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

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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.

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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