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Combination percutaneous cryotherapy and iodine-125 seed implantation for unresectable malignant thymoma: Experience in 19 patients ☆

Zhikai Zhang [a,1], Binghui Wu [a,c,1], Lizhi Niu [a,c,1], Feng Mu [b,c], Jibing Chen [a,b,*], Jialiang Li [a,b,*], Jiansheng Zuo [a,c], Kecheng Xu [a,c]

[a] Fuda Cancer Hospital, Jinan University School of Medicine, No. 2 Tangdexi Road, Tianhe District, Guangzhou 510665, China
[b] Fuda Institute of Lung Cancer, No. 2 Tangdexi Road, Tianhe District, Guangzhou 510665, China
[c] Fuda Institute of Cryosurgery for Cancer, No. 2 Tangdexi Road, Tianhe District, Guangzhou 510665, China

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ABSTRACT

Thymomas are the most common tumors of the mediastinum. These tumors often compress vital mediastinal organs and severely impact the quality of life of thymoma patients. To avoid the side effects of chemoradiotherapy, some patients with unresectable malignant thymomas have opted to undergo cryotherapy in our hospital. We reviewed the cryosurgery, nursing and follow-up records of our hospital for the past 8 years, and evaluated the safety and efficiency of cryotherapy in 19 patients with unresectable malignant thymomas. No severe complications involving the vital organs surrounding the tumor occurred during or after cryosurgery. The most common side effect was pleural effusion, which occurred in 11 patients and healed after drainage within 1 week. Cough, mediastinal and pericardial effusions, pneumothorax, mild fever and chest tightness also occurred and resolved 1 week after symptomatic treatment. Since our patients had high KPS scores and mild myasthenia gravis symptoms before the treatment, myasthenia gravis did not occur after the treatment. The progression-free survival of the patients was 14–29 months (median, 18 months), and did not differ between patients with large tumors and those with small tumors ($P = 0.6753$). In conclusion, cryotherapy is a safe and efficient method for the treatment of unresectable malignant thymoma.

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Introduction

Thymomas are the most common tumors of the mediastinum; they originate from the epithelial parts of the thymus and account for 0.2–1.5% of all malignancies [10]. In patients with thymoma, complete surgical resection with or without radiation therapy is the gold standard treatment for both early – [15,23] and late-stage [9] disease, with a 5-year survival rate of 60% for benign thymoma and 20% for malignant thymoma. Even if a complete resection cannot be achieved, the prognosis of patients with partially resected thymoma is still significantly better than that of unoperated patients [15]. To ablate the tumor in situ, several tumor-ablation techniques have been applied in the clinical treatment of solid tumors, such as radiofrequency ablation, microwave ablation and cryoablation. Of these, cryoablation has some advantages such as good visibility of the ice ball under computed tomography (CT) scanning and close approximation between the ice ball coverage area and the complete necrosis area [18,28]. To preserve the collagenous architecture [19] and the integrity of the large vessels and airways [22], percutaneous cryoablation has been widely used in the palliative treatment of several common cancers and for the simultaneous ablation of primary and metastatic lesions [3,4,26]. In 2012, a case report showed that percutaneous cryoablation may be used as a component of a multimodality treatment for the palliative control of locally advanced, treatment-refractory mediastinal tumors [33]. In this study, we retrospectively reviewed the records of 19 patients who underwent combination percutaneous cryoablation and iodine-125 seed therapy for thymoma in our hospital and were followed up for 8 years. The treatment efficacy and safety were analyzed.

Materials and methods

Ethics

The study protocol was approved by the regional ethics committee of Guangzhou Fuda Cancer Hospital. Written informed

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* Corresponding authors at: Fuda Institute of Lung Cancer, No. 2 Tangdexi Road, Tianhe District, Guangzhou 510665, China. Fax: +86 020 38993994.
E-mail address: fudaclab@gmail.com (J. Chen).

[1] These authors contributed equally to this work.

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consent was obtained from each participant in accordance with the Declaration of Helsinki.

Patient selection

Between March 2004 and January 2012, 45 patients with malignant thymoma were treated in our hospital and only 19 patients met our inclusion criteria and were enrolled in this study. Surgery, radiation and chemotherapy were deemed unsuitable in case of any of the following conditions: multifocal disease, unresectable thymoma, refusal to undergo radiation and chemotherapy, seeking of further treatment after failure of a previous treatment and advanced age. Ideal patients for thymus cryoablation were those with a Karnofsky performance status (KPS) score $\geqslant 70$; no obvious signs of myasthenia gravis (MG); platelet count, $\geqslant 80 \times 109/l$; white blood cell count, $\geqslant 3 \times 109/l$; neutrophil count, $\geqslant 2 \times 109/l$; hemoglobin level, $\geqslant 90$ g/l; prothrombin time international normalized ratio, $\geqslant 1.5$; absence of level 3 hypertension, severe coronary disease, myelosuppression, respiratory disease and acute and chronic infection; and normal heart and lung function.

In all 19 patients, malignant thymoma was diagnosed by radiological imaging and fine-needle aspiration biopsy. Enhanced CT and positron-emission tomography-CT can often distinguish thymomas from benign mediastinal lesions or lymphomas in patients with multiple mediastinal abnormalities [21]. In all, 13 patients were in stage I, and 6 patients were in stages II (3 patients), III (1 patient, with neck lymph node metastasis) or IV (2 patients, with clavicle, chest and liver metastases). Nine patients had mild symptoms of MG, and all of these patients were in stage I. There were a total of 24 masses in the patients, and all patients received their final treatments in our hospital within 8 years of follow-up.

Cryoablation procedure

Percutaneous cryotherapy was performed in all patients, and obvious intra- and extrathymic masses were completely cryoablated. Cryosurgeries were performed using an argon gas-based cryosurgical unit (Endocare, Irvine, CA) and cryoprobes with a diameter of 3 mm (Endocare). Two to eight cryoprobes were inserted into the mass via the intercostal space under CT guidance. Two freeze/thaw cycles were performed, and in each cycle, the temperature at the tip of the probe reached −180 °C. The freezing time depended on the achievement of an "ice ball," visible as a low-density area on CT images. Generally, the tumor was frozen for a maximum of 15 min and thawed for 5 min, and this cycle was repeated. A circumferential margin of at least 0.5 cm of normal tissue was frozen around the thymoma. For masses with a diameter of 5–9 cm, three or four cryoprobes were used to ensure freezing of the entire tumor; for masses with a diameter >9 cm, five to eight cryoprobes were required to ensure adequate cryolesions (Fig. 1). In addition to the primary tumor, lymph node or distant metastases were also ablated in the same operation. To avoid injuries to the trachea, thoracic aorta, nervus vagus, esophagus and myocardium (later referred to as "high-risk regions"), care was taken to avoid creating ice balls that reached these organs. Instead of cryoablation, we preferentially implanted iodine-125 seeds (Syncor Pharmaceuticals, Shanghai, China) in these regions (using a percutaneous transhepatic cholangiography [PTC] needle and a 3D treatment-planning system; usually <20 seeds) to control tumor growth. The cryoablation tract was sealed off with fibrin glue immediately after the removal of the cryoprobe to ensure hemostasis.

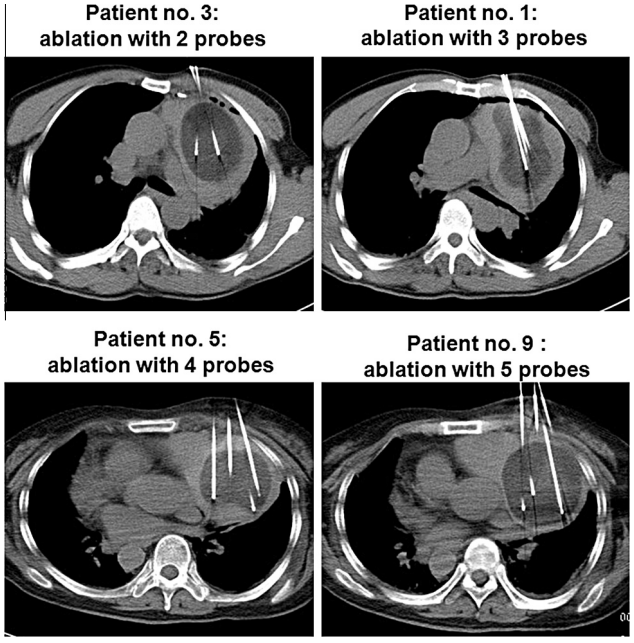

Fig. 1. Computed tomography images of four patients who underwent cryosurgery for thymoma. The white lines in the pictures are cryoprobes; the dark areas around the cryoprobes are the location of the thymoma and the ice ball.

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 [13]. Thoracic ultrasonography was performed both 1 day and 1 week after the minimally invasive treatment of primary and metastatic tumors. Follow-up dynamic CT was performed at 1 month and then at 3–4 month intervals. The revised Response Evaluation Criteria in Solid Tumors v1.1 were used to assess the response of the thymomas [7]. Three diagnostic radiologists reviewed the CT scans of every patient to determine whether progression or recurrence had occurred. The serum levels of anti-acetylcholine receptor (anti-AChR) antibodies and anti-muscle-specific tyrosine kinase (anti-MuSK) antibodies were determined to confirm the diagnosis of MG, especially if the clinical symptoms were atypical [2,25]. Progression-free survival (PFS) was calculated from the date after the cryosurgery and compared using Kaplan–Meier analysis with the log-rank test. Statistical differences were indicated by $P < 0.05$. All analyses were conducted using the GraphPad software (San Diego, CA).

Results

Clinical data

In total, 7 men and 12 women underwent cryoablation of malignant thymomas. Their ages ranged from 23 to 71 years, with a mean age of 53 years. Seven patients were diagnosed with MG after the measurement of their anti-AchR and anti-MuSK levels. Informed consent was obtained from all patients (Table 1). Twelve patients were from China, and seven patients were from Southeast Asia. All patients had been diagnosed with unresectable malignant thymoma in other centers, and they came to our hospital for cryosurgery. The thymomas were situated in the anterior compartment of the mediastinum in 14 patients, in the frontal and upper mediastinum in 3 patients and in the upper mediastinum in 2 patients.

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Table 1
Detailed data of all patients who underwent combination therapy.

No.	First admission date	Cancer stage	Gender/ age	Thymoma size on CT	MG-associated antibodies	Cryosurgery protocol	Ice ball size on CT (iodine seeds)	Progression-free survival (mo)	Adverse effects
1	3/1/2004	IV	F/38	5 × 4 cm	–	3 cryoprobes; freeze 15 min × 2 cycles	5 × 4 cm (0)	19	–
2	11/1//2004	I	F/53	3 × 2.2 cm	+	2 cryoprobes; freeze 10 min × 2 cycles	2.8 × 2.2 cm (6)	29	Mediastinum effusion
3	4/16/2005	III	F/64	4 × 3 cm	–	2 cryoprobes; freeze 10 min × 2 cycles	4 × 3 cm (0)	18	Slight fever, Pleural effusion (left)
4	7/25/2008	II	M/57	9 × 6 cm	–	4 cryoprobes; freeze 15 min × 2 cycles	8 × 6 cm (10)	14	–
5	10/1/2008	I	F/41	6 × 5.2 cm	+	4 cryoprobes; freeze 10 min × 2 cycles	6 × 4.5 cm (6)	21	Cough, Pleural effusion (left)
6	8/9/2008	I	F/51	6.5 × 4 cm	–	4 cryoprobes; freeze 10 min × 2 cycles	6 × 4 cm (4)	18	–
7	7/14/2009	I	F/45	8 × 5 cm	–	4 cryoprobes; freeze 15 min × 2 cycles	7.5 × 5 cm (6)	23	Cough, Pleural effusion (right)
8	10/3/2009	I	M/62	3 × 2 cm	+	2 cryoprobes; freeze 10 min × 2 cycles	3 × 2 cm (0)	15	Pleural effusion (bilateral)
9	1/4/2010	I	F/59	10 × 7 cm	–	5 cryoprobes; freeze 15 min × 2 cycles	8 × 7 cm (12)	22	Pleural effusion (bilateral), Pericardial effusion
10	1/25/2010	IV	M/54	3.2 × 1.8 cm	–	2 cryoprobes; freeze 10 min × 2 cycles	3 × 1.8 cm (6)	15	Cough
11	2/29/2010	I	M/55	9.4 × 8 cm	–	5 cryoprobes; freeze 15 min × 2 cycles	9 × 8 cm (4)	21	Pleural effusion (left)
12	4/23/2010	I	F/60	4.5 × 4.1 cm	+	2 cryoprobes; freeze 10 min × 2 cycles	4 × 4 cm (8)	24	Pleural effusion (left)
13	5/20/2010	I	F/58	10 × 6.6 cm	–	6 cryoprobes; freeze 15 min × 2 cycles	10 × 6.6 cm (0)	17	Pleural effusion (right), Pneumothorax
14	5/27/2010	IV	M/57	6.5 × 5.2 cm	–	4 cryoprobes; freeze 15 min × 2 cycles	6.5 × 5.2 cm (0)	16	Pleural effusion (left)
15	6/14/2010	I	F/71	5.4 × 4.3 cm	+	4 cryoprobes; freeze 10 min × 2 cycles	5 × 4 cm (6)	18	Cough
16	10/25/ 2010	I	F/67	5 × 4.4 cm	–	4 cryoprobes; freeze 10 min × 2 cycles	5 × 4 cm (4)	16	Chest tightness
17	11/6/2010	II	F/59	5.8 × 5 cm	–	4 cryoprobes; freeze 10 min × 2 cycles	5 × 5 cm (6)	20	Pleural effusion (left)
18	12/26/ 2011	I	M/23	10.1 × 7.6 cm	+	6 cryoprobes; freeze 15 min × 2 cycles	8.5 × 7.6 cm (15)	17	Pneumothorax
19	1/13/2012	I	M/37	12.6 × 12 cm	+	8 cryoprobes; freeze 15 min × 2 cycles	10.4 × 9 cm (18)	14	Pleural effusion (right)

CT, computed tomography; MG, myasthenia gravis.

Thirteen of the 19 patients have received implanted iodine-25 seeds around the cryozone, ranging from 4–18 seeds.

Perioperative outcomes

All percutaneous cryoablations of primary and metastatic malignant thymomas were performed successfully. No severe complications, such as heart injury (detected by heart rate, and systolic and diastolic arterial pressure throughout cryosurgery; Supplemental Table 1) and injury to the surrounding important organs and nerves, occurred during or after cryosurgery. Many minor side effects occurred after cryoablation and were resolved with or without symptomatic treatment. Moderate pleural effusion was found in 11 patients (left pleura, 6 patients; right pleura, 3 patients; bilateral effusion, 2 patients) and healed within 1 week after closed drainage of the pleural cavity. Four patients developed coughing and recovered within 2 weeks. Mediastinal and pericardial effusion and pneumothorax occurred in one patient and each disappeared 1 week after drainage. One patient developed a slight fever and one developed chest tightness, which resolved spontaneously in 3 days. Although the frozen tumor swells shortly after cryoablation, the patients did not complain of any additional discomfort after the treatment. No other side effects were found in these patients.

PFS of patients after cryosurgery

In our therapeutic protocol for unresectable thymoma, tumor parts located in low-risk regions were cryoablated and tumor parts in high-risk regions were treated with iodine-125 seed implantation. This treatment reduced the main body of the lesions considerably (Fig. 2). We next determined the efficacy of tumor ablation and the duration of tumor growth control. The PFS of the 19 study patients was 14–29 months (median survival, 18 months). In patients with tumors whose major diameters were 3–7.9 and 8–11 cm, the median PFS was 18 and 17 months, respectively; there was no significant difference between these two groups ($P = 0.6753$, log-rank test; Fig. 3). Since our patients had high KPS scores and mild MG symptoms before the treatment, MG did not occur after the treatment, and MG-related antibodies have not been continually attended. Patients in whom progression of malignant thymoma was detected on thoracic CT underwent repeat cryotherapy, and the PFS for second cryosurgery is to be further studied.

Discussion

Complete surgical resection is the mainstay of the treatment of thymoma; however, numerous thymoma patients have unresectable tumors. In 2012, Spaggiari et al. reported that patients with

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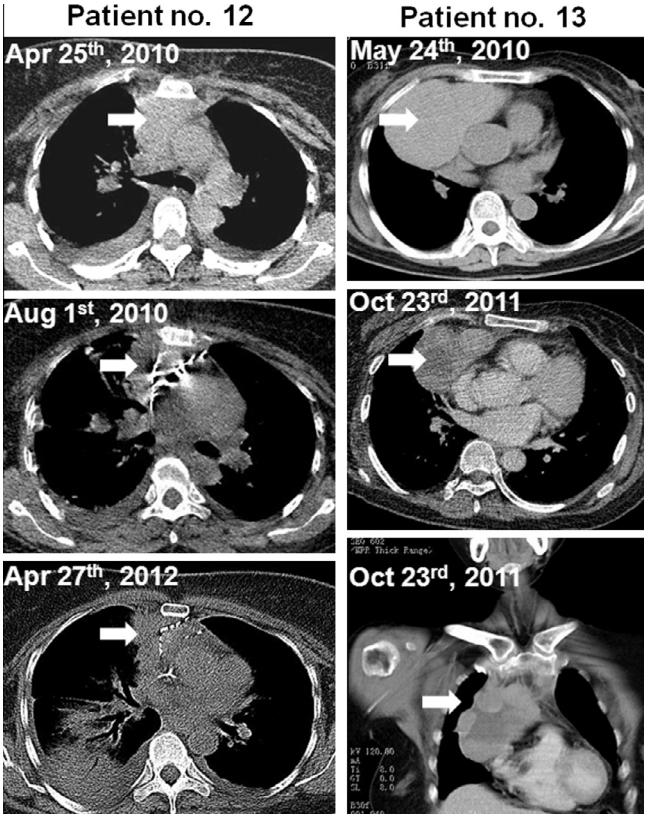

Fig. 2. Complete, durable responses in two thymoma patients who underwent cryosurgery. The white arrows indicate the thymoma. The figures on the left are enhanced computed tomography (CT) images of patient no. 12 before and 24 months after cryosurgery and iodine-125 seed implantation. The figures on the right are enhanced CT images of patient no. 13 before and 17 months after cryosurgery.

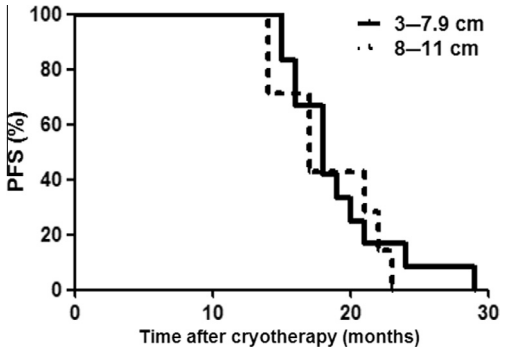

Fig. 3. Progression-free survival (PFS) of patients grouped according to thymoma size. The patients were divided into two groups based on the major diameter of the tumor, i.e., <8 cm and ⩾8 cm. The PFS did not differ between the two groups ($P = 0.6753$, log-rank test).

poor general status and intolerance to thoracic surgery; extensive adhesions of the lungs, thoracic aorta, nervus vagus, esophagus and myocardium; or massive tumors are considered to be unfit for surgical resection [29]. In such patients, adjuvant radiation therapy may be used preoperatively to achieve operability [1,20] and postoperatively after incomplete resection [11]. However, the side effects of radiation (short-term sequelae: pneumonitis, pericarditis; long-term sequelae: coronary stenoses) need to be kept in mind at the time of therapeutic decision making [17]. Chemotherapy can also be recommended for patients with unresectable recurrent disease or disseminated metastasis [12]. Currently, tumor-ablation techniques such as cryoablation can be used to induce tissue necrosis within the tumor; these techniques play a role similar to that of surgical resection. Yamauchi et al. [33] reported that percutaneous cryoablation may be a treatment option for the palliative control of locally advanced, treatment-refractory mediastinal tumors.

In this study, we performed percutaneous cryoablation of unresectable malignant thymomas in 19 patients; we also percutaneously implanted iodine-125 seeds in the vicinity of the ice ball to ensure tumor cell death and reduce recurrence. Because ice ball formation can be monitored in real time, no severe complications, such as injury to the heart, esophagus or lung, occurred during or after cryosurgery. Moderate pleural, mediastinal and pericardial effusions and pneumothorax were observed and treated with drainage. Although tumor reduction only occurred sometime after the cryoablation, all patients could withstand the tumor edema that occurred soon after the cryosurgeries and gradually eased over the next few months. In our experience, percutaneous cryoablation is a relatively safe technique for the treatment of unresectable malignant thymoma.

PFS is a key indicator of the curative effect of thymoma treatments, and tumor size (⩾8 cm) has generally been considered an independent predictor of thymoma recurrence [27,31]. We divided the 19 study patients into two groups based on the major diameter of the tumor (<8 cm or ⩾8 cm), and statistically analyzed the PFS of the patients in both groups. No significant difference in PFS was found between the two groups, and in both groups, recurrence first occurred 14 months after the treatment. Recurrent thymoma can be treated by repeated surgical resection [5], and total resection can be achieved in 62% of all reoperated patients [6]. We, therefore, successfully repeated cryoablation in nearly all the 19 patients after they developed tumor recurrence. However, the clinical value of this treatment strategy needs to be investigated further. It is generally acknowledged that postoperative radiation plays a role in the treatment of patients with incomplete resections and has been used in selected patients following complete resection of recurrent thymoma [30]. During cryotherapy, the auxiliary application of iodine-125 seeds can facilitate the control of tumors in high-risk regions; however, recurrence may occur with a decrease in the radiation levels of the implanted seeds. Looking from the long-term effects, our combined therapy has some advantages comparing with surgery and chemoradiation: ablation method is simple, rate of reoperating can reach to 100% after tumor recurrence; by local implantation of iodine-125 seeds, and the PFS is persistent and stable, with far less side effects than the chemoradiation.

Besides histology and tumor cell type, other factors that influenced patient survival included the tumor stage (TNM [32] or Masaoka-Koga classification [14]) and the presence of symptoms such as MG symptoms as a warning sign at an early stage [24]. Thymomas associated with MG tended to be less aggressive, as they were diagnosed at an earlier stage and had lower recurrence rates [8,16]. Consequently, MG can be regarded as a positive prognostic factor for thymomas and has been associated with one-fourth of thymomas [15]. In our study, none of the patients had severe paralysis of the limbs and respiratory muscles. The reasons underlying this phenomenon need to be researched, but we should not release focusing on the associated symptoms; if obvious muscle weakness is present, effective drug therapy should be administered to ease breathing difficulties, and thymoma removal should only be considered thereafter.

In conclusion, combination percutaneous cryotherapy and iodine-125 seed implantation may be an alternative multimodality treatment for unresectable malignant thymoma. The impact of this therapy in a greater number of patients, the long-term survival of patients following this therapy and the role of combination with other therapies await further research.

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Disclosure

The author declares no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cryobiol.2013.06.008.

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