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Alleviating the pain of unresectable hepatic tumors by percutaneous cryoablation: Experience in 73 patients ☆

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ABSTRACT

Pain caused by liver tumors can be alleviated by cryoablation, but little is known about the analgesic effects and duration of pain alleviation. We retrospectively reviewed the changes in the severity of pain before and after percutaneous cryoablation of hepatic tumors. Each patient enrolled in this study had a single hepatic tumor; patients with large tumors (major diameter, ⩾5 cm) underwent transarterial chemoembolization (TACE) first and then cryoablation. Severe abdominal pain that was not controlled with long-lasting oral analgesics was treated with opioid injections. In all 73 study patients, severe abdominal pain was gradually eased 5 days after cryosurgery, completely disappeared after 15 days and did not recur for more than 8 weeks. There were no differences in analgesic effects between patients with hepatocellular carcinomas and those with liver metastasis ($P > 0.05$). The patients were divided into four groups depending on their pain outcomes: (i) immediate relief ($n = 6$), severe abdominalgia was no longer present after cryosurgery; (ii) delayed relief ($n = 11$), severe abdominalgia disappeared gradually within 15 days after the cryosurgery; (iii) always pain-free ($n = 39$), severe abdominalgia was not present before or after treatment; and (iv) new pain ($n = 17$), abdominalgia developed after treatment and disappeared within 15 days. In summary, percutaneous cryoablation of hepatic tumors caused short-term pain in some patients, but this pain disappeared within 15 days. Moreover, the pain-relieving effect of this treatment was sustained for at least 8 weeks, without severe side effects.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and 80% of HCC tumors are unresectable at the time of diagnosis. Cryoablation, which induces tumor tissue necrosis by ice ball formation, has been used for the management of unresectable HCC [12,27,29] and metastatic liver cancer [3]. Percutaneous cryoablation can prolong the survival of patients with metastatic HCC and improve their quality of life. Patients with advanced-stage tumors or tumor recurrence have poor health-related quality of life (HRQOL) [23,25,26]. Cancer-associated pain is common among patients with hepatic tumors and requires clinical treatment, as it can worsen the patients' quality of life. With the growth of liver tumors, severe abdominal pain occurs in most patients, whether they have primary HCC or liver metastasis [4,6,21]. Visceral cancer pain is usually described as a bloating pain in the abdomen, accompanied by pain in the shoulder, chest, upper limb, neck, back, lumbar spine or elsewhere. Alleviation of the pain of hepatic tumors with cryoablation has often been reported in the literature [19], and we have previously reported on the phenomenon of pain emerging after hepatic cryosurgery [27,28]. However, no study has focused on the extent and duration of pain alleviation in HCC patients.

In this study, we retrospectively reviewed the clinical data of 73 patients who underwent cryosurgeries of hepatic tumors in our hospital. As a cytoreductive method, transarterial chemoembolization (TACE) was used to shrink large hepatic tumors (major diameter, ⩾5 cm) before tumor cryoablation. Seventeen patients complained about significant symptoms of abdominal pain before and/or after TACE. As the main ablative method, percutaneous cryoablation can completely alleviate the abdominalgia, and the reasons underlying these changes was discussed in this article.

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Patients 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 December 2011 and January 2013, 73 patients with single hepatic tumor underwent percutaneous cryoablation in our hospital, including 29 patients with HCC and 44 patients with metastatic hepatic tumors. In all patients, the diagnoses were confirmed by imaging and pathological examinations. The sizes of hepatic tumors varied greatly, with major diameters ranging from 1.3 to 8 cm (average, 5.5 cm). Severe abdominal pain was present in 17 patients (11 with HCC, 6 with metastatic hepatic tumors) before cryosurgery.

Open surgery and targeted drug delivery were deemed unsuitable in any of the following situations: multifocal disease, unresectable hepatic tumor, refusal to undergo surgery or receive targeted drugs, seeking of further treatment after failure of targeted drugs and poor general condition (i.e., hypertension, ascites). In order to solve the tumor in liver, all the patients chose cryoablation, no matter with or without tumor pain. Ideal patients for liver cryoablation were those with the following characteristics: Karnofsky performance status (KPS) score $\geqslant 70$; 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; prothrombin time international normalized ratio $\geqslant 1.5$; hepatic tumor not obviously invading the gallbladder, diaphragm or large vessels; absence of level 3 hypertension, severe coronary disease, myelosuppression, respiratory disease and acute or chronic infection; and adequate hepatic function (bilirubin < 30 μM, aminotransferase < 60 U/l and Child–Pugh score A or B) and renal function (serum creatinine < 130 μM, serum urea < 10 mM).

Tace

Before cryosurgery, the preferred treatment for the 35 patients with large hepatic tumors (major diameter, $\geqslant$5 cm) was TACE [2,29], which has been described in our former work [12]. A French vascular sheath was placed into the femoral artery, and a 0.035-inch diameter catheter was advanced into the celiac and superior mesenteric arteries. A contrast medium was injected into the arteries during rapid-sequence radiographic imaging. Arterial branches supplying the tumors were then located. The venous phase was examined carefully for patency of the portal veins. A 0.018-inch diameter Tracker catheter was advanced through the Mickaelson catheter to the arterial branches supplying the tumors. A mixture of doxorubicin (50 mg), mitomycin (10 mg) and lipiodol (4–15 ml) was injected into the arterial branches until hemostasis was achieved. A second TACE was performed on tumors that showed no shrinkage 2 weeks after the procedure.

Cryoablation

Cryosurgeries of hepatic tumors were performed on all 73 patients. Using an argon gas-based cryosurgical unit (Endocare, Irvine, CA, USA), cryosurgery of two freeze/thaw cycles were performed. For masses of diameter 1.3–3 cm, one cryoprobe (3 mm in diameter) was used under ultrasonographic guidance; for masses of diameter 3–5 cm, two cryoprobes were used; for masses of diameter 5–8 cm, three cryoprobes were used. The duration of freezing was dependent on the achievement of an ice ball, visible as a hypoechoic region on ultrasonography. Generally, the maximal freezing time was 15 min, followed by natural thawing for 5 min; this cycle was then repeated. A margin of at least 1 cm of normal hepatic tissue was frozen circumferentially around the tumor. The tracts formed were sealed with fibrin glue immediately after the removal of the cryoprobes to ensure hemostasis.

Pain medication principles and programs

Clinical practice guidelines developed by the National Comprehensive Cancer Network [13] and the American Pain Society [1] emphasize the essentiality of comprehensive pain assessment. Initial and ongoing assessment of pain includes the evaluation of pain intensity using a visual analogue scale (VAS) ranging from 0 (indicating no pain) to 10 (indicating the worst pain imaginable). In our hospital, pain scores of 5–10 are defined as severe pain, and our medication principles and programs reference international practices as follows [10,11,17]: (i) According to the degree and pattern of pain, analgesics such as Oxycontin or MS Contin are delivered at the first available opportunity to reduce pain to below the pain threshold. (ii) In patients with mild pain, non-steroidal anti-inflammatory drugs (e.g., ibuprofen, celecoxib) are optional. If the results with these are not good, weak opioid drugs (e.g., tramadol, fentanyl) are added; if the pain continues, strong opioid drugs (e.g., morphine, pethidine hydrochloride) are used. (iii) For severe pain, two or more analgesics are combined to enhance pain relief and reduce drug consumption and complications. (iv) Analgesics are used alternately to prevent the development of resistance, and doses increased from low to high until the pain stops. (v) The side effects of pain medication are actively prevented and controlled.

All episodes of newly emerging severe pain (VAS score, 5–10) were quickly relieved by opioid drugs and recorded in detail, including pretreatment (from day −5 to day 0) and posttreatment (from day 1 to complete relief of abdominalgia) pain. Because abdominalgia is the predominant type of hepatic tumor pain, other types of pain (e.g., at puncture sites, lymph nodes, metastatic lesions) were not included in this study. Since an overwhelming majority of patients were taking long-lasting oral analgesics, purgative medicines were generally provided to all patients to prevent constipation.

Statistical analysis

Bonferroni's multiple comparison tests were used to compare the number of patients with severe abdominalgia during different time periods. The chi-square test was used to compare differences in severe abdominalgia between patients with HCC and liver metastases. All statistical analyses were conducted using GraphPad Prism 5 (GraphPad software, San Diego, CA, USA). $P < 0.05$ was considered to indicate a statistical difference; $P < 0.01$ or $P < 0.001$ was considered to indicate a significant difference.

Results

Perioperative outcomes

All percutaneous cryoablations of HCC and liver metastasis were performed successfully. No severe complications such as liver cracking or failure or acute renal failure with myoglobinuria were detected after cryoablation, but many mild side effects occurred. All the affected patients recovered with or without symptomatic treatment. Slight hepatic bleeding occurred in 12 patients (17%) and resolved within 5 days after the injection of hemostatic agents.

Liver capsular cracking was found in one patient (2%) but resolved after blood transfusion. Transient thrombocytopenia occurred in 14 patients (19%) within 1 week following cryoablation; four of these patients received platelet transfusions and three received interleukin-11 injections. Four patients (5%) who had tumors in the right lobe developed asymptomatic right-sided pleural effusions close to the dome of the diaphragm; these disappeared spontaneously within 2–3 weeks. Two patients (3%) developed liver abscess at the site of cryoablation at 2 and 4 days, respectively, after the procedure; they recovered with antibiotics and drainage treatment. No obvious side effects associated with TACE were found during the perioperative stage.

Changes in the number of patients with abdominalgia after cryosurgery

During the 13-month study period (December 2011–January 2013), detailed data of the 73 patients were collected. By TACE, all major diameter of liver tumors were controlled to less than 5 cm. Whether or not received TACE therapy, we only investigated the pain degree affected by liver cryosurgery. Among the 29 HCC patients, severe abdominalgia was found in 8 patients before cryosurgery and 18 patients after cryosurgery (Fig. 1A); among the 44 patients with liver metastasis, severe abdominalgia was found in 9 patients before cryosurgery and 27 patients after cryosurgery (Fig. 1B). The changes in the number of patients with abdominalgia after cryosurgery were similar in both groups of patients, with no statistical difference ($P = 0.6035$, chi-square test; $n = 62$, theoretical frequency = 7.1, 18.9, 9.9 and 26.1). Therefore, the pain relief data for both groups of hepatic tumors could be combined for further analysis. During the 5 days before cryosurgery, 56 patients had no pain; the remaining 17 patients had a total of 49 episodes of severe abdominalgia (one episode, four patients; two episodes, seven patients; three episodes, one patient; five episodes, two patients; six episodes, three patients). During the 5 days after the liver cryosurgeries, 45 patients had no pain; the remaining 28 patients had a total of 66 episodes of severe pain (one episode, eight patients; two episodes, ten patients; three episodes, five patients; four episodes, two patients; five episodes, three patients), with no statistical difference from the number pain episodes before treatment (0.90 ± 1.40 vs. 0.67 ± 1.52, $P > 0.05$). Severe abdominal pain diminished gradually and disappeared completely within 15 days after the cryosurgeries (Fig. 1C). Abdominalgia had not recurred by the 8-week follow-up visit.

Postoperative analgesic effect

Although severe abdominal pain after cryosurgery could be completely alleviated within 15 days, the individual pain outcomes of the patients within 5 days after cryosurgery showed a high degree of heterogeneity. Patients were divided into four groups depending on their posttreatment pain outcomes: (i) immediate relief ($n = 6$), severe abdominalgia was no longer present after the cryosurgery, (ii) delayed relief ($n = 11$), severe abdominalgia gradually disappeared within 15 days after the cryosurgery, (iii) always pain-free ($n = 39$), severe abdominal pain was not present before or after treatment and (iv) new pain ($n = 17$), abdominal pain was absent before treatment, but developed after treatment and disappeared within 15 days. Among the 11 patients with delayed relief, there was no statistical difference in the number of patients with abdominalgia 5 days before and after treatment ($P > 0.05$); in these patients, the pain diminished gradually and disappeared completely within 15 days after the cryosurgeries (Fig. 2A). Among the 17 patients with new pain, the number of patients with severe abdominalgia increased significantly after the liver cryosurgeries ($P < 0.001$); in these patients, the pain diminished gradually and disappeared completely within 15 days after the cryosurgeries (Fig. 2B).

Relationships between pain relief and tumor characteristics

To investigate the reasons underlying the heterogeneity of postoperative analgesic effects, we classified the basic clinical data of the 73 patients according to their pain outcomes (Table 1). The major diameters of the tumors in the "new pain" and "delayed relief" groups were significantly longer than those of the tumors in the "immediate relief" group (both $P < 0.05$) and "always pain-free" group (both $P < 0.001$). With regard to tumor location, the probability of a peripheral hepatic tumor in the immediate relief, delayed relief, always pain-free and new pain groups was 0%, 73%, 10% and 88%, respectively.

Discussion

Cryoablation and/or TACE are alternative treatments for medium-to-large, unresectable liver cancers, and the 5-year survival and local progression rates after these treatments were found to be 23% and 24%, respectively [16,20]. We retrospectively analyzed the long-term survival rates of patients with metastatic HCC in our hospital and found that percutaneous cryoablation in these patients was associated with at least three advantages: (i) Only mild side effects occurred after the first cryosurgery, and all of them resolved within 2 weeks after the surgery, with or without symptomatic treatment. (ii) The overall survival (OS) of patients who underwent cryoablation of multiple lesions was significantly longer than that of patients who received no treatment (median: 26 vs. 3.5 months, $P < 0.001$). (iii) In the first 2 weeks after cryosurgery, the VAS pain score decreased to 0–3 in 76% of the patients with pretreatment abdominal pain; this was accompanied with a 50% decrease in analgesic usage and a ⩾20-point increase in the KPS

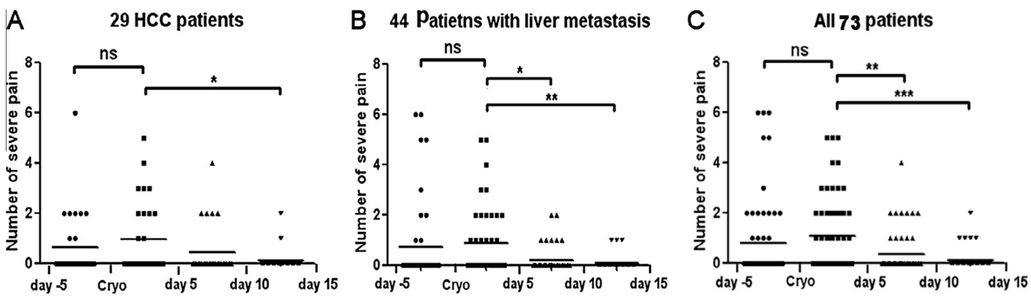

Fig. 1. Number of patients with severe abdominalgia before and after liver tumor ablation. Bonferroni's multiple comparison tests were used for all comparisons. (A) Data for 29 patients with hepatocellular carcinoma (HCC) and (B) 44 patients with liver metastasis. (C) Data for all 73 patients. Horizontal lines represent the mean number of patients with severe abdominalgia. The ns represents no statistical difference, * represents $P < 0.05$, ** represents $P < 0.01$, *** represents $P < 0.001$.

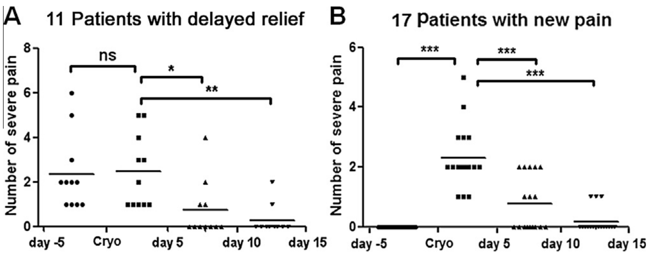

Fig. 2. Change trends in the number of patients with severe abdominalgia in the "delayed relief" and "new pain" groups. Change trends for the "immediate relief" and "always pain-free" groups are not shown. Bonferroni's multiple comparison tests were used for all comparisons. (A) Data for the delayed relief group. (B) Data for the new pain group. Horizontal lines represent the mean number of patients with severe abdominalgia. The ns represents no statistical difference, * represents $P < 0.05$, ** represents $P < 0.01$, *** represents $P < 0.001$.

score [12]. These results suggested that hepatic cryoablation effectively alleviated visceral cancer pain, and therefore, the present study analyzed the pain outcomes of patients with severe abdominal pain after percutaneous cryoablation of unresectable hepatic tumors.

Severe pain has been well documented as one of the most frequent and distressing symptoms of cancer, and has been shown to adversely affect quality of life [5,9,15]. There are three main causes of pain in patients with liver cancer: the tumor itself (e.g., increased tension on the liver capsule, central necrosis of the tumor, tumor thrombi blocking blood vessels and resulting in tissue ischemia), extrahepatic metastasis (e.g., pain in the lungs, bones, peritoneum) and treatment (e.g., complications caused by surgery or chemoradiation) [6]. Conventional approaches to the relief of cancer pain include radiation, palliative surgery and opioid and non-opioid analgesics; however, it has been reported that only 50% of patients with metastatic cancer have adequately controlled pain [22]. The use of radiofrequency ablation, TACE and cryoablation for pain palliation in patients with hepatic tumors has been reported. Patients treated with radiofrequency ablation or combination TACE-radiofrequency ablation have been reported to have a better HRQOL than those treated with only TACE [25]. In our previous retrospective analysis of a large sample of patients, emerging abdominalgia [28] and relief of abdominalgia [12] were both reported after liver cryosurgery. Among patients with hepatic tumors, back pain (which could be due to metastases to lymph nodes or other organs), abdominal pain (which may be caused by eccentric tumor growth and Increase tension on the liver capsule) and puncture point pain are common. However, in this study, we focused on the alleviation of only abdominal pain by percutaneous cryoablation; the effects of liver cryoablation on other factors of life quality are still under further investigation.

We performed percutaneous cryoablation on 73 patients with unresectable hepatic tumors. TACE was carried out before percutaneous cryoablation when the tumor diameter was ⩾5 cm [12,25]. Interestingly, severe abdominalgia was not obviously eased within 5 days after the cryosurgeries, and was present until 15 days after cryosurgeries (Fig. 1C). There was no difference in the frequency of severe abdominalgia between patients with HCCs and those with metastatic hepatic tumors (Fig. 1A and B). The patients were divided into four groups, depending on their pain outcomes after cryosurgery: immediate relief, delayed relief (within 15 days), always pain-free (no pain before or after treatment) and new pain (no pain before treatment; pain developed after treatment and disappeared within 15 days). Patients who experienced immediate relief may have had pain caused by central tumor necrosis and/or tumor thrombus, as this pain can be rapidly and completely resolved by percutaneous cryoablation. However, cryoablation can also induce pain by causing significant hepatic edema that increases the tension on the liver capsule. As the edema resolves over time, the pain is reduced gradually. In the "delayed relief" group, large tumors (major diameter 3–5 cm) accounted for 81%, and 73% tumors located at the hepatic peripheral; in the "new pain" group, large tumors accounted for 88%, and 88% tumors located at the hepatic peripheral (Table 1). Thus, it is not surprising that cryosurgery of relatively large tumors and peripheral hepatic tumors may increase the tension on the liver capsule and lengthen the duration of pain, some patients showed delayed pain relief and some patients showed new pain after the cryosurgery (Fig. 2). Consistent with this, most tumors in the always pain-free group were small and centrally located, while most tumors in the new pain group were large and peripherally located. At 15 days after cryoablation, abdominal pain was alleviated in all patients in this study; this was obviously longer than the time required for pain relief in patients with unresectable pancreatic cancer in our previous study [14].

Table 1
Basic clinical data of patients with hepatic tumors.

		Immediate relief ($n = 6$)	Delayed relief ($n = 11$)	Always pain-free ($n = 39$)	New pain ($n = 17$)
Sex	Male	2	7	23	8
	Female	4	4	16	9
Nationality	China	3	3	20	6
	Southeast Asia	1	4	11	5
	Middle East	2	4	8	6
Tumor origin	HCC	3	5	21	6
	Liver metastasis	3	6	18	11
Age (yr)	Average	25–62	42–63	36–75	37–80
	Range	45	52	57	59
Tumor major diameter (after TACE)	1–1.9 cm	1	0	16	0
	2–2.9 cm	2	2	11	2
	3–3.9 cm	3	4	12	4
	4–5 cm	0	5	0	11
Tumor location	Hepatic peripheral	0	8	4	15
	Hepatic center	5	3	35	2
Mean of severe abdominalgia	5 days before cryo	3.83 ± 2.04	2.36 ± 1.69	0	0
	5 days after cryo	0	2.45 ± 1.63	0	2.29 ± 1.05
	5–10 days after cryo	0	0.73 ± 1.27	0	0.76 ± 0.90
	10–15 days after cryo	0	0.27 ± 0.65	0	0.18 ± 0.39

The limitations of this study should be noted. First, in most patients, TACE was performed first to create the opportunity for cryosurgery; early interruption of blood supply may inhibit the development of cancer pain, and this interruption may have prolonged effects [7,8,18,19,24,25]. Second, in addition to the hepatic tumor itself, severe pain can be caused by metastases to the celiac lymph nodes and other organs as well as by the cryoprobe puncture wound; these causes of pain need to be addressed together with hepatic pain. Third, the VAS method of pain evaluation has a degree of subjectivity; therefore, instead of measuring precise pain scores, we counted the number of patients with severe abdominalgia that could be eased only through the injection of opoids.

Observed from the current, percutaneous cryosurgery with or without TACE is an effective and safe method for the management of pain in patients with primary or metastatic hepatic tumors. However, the diversity of groups and the number of patients are limited to draw statistical conclusions in this study, and further study is needed.

Disclosure

The authors declare that there are no conflicts of interest.

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