Cryobiology 67 (2013) 225–229

Contents lists available at ScienceDirect

Cryobiology

journal homepage: www.elsevier.com/locate/ycryo

Treatment of central type lung cancer by combined cryotherapy: Experiences of 47 patients ☆

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ARTICLE INFO

Article history:
Received 19 July 2013
Accepted 25 July 2013
Available online 31 July 2013

Keywords:
Central type lung cancer
Percutaneous cryosurgery
Airway stenting
Endobronchial cryosurgery

ABSTRACT

Most patients with central type lung cancer (CTLC) are not candidates for surgery; systemic chemotherapy and external beam radiotherapy are the main treatments but have not greatly affected patient outcome. Combined percutaneous and endobronchial cryotherapy has been used successfully to treat CTLC; this study aimed to determine its feasibility and safety. Forty-seven patients with unresectable CTLC (22 endotracheal, 26 tracheal wall and 21 extratracheal tumors) underwent 69 sessions of combined percutaneous cryosurgery, endobronchial cryosurgery and airway stenting. The long diameter of all tumors was <5 cm. Biopsy showed non-small cell lung cancer (NSCLC) in 40 patients (medium or well differentiated in 20 cases, poorly differentiated in 20) and small cell lung cancer (SCLC) in seven. Within 3 days after treatment, ventilatory capacity and performance status had obviously increased and cough, signs of dyspnea, hemoptysis and atelectasis improved significantly, but symptoms of pneumothorax and pleural effusion emerged. After 2 weeks, all complications had disappeared completely, as had cough. Progression-free survival (PFS) for endotracheal tumors (8 ± 4 months) was shorter than that for tracheal wall (13 ± 6 months, $P < 0.05$) and extratracheal (14 ± 8 months, $P < 0.01$) tumors. The PFS of NSCLC (11 ± 5 months) was significantly longer than that of SCLC (4 ± 2 months, $P < 0.0001$). The PFS of medium or well differentiated CTLC (15 ± 8 months) was significantly longer than that of poorly differentiated CTLC (7 ± 3 months, $P < 0.0001$). In conclusion, combined cryotherapy is a safe and effective treatment for CTLC, with PFS largely influenced by tumor location and pathologic type.

Introduction

Central type lung cancer (CTLC) is defined as lung cancer located in close proximity to the trachea, bronchial tree, major vessels, esophagus or heart. Most patients with CTLC are unsuitable for surgery because of the tumor location, metastatic disease, poor respiratory function or other major organ problems. Approximately 30% of lung cancer patients present with a large carcinoma obstructing the trachea or main bronchi and causing distressing atelectasis, cough, breathlessness, hemoptysis and recurrent infections; such tumors may lead to gradual asphyxiation [1]. It is important to both alleviate these symptoms and improve the survival of patients with CTLC.

Cryosurgery, which induces cell necrosis by alternate freezing and thawing of target tissue, has emerged as a minimally invasive curative technique for lung cancer [18,19,27,29]. For the treatment of CTLC, cryotherapy has many advantages, including good visibility of the ice ball on computed tomography (CT), complete necrosis of the area covered by the ice ball [9,17,24], less damage to collagen rich structures (e.g. large vessels and airways) [11,14], avoidance of damage to the inferior vena cava [2,25], less postoperative pain, and low morbidity and mortality [14,27]. Cryosurgery can be performed under CT guidance using thin needles to puncture extrabronchial tumors and induce tissue necrosis, or can be conducted via an endobronchial approach to clear obstruction of the trachea and bronchus using a flexible bronchoscope [8]. We conducted a retrospective review of 47 patients with CTLC identified from our hospital's database. Patients with extrabronchial tumors underwent percutaneous cryoablation; those with endobronchial tumors underwent endobronchial cryosurgery and airway stenting.

☆ *Statement of funding:* This research was supported by the Cancer Research Fund of Fuda Cancer Hospital, Guangzhou, China.

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http://dx.doi.org/10.1016/j.cryobiol.2013.07.003

Material and methods

Ethics

The study protocol received ethical approval from the Regional Ethics Committee of Guangzhou Fuda Cancer Hospital. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

Patient selection

Between October 2010 and October 2012, 47 patients with CTLC met our inclusion criteria and were enrolled in the study. Surgery, radiation therapy and chemotherapy were deemed unsuitable in any of the following circumstances: patient physically unable to survive pneumonectomy; unresectable tumor (invasion of proximal pulmonary artery, proximal pulmonary vein or chest wall [15]); patient refused to undergo chemoradiation therapy; patient seeking further treatment after failure of previous surgery or chemoradiation therapy; and advanced age. Ideal patients for cryoablation are those with: platelet count $\geqslant 80 \times 10^9$/l; white blood cell count $\geqslant 3 \times 10^9$/l; neutrophil count $\geqslant 2 \times 10^9$/l; hemoglobin $\geqslant 90$ g/l; normal heart function; and absence of level 3 hypertension, severe coronary disease, myelosuppression, brain metastasis, respiratory disease, and acute and chronic infection.

The diagnosis of CTLC in all patients was confirmed by CT and radiography; pathologic type was determined by fine needle aspiration biopsy, hematoxylin and eosin staining and immunohistochemical staining. Intra- and extrapulmonary tumors were distinguished by CT and positron emission tomographic CT. Thirty-one patients had stage IV disease (three metastases in pleura, 15 in contralateral lung, five in liver and 16 in bone) and 18 patients had stage III disease (hilar lymph node metastases in eight, mediastinal lymph node metastases in 10).

Percutaneous cryosurgery

Percutaneous cryosurgery was performed in patients with endotracheal, tracheal wall or extratracheal CTLC. After induction of general anesthesia, a single cryoprobe (1.7 mm in diameter; Endocare, Irvine, CA) was inserted through the rib space into the center of each extratracheal tumor under CT guidance and from the front of the body (Fig. 1A). Cryosurgery was then conducted using an argon gas based cryosurgical unit (Endocare); two freeze/thaw cycles were performed, each reaching a temperature of -180 °C at the tip of the probe. The duration of freezing was dependent on the achievement of an ice ball visible as a low density area on CT; generally, the maximal freezing time was 15 min, with thawing for 5 min. A margin of at least 0.5 cm of normal tissue was frozen circumferentially around extratracheal tumors. In addition to cryoablation of the primary tumor, lymph node and distant metastases were ablated during the same procedure. The tract formed by the cryoprobe was sealed off with fibrin glue immediately after removal of the probe to ensure hemostasis.

Endobronchial cryosurgery

In patients with endotracheal CTLC, endobronchial cryosurgery was performed first to treat the endobronchial part, followed by percutaneous cryosurgery to treat the extrabronchial part. After induction of short acting intravenous general anesthesia, cryosurgery was undertaken using a flexible bronchoscope (2.4 mm) and a Joule–Thomson type probe (Spembly Medical, Andover, UK), with nitrous oxide as the cryogen. A temperature of approximately -70 °C was achieved at the probe tip. The distal tip of the bronchoscope was placed about 5 mm above the lesion and the cryoprobe was inserted through the bronchoscope and applied to the tumor. The tumor was frozen for about 3 min until completely covered by the ice ball. Smaller tumors were pulled out immediately with the probe; for tumors that covered wider areas of the bronchial tree, the above treatment was repeated several times to remove the necrotic tumor material. Biopsy forceps were used to clear any remaining tumor.

After endobronchial cryosurgery, the trachea and bronchus could be seen to be completely clear of obstruction. The patency rate after first cryosurgery was usually more than 60% and reached 100% after two or three sessions. Atelectasis was relieved quickly after airway patency had been achieved (Fig. 1B). Bleeding from the site of biopsy or cryosurgery was contained by local spraying of epinephrine (adrenaline; concentration 1:1000) and thrombase; severe cases were treated by direct pressure with a dry cotton ball or with an argon knife.

Airway stenting

In patients with extratracheal CTLC, airway stenting was considered in those in whom it was impossible to restore more than 50% of the lumen even after airway dilatation or who required repeated airway dilatation. One to three airway stents were used according to the situation of the airway obstruction [22]; Ultraflex tracheobronchial stents (Boston Scientific, Natick, MA), Dynamic (Y) stent systems (Boston Scientific) and AERO stents (Merit Medical Endotek, South Jordan, UT) were used. Ultraflex stents comprise a single strand nitinol alloy and are available in both covered and uncovered models; the AERO tracheobronchial stent is a fully covered hybrid stent (Fig. 1C). Covered stents were generally used for patients with endoluminal disease, whereas uncovered stents were used for patients with airway obstruction due to external compression. Dynamic (Y) stents were used for carinal disease or tracheoesophageal fistula. The diameter of the bronchial stents was 12–14 mm and that of the tracheal stents was 16–20 mm.

Postoperative management

Vital signs after cryosurgery were monitored routinely for 6–24 h along with oxygen uptake and atomization inhalation. The patients were encouraged to cough and expectorate early post-surgery. The effects of treatment and respiratory function were assessed 1 week after the procedure. Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured using a Microlab 3000 turbine spirometer (KeTai Medical Instrument Co. Ltd., Ningbo, China); patients in whom the trachea or bronchus was still blocked were treated again. Karnofsky Performance Status (KPS) and Zubrod/Eastern Cooperative Oncology Group/World Health Organization Performance Status (ZPS) scores were used to evaluate the patients' performance status before and after combined cryotherapy [15].

Evaluation and statistical analysis

Complications were recorded and classified in accordance with the Common Terminology Criteria of Adverse Events v4.0. Radiographic local tumor control was assessed using image-guided tumor ablation criteria [4]. For patients with preoperative obstructive atelectasis, relief of obstruction was checked within 1 week after treatment by chest radiography (Fig. 1D). Follow-up dynamic CT was performed at 1 month intervals. The revised Response Evaluation Criteria in Solid Tumors v1.1 were used to assess the response of thymomas [3]. Three diagnostic radiologists reviewed the CT scans for every case to determine whether

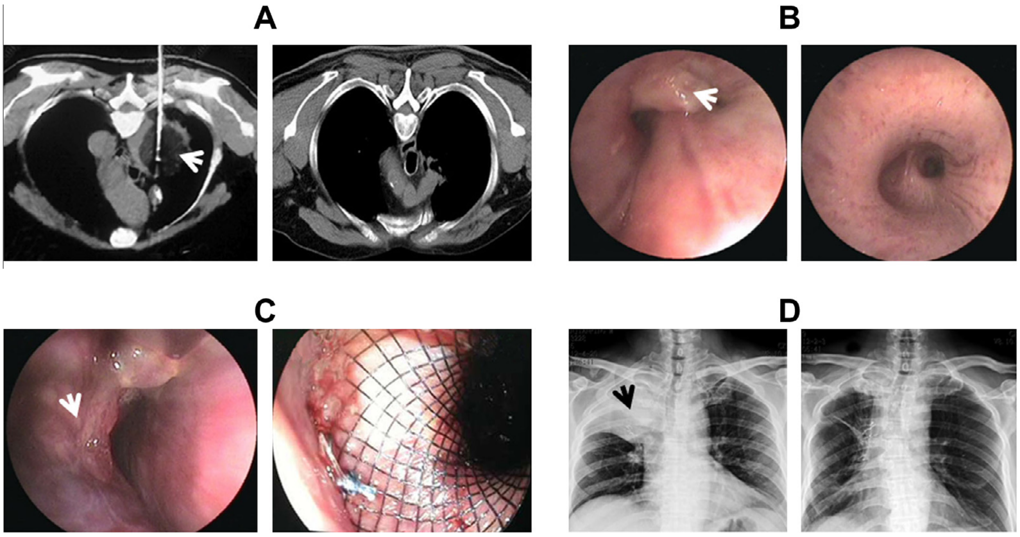

Fig. 1. Combined cryotherapy for central type lung cancer (CTLC). (A) During (left; arrow head shows the cryoprobe and low density cryozone) and 3 months after (right) percutaneous cryoablation, an extratracheal tumor was eliminated under computed tomography guidance. (B) Before (left; arrow head shows the intratracheal tumor) and after (right) endobronchial cryosurgery, an endotracheal tumor was eliminated on bronchoscopy. (C) Before (left; arrow head shows stenosis of the tracheal wall) and after (right) airway stenting, pressure caused by an extratracheal tumor was removed on bronchoscopy. (D) Before (left; arrow head shows atelectasis caused by CTLC) and after (right) combined cryotherapy, segmental atelectasis was removed under radiographic guidance.

progression or recurrence had occurred. A Wilcoxon matched pairs signed rank sum test was performed on the clinical findings to identify any differences between pre- and post-cryosurgery measurements. Progression-free survival (PFS) was calculated from the date of each session of cryosurgery. The effect of tumor location on PFS was examined using Bonferroni's multiple comparison tests; the effect of pathologic type was evaluated using Kaplan–Meier analysis with the log-rank test. Statistically significant differences were indicated by $P < 0.05$. All analyses were conducted using GraphPad software (San Diego, CA).

Results

Clinical data

Informed consent was obtained from all 47 patients for all 69 sessions. Twenty-two patients were from China, 14 from Southeast Asia and 11 from the Middle East. All patients were diagnosed with CTLC in other centers and came to our hospital for cryosurgery. When they were first seen in our hospital, their ages ranged from 31 to 82 years, with a mean age of 57 years. Twenty-two patients had endotracheal pulmonary tumors, 26 had tumors of the tracheal wall and 21 had extratracheal tumors. Seven patients had small cell lung cancer (SCLC) and 40 had non-small cell lung cancer (NSCLC). Twenty-three tumors were adenocarcinomas and 17 were squamous cell carcinomas; 20 tumors were medium or well differentiated and 20 were poorly differentiated. The 47 patients underwent 69 sessions of combined cryotherapy (one for 32 patients, two for 10 patients, three for three patients and four for two patients). All pulmonary tumors were solitary and the long diameter of extratracheal parts was in all cases less than 5 cm.

Perioperative outcomes

All cryosurgical procedures for CTLC were performed successfully, with no treatment related deaths or conversions to chemotherapy. The results of respiratory function tests, performance status scores and symptoms before and 3 days after combined cryotherapy are given in Table 1. After 2 weeks, all complications had disappeared completely, as had cough.

PFS after cryosurgery

In all cases, endotracheal, tracheal wall and extratracheal CTLCs were removed by combined cryosurgery. Recurrence and progression of disease were monitored by CT. Following 69 sessions of cryosurgery, the overall PFS was 11 ± 7 months (95% CI 9–13 months); the PFS for endotracheal tumors ($n = 22$, 8 ± 4 months; Fig. 2A) was shorter than that for tracheal wall ($n = 26$, 13 ± 6 months, $P < 0.05$) and extratracheal ($n = 21$, 14 ± 8 months, $P < 0.01$) tumors. The PFS for NSCLC ($n = 59$, 11 ± 5 months; Fig. 2B) was significantly longer than that for SCLC ($n = 10$, 4 ± 2 months, $P < 0.0001$); the PFSs for adenocarcinoma ($n = 33$, 12 ± 9 months; Fig. 2C) and squamous cell carcinoma ($n = 26$, 11 ± 6 months, $P = 0.7217$) were not statistically different. The PFS of medium or well differentiated CTLC ($n = 32$, 15 ± 8 months; Fig. 2D) was significantly longer than that of poorly differentiated CTLC ($n = 27$, 7 ± 3 months, $P < 0.0001$).

Discussion

The location of CTLC can be classified as endotracheal, tracheal wall or extratracheal. For endotracheal CTLC, many thermal ablation

Table 1
Clinical findings in 47 patients undergoing combined cryotherapy. Measurements were made before and within 3 days after 69 sessions of treatment and analyzed using a Wilcoxon matched pairs signed rank sum test.

	Before cryosurgery (Mean ± SD)	After cryosurgery (Mean ± SD)	*P* value
FEV1 (litres)	1.41 ± 0.58	1.94 ± 0.49	<0.05
FVC (litres)	1.89 ± 0.65	2.25 ± 0.59	<0.05
KPS	50 ± 6	75 ± 7	<0.05
ZPS	3.1 ± 0.8	2.1 ± 0.6	<0.05
	% of all sessions	% of all sessions	
Cough	87.6	64.2	<0.01
Dyspnea	96.3	54.6	<0.001
Haemoptysis	10.2	6.1	<0.05
Chest pain	34.5	32.4	>0.05
Atelectasis	21.4	0	<0.001
Pneumothorax	0	18.2	<0.001
Pleural effusion	10.5	30.3	<0.001

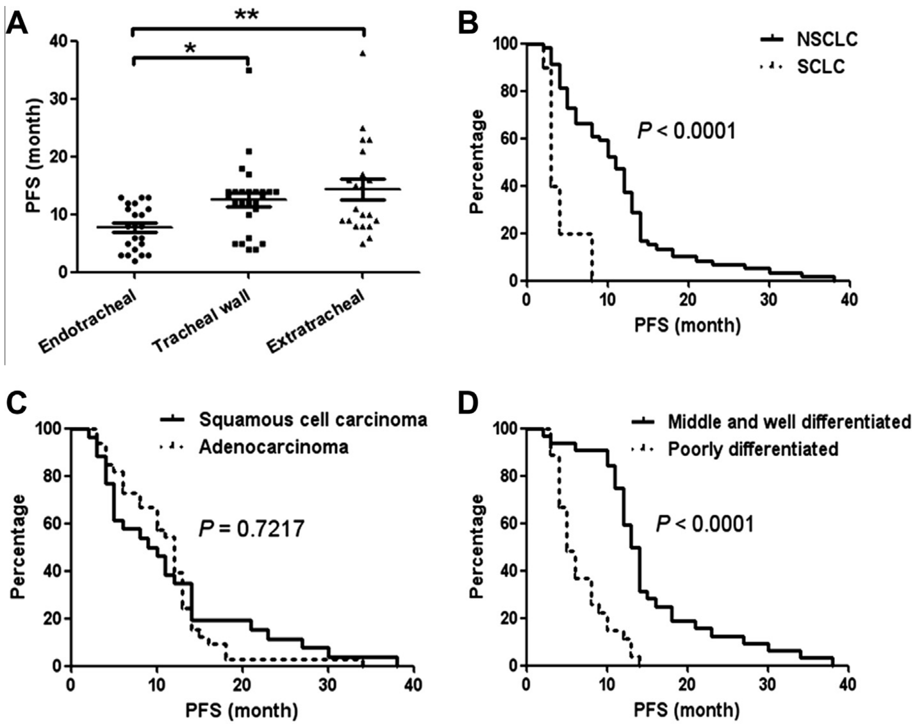

Fig. 2. Effect of tumor characteristics on progression-free survival (PFS). (A) Tumor location. Bonferroni's multiple comparison test was used. Horizontal lines in the scatter dot plot represent the mean and standard deviation; $^{*}P < 0.05$, $^{**}P < 0.01$. (B) NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer. (C) Pathologic type. (D) Degree of differentiation. The log-rank test was used.

approaches have been developed to relieve the distressing breathlessness, cough and obstructive pneumonia and improve respiratory function and performance status, including photodynamic therapy [7,26], brachytherapy [20,21], laser therapy [6], airway stenting [22] and endobronchial cryosurgery [15]. Among patients with extratracheal CTLC, only a minority are candidates for surgery [12,16,30], and chemotherapy and external beam radiation therapy have not greatly affected patient outcomes [5,23]. However, many thermal ablation methods can significantly improve quality of life and prolong survival time, including radiofrequency ablation, microwave ablation and cryoablation [25]. Cryotherapy can be performed simultaneously on extratracheal CTLC and endotracheal tumors. In the present study, endobronchial cryotherapy and airway stenting were used for endobronchial tumors and percutaneous cryosurgery for extratracheal tumors in 47 patients, and lung function, complications and PFS were assessed.

Because most CTLC patients suffer atelectasis, cough, breathlessness, hemoptysis and recurrent infections, and because these tumors may cause gradual asphyxiation and death [1], relief of symptoms and improvement of respiratory function are of great importance in the treatment of CTLC. In the present study, cough, dyspnea, hemoptysis, chest pain, atelectasis, pneumothorax and pleural effusion were the predominant complications after cryosurgery, but with symptomatic treatment all had disappeared completely 2 weeks after the procedure. Within 3 days after treatment, FEV1 and FVC, which were measured to evaluate respiratory function, had markedly increased, and increased KPS and decreased ZPS scores indicated obvious improvement of ventilatory capacity (Table 1) due to relief of obstruction of the trachea or main bronchus. Symptoms of pneumothorax and pleural effusion increased significantly after cryosurgery and may have been related to lung or bronchial injury caused by the procedure.

PFS was used to access the therapeutic effect of cryotherapy. The overall PFS was 11 ± 7 months. Regular chest CT demonstrated recurrence and progression of disease in all patients within 38 months after treatment. This finding shows that cryosurgery cannot completely ablate tumor and has only a palliative effect. Patients with recurrent disease need further cryosurgery to alleviate their symptoms. We also analyzed PFS according to tumor location, pathologic type and differentiation status. The PFS for endotracheal tumors was shorter than that for tracheal wall and extratracheal tumors (Fig. 2A), possibly because endotracheal tumors are more difficult to ablate and minimal residual tumor may be the source of recurrence. Because the growth rate and metastatic ability of SCLC are much greater than those of NSCLC [13,31], it is unsurprising that the PFS for NSCLC ($n = 59$, 11 ± 5 months; Fig. 2B) was significantly longer than that for SCLC ($n = 10$, 4 ± 2 months, $P < 0.0001$). Although the biological characteristics of adenocarcinoma and squamous cell carcinoma are quite different [10], their PFSs ($n = 33$, 12 ± 9 months and $n = 26$, 11 ± 6 months, respectively, $P = 0.7217$; Fig. 2C) were not statistically different. Differentiation status may reflect growth rate and metastatic ability [28], and the PFS of medium and well differentiated CTLC ($n = 32$, 15 ± 8 months; Fig. 2D) was significantly longer than that of poorly differentiated CTLC ($n = 27$, 7 ± 3 months, $P < 0.0001$). Thus, the PFS of CTLC patients treated with cryotherapy was closely related to tumor location, pathologic type and differentiation status. For patients with poorly differentiated SCLC or endotracheal tumors, PFS is relatively short and another therapy such as iodine-125 seeds [18,19] or chemotherapy may be needed to prolong survival.

In conclusion, our results suggest that combined cryotherapy is a relatively safe and feasible treatment modality for CTLCs that are unsuitable for resection. We will continue to monitor our patients for their long term outcome. Given the embryonic nature of cryotherapies and their combination, it is reasonable to expect improved outcomes with additional refinements in technique and randomized controlled trials.

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