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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, $\geqslant$5 cm) underwent transarterial chemoembolization (TACE) first and then cryoablation. Severe abdominal pain that was not controlled with long-lasting oral analgesics was treated with opioid injections. In all 73 study patients, severe abdominal pain was gradually eased 5 days after cryosurgery, completely disappeared after 15 days and did not recur for more than 8 weeks. There were no differences in analgesic effects between patients with hepatocellular carcinomas and those with liver metastasis ($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, $\geqslant$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.