1999;15:764–768.	153 patients.	Case series. Same centre as Maiwand et al, 2004. ¹	Significant improvement in lung function. Median survival = 12.9 months. 7.2% complication rate.
Noppen M, Meysman M, Van Herreweghe R et al. Bronchoscopic cryotherapy: preliminary experience. <i>Acta Clinica Belgica</i> 2001;56:73–77.	12 patients. Mean follow-up = 4 months.	Case series. Mixed patient group.	No complications. No recurrences.
Sanderson DR, Neel, HB III, Fontana RS. Bronchoscopic cryotherapy. <i>Annals of Oncology, Rhinology & Laryngology</i> 1981;90:354–358.	28 patients.	Case series.	Improvement = 54% (15/28). Fatal complications = 3% (2/60)
Walsh DA, Maiwand MO, Nath AR et al. Bronchoscopic cryotherapy for advanced bronchial carcinoma. <i>Thorax</i> 1990;45:509–513.	33 patients.	Case series. Same centre as Maiwand et al, 2004. ¹	Improved lung function = 58% No important complications.

Appendix B: Literature search for cryosurgery for malignant endobronchial obstruction

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

1	cryotherap\$.tw. (2982)
2	cryoprob\$.tw. (422)
3	cryosurger\$.tw. (2415)
4	(cryo\$ adj3 surg\$).tw. (839)
5	(cryo\$ adj3 therap\$).tw. (745)
6	(freez\$ adj3 therap\$).tw. (35)
7	cold therap\$.tw. (81)
8	exp CRYOTHERAPY/ (1774)
9	exp CRYOSURGERY/ (8305)
10	or/1-9 (11761)
11	(bronch\$ adj2 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma or malignant or obstruct\$)).tw. (15356)
12	(endobronch\$ adj2 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma or malignant or obstruct\$)).tw. (540)
13	(intrabronch\$ adj2 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma or malignant or obstruct\$)).tw. (44)
14	exp Bronchial Neoplasms/ (8636)
15	exp Carcinoma, Bronchogenic/ (6849)
16	or/11-15 (23204)
17	airway obstruction\$.tw. (7468)
18	exp Airway Obstruction/ (13003)
19	(17 or 18) and 16 (966)
20	16 or 19 (23204)
21	10 and 20 (84)
22	limit 21 to human (79)
23	from 22 keep 1-79 (79)