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Cryotherapy for local recurrent dermatofibrosarcoma protuberans: Experience in 19 patients ☆

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ABSTRACT

Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive, cutaneous, malignant tumor characterized by a high propensity for local relapse. Wide and deep local excision with reconstructive surgery is the current standard therapy for DFSP, with a local recurrence rate (LRR) of nearly 40%. In this study, we cured 19 patients with local recurrence of DFSP with 39 sessions of percutaneous cryoablation performed between July 2004 and August 2008. The LRRs after one, two and three cryosurgery sessions per patient were 68%, 54% and 0%, respectively. Moreover, the LRR did not differ with tumor location or size. Furthermore, all patients had a progression-free survival of >5 years. Only minor complications such as fever, local edema, mild nerve injury and local pain occurred, and were resolved within 1 week with symptomatic treatment. In our experience, percutaneous cryoablation is a relatively safe and efficient technique for the treatment of local recurrence of DFSPs.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive, cutaneous, malignant tumor characterized by a high propensity for local relapse and low metastatic potential [1]. Although DFSP accounts for less than 0.1% of all malignant neoplasms, it represents the most frequent skin sarcoma (nearly 1% of all soft-tissue sarcomas), more than 1% of all head and neck malignancies and 7% of all head and neck sarcomas [25]. Approximately 85–90% of all DFSPs are low-grade tumors. The remaining 10–15% contains a component of high-grade fibrosarcoma [1]. Surgical excision with meticulous pathological evaluation of the tumor margins is the standard treatment for DFSP and is associated with a local recurrence rate (LRR) as low as 1% [4]. Apart from incomplete excision, which leads to local recurrence, there are other challenges in the surgical treatment of DFSP, including preservation of healthy tissue and excision of the characteristic villous extensions into subcutaneous fat, fascia and muscles [1]. However, surgical treatment is indicated even if complete resection cannot be achieved, as the prognosis of patients with partially resected DFSP is still significantly better than that of unoperated patients [9]. For in situ ablation of the remaining tumor, several techniques that are used in the clinical treatment of solid tumors can be applied, such as radiofrequency ablation, microwave ablation and cryoablation. Of these, cryoablation has some advantages such as good visibility of the ice ball, close approximation between the area covered by the ice ball and the area of complete necrosis [10,17], relatively little pain [26], good wound healing [6,20] and possible anti-tumor immune response leading to control of local recurrence [5,6].

Patients with local recurrence of DFSP who refuse surgery have extremely limited treatment options. To determine whether cryotherapy is a therapeutic alternative in such patients, we retrospectively reviewed 19 patients with local recurrence of DFSP, which was treated by cryoablation with an argon–helium cryosurgical system. The safety and efficiency of cryotherapy for local recurrence of DFSP are discussed in detail.

Patients and methods

Ethics

The study protocol was approved by the regional ethics committee of Guangzhou Fuda Cancer Hospital. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

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Patient selection

This study involved 19 patients with local recurrence of DFSP (without fibrosarcomatous areas), which was diagnosed using pathological examination and computed tomography (CT) between July 2004 and August 2008. After the diagnosis of DFSP, the patients visited our hospital to undergo cryosurgery. In all patients, local recurrence had occurred after surgical treatment. Seven patients (37%) had symptoms of pain and tenderness; none of the other patients had any symptoms. All patients refused surgery and radiotherapy owing to the side effects of skin injury, reconstructive surgery and failure of previous surgery. They all underwent cryotherapy in our hospital. Due to the superficial location of the tumor, conventional evaluation indexes of visceral freezing (e.g., Karnofsky performance status score, blood cell counts, coagulation tests and heart-, lung- and liver- function tests) were not needed before cryosurgery.

Cryoablation procedure

All cryosurgeries were performed under local anesthesia to enable communication with the patient during the procedure. The cryosurgeries were performed using an argon gas-based cryosurgical system and cryoprobes with a diameter of 3 mm (Endocare, Irvine, CA). Three-to-eight cryoprobes were inserted into the mass under CT guidance to ensure freezing of the entire tumor: three or four cryoprobes for masses with a diameter of 5–9 cm and five-to-eight cryoprobes for masses with a diameter >9 cm (Fig. 1). The temperature at the tip of the probe reached −120 °C, and a two freeze/thaw cycle protocol was used for all cryoablations. Generally, the tumor was frozen for a maximum of 15 min and thawed for 5 min, and this cycle was repeated; the actual freezing time for each patient depended on the achievement of an ice ball, which was visible as a low-density area on CT images. A circumferential margin of 3–5 cm of normal tissue was included in the ice ball.

To avoid severe damage to important motor nerves in the head and neck (e.g., the trigeminal, facial and vagus nerves), upper limbs (e.g., median, ulnar, radial and axillary nerves) and lower limbs (e.g., femoral and sciatic nerves), patients were asked to move their limbs when an ice ball was formed close to an important nerve. The freezing process was stopped immediately if the patients complained of mild numbness. In addition, to avoid severe damage to the local skin, the edge of the ice ball was kept away from the epidermis, and warm water (about 37 °C) was continually poured on the skin above the frozen tissue. The cryoablation tract was sealed with fibrin glue immediately after the removal of the cryoprobes to ensure hemostasis.

Evaluation and statistical analysis

In our therapeutic protocol for local recurrence of DFSP, tumors located in the subcutaneous compartment were cryoablated, and care was taken to avoid damaging any large nerves or blood vessels. We also determined the efficiency of tumor ablation and the duration of tumor control (PFS). Local tumor control was assessed using radiographic criteria for image-guided tumor ablation [8]. After the cryosurgeries, patients underwent monthly follow-up examinations, during which particular attention was paid to the inspection and palpation of the scar [12]. DFSP most commonly disseminates hematogenously to the lungs, particularly, if the lesion is advanced or recurrent; therefore, a chest radiograph was

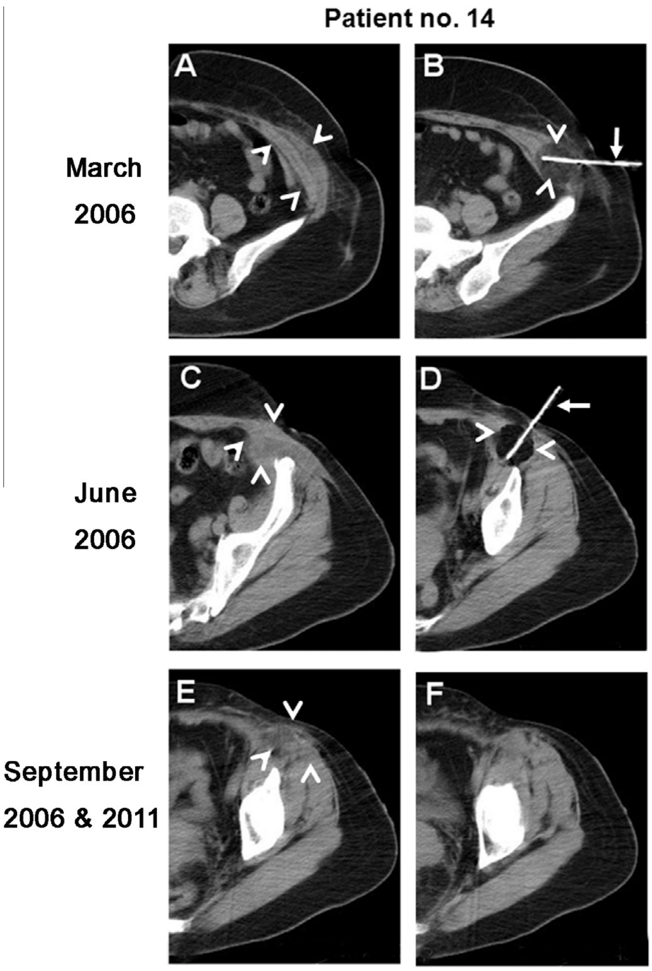

Fig. 1. Computed tomography images of a patient who underwent two sessions of cryosurgery for an abdominal DFSP. The arrowheads show the tumor area. The white line shows the cryoprobe. The dark area around the cryoprobe is the ice ball.

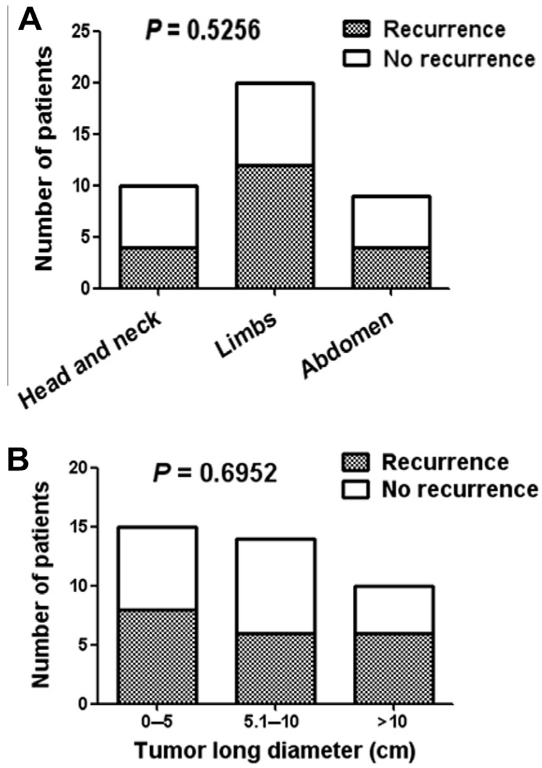

Fig. 2. Local recurrence rate after the 39 cryosurgeries (19 patients) was analyzed according to tumor location (A) and tumor size (B), using the chi square test.

obtained for all patients, and chest CT was performed if the radiographs showed possible pulmonary metastases [12].

Progression-free survival (PFS) was calculated from the day after the cryosurgery to the day on which tumor recurrence was detected. The LRRs after each cryosurgery were analyzed according to tumor location and tumor size by using the chi square test. Side effects after each cryosurgery were classified in accordance with the Common Terminology Criteria of Adverse Events v4.0 and analyzed according to tumor size by using the chi square 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 women and 12 men underwent cryoablation for local recurrence of DFSP. Their ages ranged from 18 to 79 years, with a mean age of 42 years. Imaging data (Fig. 2) were recorded before, during and after tumor ablation. Fourteen patients were from China, and five patients were from Southeast Asia. The DFSPs were situated in the head and neck in six patients, in the limbs in eight patients and in the abdomen in five patients.

All patients underwent cryoablation successfully, and no severe complications (e.g., limb paralysis, massive hemorrhage and obvious scar contracture) occurred. Many minor side effects occurred after cryoablation and were resolved with or without symptomatic treatment (e.g., fever, local edema, mild nerve injury and local pain). Fever occurred after 17 cryosurgery sessions: low fever (37.3–38 °C) was found after five sessions, moderate fever (38, 39 °C) was found for nine sessions and high fever (⩾39 °C) was found for three sessions. It was relieved within 3.8 ± 2.1 days (95% confidence interval [CI]: 2.7–4.8 days). Local edema occurred after 15 sessions, and was relieved within 4.9 ± 1.7 days (95% CI: 4–5.9 days). Nerve injury (mainly manifesting as mild numbness of the limb or face) occurred after six sessions, and was relieved in 6 ± 1.3 days (95% CI: 4.7–7.3 days). Local pain occurred after seven sessions, and was relieved in 4.4 ± 1.7 days (95% CI: 2.8–6 days).

Outcomes after cryosurgery

After 1–3 cryotherapy sessions, the PFS of all the patients was >5 years. The general condition and PFS of all 19 patients (39 cryosurgeries; Table 1) were obtained from the patients' clinical records. No fibrosarcomatous change, distant metastasis or severe complications occurred. The LRR was 68% (13/19; PFS, 9.5 ± 5.3 months) after a single treatment, 54% (7/19; PFS, 5.9 ± 4.2 months) after two treatments and 0% after three treatments. In patients with head and neck tumors, the LRR after 10 cryosurgeries was 40% (four cryosurgeries; PFS, 6.0 ± 5.4 months). In patients with limb tumors, the LRR after 20 cryosurgeries was 60% (12 cryosurgeries; PFS, 9.4 ± 5.5 months). In patients with abdominal wall tumors, the LRR after nine cryosurgeries was 44% (four cryosurgeries; PFS, 6.8 ± 3.9 months). The chi square test revealed no difference in LRR among different tumor locations ($P = 0.5256$, Fig. 2A). The timing of treatment differed among the patients, and tumor sizes varied greatly. The tumors were divided into three groups based on their major diameter on CT scans: 0–5 cm, small tumor group; 5.1–10 cm, medium tumor group; >10 cm, large tumor group. For small tumors, the

Table 1
Detailed data of all patients who underwent cryosurgeries.

No.	Gender/ age	Tumor location	1st cryosurgery			2nd cryosurgery			3rd cryosurgery		
			Tumor size (cm × cm)	PFS	Side effects (duration)	Tumor size (cm × cm)	PFS	Side effects (duration)	Tumor size (cm × cm)	PFS	Side effects (duration)
1	F/18	Head or neck	5.5 × 5.5	3 m	Local edema (4) Nerve injury (7)	6.8 × 5.4	>5 y	Local edema (5) Local pain (2) Moderate fever (3) Nerve injury(6)			
2	M/41	Head or neck	2 × 2	>5 y	Local edema (4) Local pain (6)						
3	F/29	Head or neck	3 × 2.8	>5 y	Local edema (3)						
4	F/44	Lower limb	8 × 6	11 m	Local pain (3)	5 × 4	6 m	Low fever (3) Local edema (5)	5.8 × 2.3	>5 y	Nerve injury (7) Local edema (5)
5	F/18	Lower limb	32.4 × 13.6	9 m	Moderate fever(4)	13 × 10.7	5 m	Low fever (3) Local edema (5)	10.5 × 8.6	>5 y	Local edema (7) Low fever (2)
6	M/27	Lower limb	3.4 × 9	13 m	N/A	3.4 × 2.6	>5 y	Low fever (4) Local edema (7)			
7	M/27	Abdomen	20 × 25	>5 y	Moderate fever (10)						
8	M/48	Abdomen	11.9 × 7.9	9 m	High fever (5)	10 × 6	4 m	Low fever (2)	15 × 8	>5 y	High fever (3)
9	M/53	Head or neck	10 × 10	14 m	N/A	8 × 6	>5 y	N/A			
10	M/70	Upper limb	9 × 15	17 m	Local edema (5) Moderate fever (2)	9 × 6	>5 y	Moderate fever (3) Local edema (7)			
11	M/23	Upper limb	4 × 5	19 m	N/A	4 × 3	15 m	Local edema (2)	4 × 3	>5 y	N/A
12	M/33	Head or neck	5 × 5	>5 y	N/A						
13	M/64	Lower limb	3 × 4	4 m	Local edema (2)	3 × 3	>5 y	N/A			
14	F/58	Abdomen	5 × 8	3 m	Moderate fever (2)	3.2 × 4	>5 y	Local pain (4) Nerve injury (7)			
15	F/46	Lower limb	3 × 4.6	3 m	N/A	3 × 3	5 m	N/A	10 × 7	>5 y	Moderate fever (5)
16	M/48	Head or neck	4.1 × 2.9	4 m	N/A	4.3 × 3.6	3 m	N/A	6.8 × 4.6	>5 y	High fever (7)
17	M/79	Lower limb	10.5 × 4.3	6 m	Local edema (6) Local pain (5)	6 × 5	>5 y	Local edema (7) Local pain (4)			
18	M/24	Abdomen	15.1 × 11.7	11 m	Moderate fever (3) Nerve injury (5)	9 × 11	>5 y	Moderate fever (3)			
19	F/42	Abdomen	8.2 × 6	>5 y	Local pain (7) Nerve injury (4)						

Note: m, month; y, year; N/A, not applicable; PFS, progression-free survival.

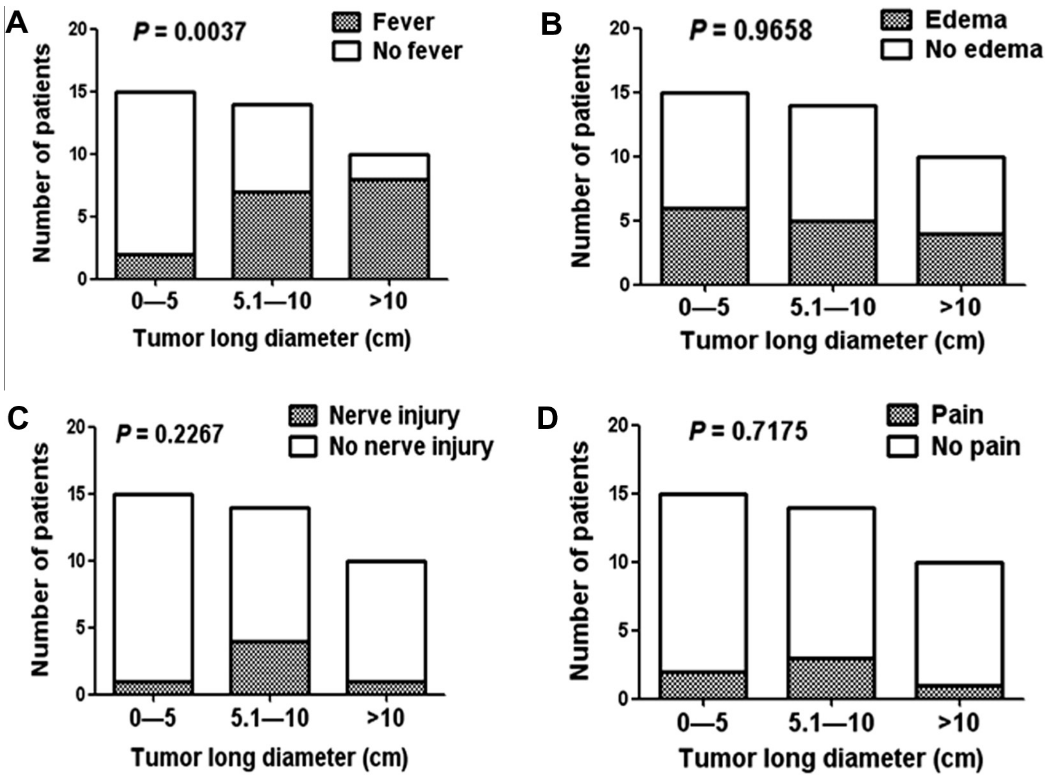

Fig. 3. Correlation of side effects with tumor size. After 39 cryosurgeries (19 patients), the incidence of fever (A), edema (B), nerve injury (C) and pain (D) was analyzed according to tumor, using the chi square test.

LRR after 15 cryosurgeries was 53% (8 cryosurgeries; PFS, 7.4 ± 6.1 months). For medium tumors, the LRR after 14 cryosurgeries was 43% (6 cryosurgeries; PFS, 8.0 ± 5.2 months). For large tumors, the LRR after 10 cryosurgeries was 60% (6 cryosurgeries; PFS, 9.5 ± 4.3 months). The chi square test revealed no difference in LRR among different tumor sizes ($P = 0.6952$, Fig. 2B).

Next, we investigated the relationship between side effects and tumor size. The incidence of postoperative fever significantly differed among the small (2/15, 13.3%), medium (7/14, 50%) and large (8/10, 80%) tumor groups ($P = 0.0037$; Fig. 3A). However, the incidence of postoperative edema ($P = 0.9658$; Fig. 3B), nerve injury ($P = 0.2267$; Fig. 3C) and pain ($P = 0.7175$; Fig. 3D) did not differ with tumor size.

Discussion

DFSP is staged using the American Musculoskeletal Tumor Society staging system, which takes into account tumor grade and compartmentalization. Stage I tumors are low-grade, intracompartmental (without extension beyond the subcutaneous compartment) lesions, and can be managed adequately with wide and deep local excision [15]. Because the shape of these tumors is always irregular, with finger-like extensions that cannot be observed with the naked eye, the recurrence rates after surgical excision range from 11% to 53% [7,20]. In some studies, radiotherapy has resulted in better long-term local control rates than surgery [6]. Although chemotherapy has been proved to be ineffective, recent studies on targeted therapy have reported very good results in disseminated cases [20]; however, the long-term outcomes remain to be determined. The 5-year relative survival rates reported in all population-based studies on DSFP can reach up to 99% [2,16,22]. In this study, 19 patients with local DFSP recurrence underwent cryoablation, and the safety and efficiency of cryotherapy were investigated. All patients refused surgery and radiotherapy, owing to the side effects of skin injury, reconstructive surgery and failure of previous surgery.

In the case of cryosurgery, the tumor ablation range is a major factor influencing LRR. The temperature at the periphery of the ice ball is 0 °C [6], and the lethal temperature for cells is at least −20 °C [19]; therefore, to induce complete tumor necrosis, the ice ball should extend at least 1 cm beyond the tumor periphery. There is some controversy about the ideal tumor margins during surgical excision of DFSP. In 1999, Lindner et al. reported that a circumferential margin of 2.5–3.5 cm improved local control of the disease [11]. In 2013, Llombar et al. noted that a circumferential margin of at least 2 cm of normal tissue around the DFSP should be removed [12]. Because of the infiltrative growth of DFSP [7,16], it is generally agreed that 3–5 cm lateral and deep margins are adequate [21,27]. Considering the infiltrative tumor growth, we aimed to create an ice ball that extended 3–5 cm beyond the tumor in our patients with local recurrence of DFSP. However, we took several precautions to avoid irreversible damage to important nerves and vessels, and the local skin, as described in the *Cryoablation procedure* section.

In this study, the LRR after a single cryoablation treatment was high; the reason for this high LRR is not clear, but inadequate cryoablation owing to the presence of major nerves and blood vessels near the tumor may be responsible. In the large tumor group, recurrence near the periphery of the frozen foci occurred at an average of 9.5 months after ablation. A second session of cryotherapy was carried out in these patients, and the LRR after both treatments was 54%; after three cryoablation sessions, this decreased to 0%. The reason for the complete control of local recurrence is unclear, but cryoablation-induced immunity [7,23] and the short follow-up duration may be possible explanations [3,8,24]. All 19 of our patients were successfully treated, with a PFS of >5 years and without fibrosarcomatous change or distant metastasis.

In our study, only minor side effects occurred after cryotherapy, such as fever, local edema, mild nerve injury and local pain, and all of these were relieved within 1 week upon symptomatic treatment. Local edema, which invariably occurs after a freezing injury, may compress the local nerves or visceral organs and worsen pain [5,13,18]. As our patients were asked to move their limbs constantly during the operation, mild facial or limb numbness only occurred after six cryosurgery sessions. The incidence of fever after cryoablation increased with increase in the tumor size (small tumors, 13.3%; medium tumors, 50%; large tumors, 80%). Besides infection, fever may be caused by strong antitumor immunity, but this mechanism needs to be investigated further [21].

We also assessed the relationship of LRR with tumor location and tumor size. The removal of head and neck tumors tends to be more conservative due to the presence of critical structures in this area and the cosmetic difficulties associated with reconstruction of the surgical defect. Therefore, DFSPs involving the head and neck region have been reported to have the highest LRR after local excision. For example, Mark et al. reported very high LRR (60%) in a series of 16 DFSP patients who underwent surgical excision [14]. In our study however, the LRR for head and neck tumors was the same as that for limb and abdominal wall tumors. Tumor size also had no relationship with LRR.

Although our sample size was small and the clinical data limited, our results suggest that percutaneous cryoablation is a relatively safe and efficient technique for the treatment of local recurrence of DFSP.

Disclosure

The author declares no conflicts of interest.

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