Int J Clin Exp Med 2016;9(4):7322-7327
www.ijcem.com /ISSN:1940-5901/IJCEM0014356

Original Article

Therapeutic effect of endotracheal cryotherapy via bronchoscopy combined with permanent implantation of radioactive particles in the treatment of tracheobronchial cancer

Yu Mao, Xiu-Yan Yang, Wei Guo, Liang Li, Ming Li, Ze-Xiang Tian, Jun-Qing Liu, Wen-Hua Zhang

Department of Thoracic Surgery, The First Hospital of Hohhot, Hohhot 010030, Inner Mongolia, China

Received August 11, 2015; Accepted December 3, 2015; Epub April 15, 2016; Published April 30, 2016

Abstract: This study aims to explore the therapeutic effect of endotracheal cryotherapy via bronchoscopy, combined with permanent implantation of radioactive particles, in the treatment of tracheobronchial cancer. In this procedure, a suitable number of radioactive particles were implanted into the basilar part of the tumor. Two weeks later, when tumor necrosis or significantly decreased activity was identified, the tumor blood supply was disrupted with cryotherapy. The remaining necrotic tumor was then resected to reduce bleeding. Patients experienced improved ventilatory function, improving the patients' quality of life. No severe complications were observed in any patients. In the 26 patients treated, a total of 156 seeds were implanted (average of 6 seeds per patient) and cryotherapy was performed 62 times (average of 2.4 times per patient). Postoperative respiratory function improved significantly, with obvious increase in the partial pressure of oxygen in the blood. Tachypnea also declined sharply. The survival time of the patients was prolonged, and their quality of life improved remarkably. Endotracheal cryotherapy via bronchoscopy combined with permanent implantation of radioactive particles for the treatment of central bronchogenic lung cancer has a potential curative effect. It is safe and easy to perform, and is a good palliative method with satisfactory treatment effect.

Keywords: Main bronchial lung cancer, minimal invasion, cryotherapy, radioactive particles

Introduction

Lung cancer has become the malignant tumor with the highest incidence [1]. According to the World Health Organization (WHO), approximately 1.3 million people die of lung cancer worldwide every year, and 85% of patients with lung cancer cannot be treated with surgery when they are admitted to the hospital. Early asymptomatic, while 85 percent of lung cancer patients in the treatment of advanced stage, unresectable. Some 30% of patients develop severe breathing difficulties because of tracheal or bronchial obstruction by the tumor and eventually die of respiratory failure [2-4]. Advanced tracheobronchial cancer often causes stenosis in the central airways, including the trachea, the left and right main bronchi, and the 5 lobar bronchi. Cancerous stricture seriously affects the patient's respiratory function, causing obvious respiratory difficulty and poor quality of life. It is the main cause of non-cancerous death in lung cancer patients. Additionally, patients with advanced tracheobronchial cancerare often in poor physical condition, which can cause them to lose the opportunity for effective treatment [5]. Minimally invasive treatment via the trachea is one of the most effective therapies for airway stenosis or occlusion caused by lung cancer, and this treatment obviously can improve the patient's quality of life. To date, the commonly used methods of minimally invasive treatment have quite limited indications and their effective period is short, resulting in rapid recurrence of intraluminal tumor and reocclusion of the trachea within a short interval.

At the beginning of the 21st century, permanent implantation of radioactive particles under the guidance of fiberoptic bronchoscopy was developed in European countries as a technique for

Table 1. General data of two groups

Index		Group	
		Experimental	Control
n		26	41
Gender	Male	15	29
	Female	11	12
Mean age		61	65
Tachypnea index grade	1	5	6
	2	15	23
	3	4	8
	4	2	4
Stenosis degree (%)	≤30	16	25
	30-60	5	9
	≥60	4	6
	100	1	1
Stenosis site	Left main bronchus	5	7
	Right main bronchus	6	6
	Left upper lobe bronchus	3	7
	Left lower lobe bronchus	2	6
	Right middle bronchus	2	2
	Right upper lobe bronchus	1	9
	Right lower lobe bronchus	7	4
TNM staging	IIIa	6	17
	IIIb	9	13
	IV	11	11
Pathological type	Squamous cell carcinoma	20	29
	Adenocarcinoma	6	11
Mean implanted particle number		6	—
Mean cryotherapy frequency		2.4	—

treating central bronchogenic lung cancer. In 2007, this treatment was carried out in China [6, 7]. Since then, cryotherapy for lung cancer has become more widespread. Radioactive particles can provide continuous tumor cell killing [8] and can achieve therapeutic effects that cannot be achieved by external radiation exposure [9]. Cryotherapy can freeze tumors repeatedly, thereby blocking their blood supply [10, 11]. The tumor can then be removed as quickly as possible, with less bleeding. The patients' ventilatory function can be improved effectively and quickly, thereby improving their quality of life. It may also create highly favorable conditions for additional, more beneficial therapies. However, there are few reports to date regarding this method. From January 2010 to December 2010, internal exposure technology with radioactive particles combined with endotracheal minimally invasive cryotherapy was successfully performed in our department for 26 patients with malignancy in the lumen of the central airways, achieving satisfactory effects. Here we report the results of these procedures.

Materials and methods

Clinical data

Inclusion criteria: 1) Patients had to be pathologically or histologically diagnosed with primary central lung cancer; 2) No curative radical surgery could be possible due to either the patient's tumor node metastasis (TNM) staging or other medical reasons; 3) Radiotherapy or chemotherapy could not be tolerated for medical reasons or had been rejected by the patient; 4) There had to be no contraindication for examination by bronchofiberscope; 5) Patients had to have a life expectancy of more than 3 months; 6) The distal lung tissue had to have relatively normal lung function; 7) Obstructive pneumonia and pulmonary function had to be expected to improve significantly after the removal of the central bronchial obstruction; 8) The life expectancy must have been anticipated to be prolonged by more than 6 months after treatment.

This study enrolled 26 patients (experimental group) with central bronchial lung cancer who received endotracheal minimally invasive cryotherapy combined with permanent implantation of radioactive particles in the First Hospital of Hohhot (Inner Mongolia, China). The patients ranged in age from 48 to 74 years (mean 61 years). The main clinical symptoms observed included dyspnea, cough, hemoptysis, and expectoration. The tachypnea index used for our study was: grade 0, no breathlessness when climbing stairs; grade 1, breathlessness when climbing stairs; grade 2, breathlessness when walking horizontally; grade 3, breathlessness when moving; grade 4, breathlessness when lying quietly in bed. Enhanced computed

Table 2. Comparison of survival time

Group	Cases	Survival time (months)
Control group	41	3.42±1.26
Experimental group	26	8.84±2.17

tomography (CT) examination showed occlusion or stenosis of a central airway, accompanied by atelectasis or obstructive pneumonia. A total of 156 ^{125}I radioactive particles were implanted into the 26 patients, with 4-9 particles (mean 6 particles) per patient. Cryotherapy was performed 62 times in total, with a mean of 2.4 treatments per patient. Approximately 3 months after the procedure, all patients received chemotherapy. A total of 41 patients (51-79 years old, mean 65 years) with advanced non-small cell lung cancer (NSCLC) receiving standard chemotherapy in the same hospital during the same period were recruited as a control group. The age, sex, and TNM staging of the groups were similar. The general characteristics of both the groups are shown in **Table 1**. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the First Hospital of Hohhot. Written informed consent was obtained from all participants.

Treatment

After calculating the radioactive particle number, parts, and the angle of implantation under the guidance of the treatment planning system, a bronchofiberscope (Olympus, Japan) was pushed into the airway until it reached the lesion. Then the particle-implanting apparatus was inserted into the basal avascular area of the lesion from the distal partof bronchofiberscope, and the ^{125}I radioactive particles (Atomic Hi-tech Co., Ltd, China) were implanted following the indication of the planning system, with a distribution interval of 0.5 cm to 1 cm [12]. Two weeks later, CT scan and bronchofiberscope examination were repeated for each patient. When tumor necrosis or significantly decreased vascular activity was identified, the residual tumor tissue was frozen repeatedly using a cryotherapy knife (Beijing Kooland Science and Technology Co., LTD, China) to block its blood supply. Subsequently, the tumor tissue was removed as soon as possible.

Statistical analysis

The physiological and psychological changes in quality of life were comprehensively evaluated using survival time analysis, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORQLQ-LC I3, Chinese version) and the evaluation of total quality of life, in order to evaluate the treatment effect.

The data were analyzed using SPSS 16.0 software. The independent sample *t*-test was used to analyze differences in the survival time, preoperative total quality of life, and scores of EORQLQ-LC I3 between the experimental group and the control group.

Results

Treatment outcomes

The procedures were completed without difficulty, and no serious complications were observed. There were 23 cases with bleeding from a few ml to 10 ml, all of which could be stopped by sprinkling adrenaline locally. One patient expectorated a ^{125}I radioactive particle the day after the procedure. After the procedure, all patients demonstrated significant improvement in their clinical symptoms, especially in breathlessness, which was relieved to different degrees. Two weeks after the procedure, there were 5 cases with a tachypnea index of grade 0, 14 cases of grade 1, 6 cases of grade 2, and 1 case of grade 3. The enhanced CT reexamination revealed that the strengthen of the lesion reduced slightly 1 week after the operation, and the position of the ^{125}I particle had not changed compared to their position before cryotherapy. One month later, 24 patients had enlarged tracheal lumens compared with the original obstruction, 21 had improvement from their obstructive pneumonia and atelectasis, and 13 had near-relief of symptoms. Three months after the procedure, the ^{125}I particles began to gather, but in 7 of the patients, the tumors had grown. Biopsy obtained through fiberoptic bronchoscopy revealed significant necrosis in the tumor, which was then frozen and removed again. By 6 months after the operation, the ^{125}I particles had aggregated significantly and necrotic tumor tissues were found in 2 patients, who were then able to receive cryotherapy again. By 12 months after the initial procedure, the ^{125}I particles had aggregated further and more significantly.

Table 3. Comparison of overall survival quality evaluation and Lung-cancer-specific quality of life questionnaire of European Organization for Research and Treatment of Cancer (EORQLQ-LCI3)

Group	Cases	EORQLQ-LCI3	Physiological function status	Doctor and disease	Emotional, social and family status	Overall survival quality
Control group						
Bbefore treatment	41	17.63±2.77	15.35±2.42	17.76±2.86	23.72±3.76	101.25±6.58
After treatment	41	16.13±3.58	11.98±2.78	15.59±2.24	21.86±2.89	94.36±5.78
Experimental group						
Before treatment	26	18.19±3.12	14.29±2.78	17.19±3.21	22.69±3.26	99.48±5.35
After treatment	26	23.79±4.16	17.59±2.98	25.56±3.76	48.54±3.64	128.56±5.75

At 3 months after the procedure, (Vinorelbine+ cisplatin) or (gemcitabine+ cisplatin) chemotherapy was administered to all patients according to their recovery. After chemotherapy, the patients' symptoms improved markedly and their quality of life improved. With a follow-up time of 3 months to 12 months, 3 patients had died of multiple organ failure, while all other patients remained alive.

Evaluation of the therapeutic effect

The survival time in the experimental group was significantly better than that of the control group (t=3.976, $P<0.05$) (**Table 2**), whereas no statistical difference was found in the total quality of life and EORQLQ-LC I3 between the groups (t=0.412 and 1.119, respectively; $P>0.05$), indicating that the main factors between the groups were balanced and comparable. The total quality of life and scores of EORQLQ-LC I3 before and after the treatment were compared using a paired t-test. The EORQLQ-LC I3 scores improved remarkably in both the groups (t=4.151 and 25,862, respectively; $P<0.05$) (**Table 3**).

Discussion

Endotracheal minimally invasive treatment is one of the most effective ways to treat lung cancer-caused airway stenosis or occlusion. It can dramatically improve the patient's quality of life. Advanced central lung cancer often causes stenosis in the central airways, including the trachea, the left and right main bronchi, and the 5 lobar bronchi. Cancerous stenosis seriously affects respiratory function in these patients, causing obvious difficulty in breathing and poor quality of life. Owing to poor physical conditions, patients may lose the opportunity for effective treatment. There are now many commonly used minimally invasive methods, such as high-frequency electric knife, cryotherapy, microwave, and laser. However, these treatment methods have quite limited indications and their effective period is short, leading to rapid recurrence and short time intervals to reobstruction of the lumen.

Cryosurgery is a method to destroy the biological material in cells by freezing. In this method, the water in cells freezes. The cells stop dividing and are dissolved, which causes vascular endothelial necrosis, micro-thrombosis formation, and ischemic injury [13, 14], leading to cell necrosis [15]. This method has obvious advantages, and the depth of tissue damage is easier to control without damaging cartilage. Moreover, it has no high frequency electric effect. Thus, cryotherapy can be used for patients with pacemakers. Release of γ-rays from ^{125}I radioactive particles has an available irradiation range of 17 mm in tumor tissues, with a half-life of 59.6 days. Implantation of ^{125}I radioactive particles into tumor tissues can achieve sustained release of low energy radiation, which can kill tumor cells continually and uninterruptedly, in order to achieve a greater therapeutic effect than can be achieved by external exposure [16].

Implantation of ^{125}I radioactive particles causes vascular occlusion in tumors, leading to tumor cell necrosis and remarkable decreasedactivity [17-19]. However, the desquamation of the necrotic tissues may be induced by cough and other factors [20], subsequently causing unpredictable bleeding. Thus, after the implantation of ^{125}I radioactive particles, if tumor necrosis or significantly decreased activity is identified, the necrotic tissues should be removed rapidly once or several times using a frozen knife. This procedure can not only reduce the probability of bleeding but also get through the trachea as quickly as possible. Effective improvement of ventilatory function can improve patients' quality of life and may allow for additional treatments, such as a sleeve shape forming operation, radiotherapy, and chemotherapy. Thus, implantation of ^{125}I radioactive particles combined with cryotherapy is used as a transitional operation. Cryotherapy can be repeated many times, addressing the problem of cavity tumor recurrence and lumen obstruction whenever these occur.

It is important to note that the implanted particles may be expectorated at any time by a choking cough or following post-radiation necrosis, which may cause radiation pollution. Thus, the patients and their families should be informed of this possibility before surgery.

In summary, the combined application of cryotherapy, internal exposure of radioactive particles and fiberoptic bronchoscopy in the treatment of central bronchogenic lung cancer can achieve a positive therapeutic effect and is easy and safe to perform. Thus it can be used as a palliative treatment and is worthy of being popularized.

Disclosure of conflict of interest

None.

Address correspondence to: Yu Mao, Department of Thoracic Surgery, The First Hospital of Hohhot, No. 150 South Second Ring Road, Hohhot 010030, Inner Mongolia, China. Tel: +86 13847133420; Fax: +86 471 5281234; E-mail: yumaocn@163.com

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