P.O.Box 2345, Beijing 100023,China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2003;9(12):2686-2689
World Journal of Gastroenterology
 ISSN 1007-9327

• LIVER CANCER •

Percutaneous cryoablation in combination with ethanol injection for unresectable hepatocellular carcinoma

Ke-Cheng Xu, Li-Zhi Niu, Wei-Bin He, Zi-Qian Guo, Yi-Ze Hu, Jian-Sheng Zuo

Ke-Cheng Xu, Li-Zhi Niu, Wei-bin He, Zi-Qian Guo,Yi-Ze Hu, Jian-Sheng Zuo, Fuda Cancer Hospital of Guangzhou,Guangzhou 510300, Guangdong Province, China
Correspondence to: Dr. Ke-Cheng Xu, Fuda Cancer Hospital of Guangzhou, Guangzhou 510300, Guangdong Province, China. xukc1818@sina.com
Telephone: +86-20-84196175 **Fax:** +86-20-84195515
Received: 2003-03-10 **Accepted:** 2003-05-16

Abstract

AIM: To evaluate the effectiveness and safety of percutaneous hepatic cryoablation in combination with percutaneous ethanol injection (PEI) in patients with unresectable hepaocellular carcinoma (HCC).

METHODS: A total of 105 masses in 65 HCC patients underwent percutaneous hepatic cryoablation. The cryoablation was performed with the Cryocare system (Endocare, Irvine, CA, USA) using argon gas as a cryogen. Two freeze-thaw cycles were performed, each reaching a temperature of -180 ℃ at the tip of the probe. PEI was given in 36 patients with tumor masses larger than 6 cm in diameter 1-2 weeks after cryoablation and then once per week for 4 to 6 sessions. The efficacy was evaluated with survival, change of tumor size and alpha-fetoprotein (AFP) levels.

RESULTS: During a follow-up duration of 14 months in average with a range of 5 to 21 months, 33 patients (50.8 %) were free of tumors, 22 patients (33.8 %) alive with tumor recurrence: two had bone metastases, three were found to have lung metastases, and the remaining 17 recurrences occurred in the liver, of whom only 3 developed a cryosite recurrence. Among the 41 patients who were followed up for more than one year, 32(78 %) were alive despite of tumor recurrence. Seven patients (10.8 %) died due to disease recurrence. Three patients (4.6 %) died due to some noncancer-related causes. Among the 43 patients who had a CT scan available for review, 38 (88.4 %) had a shrinkage of tumor mass. Among the 22 patients who received biopsies of cryoablated tumor mass, all biopsies except one, showed only dead or scar tissues. Of the patients who had an increased AFP preablatively, 91.3 % had a decrease of AFP to normal or nearly normal levels during postablative 3-6 months. Complications of cryoablation included liver capsular cracking in one patient,transient thrombocytopenia in 4 patients and asymptomatic right-sided pleural effusions in 2 patients. Two patients developed liver abscess at the previous cryoablation site at 2 and 4 months, respectively, following cryoablation, and was recovered after treated with antibiotics and drainage.

CONCLUSION: Percutaneous cryoablation offers a safe and possibly curative treatment option for patients with HCC that cannot be surgically removed, and its integration with PEI, may serve as an alternative to partial liver resection in selective patients.

Xu KC, Niu LZ, He WB, Guo ZQ, Hu YZ, Zuo JS. Percutaneous cryoablation in combination with ethanol injection for unresectable hepatocellular carcinoma. *World J Gastroenterol* 2003; 9(12): 2686-2689
http://www.wjgnet.com/1007-9327/9/2686.asp

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common and lethal cancers. Curative surgical resection of HCC is considered to be the optimal treatment. Unfortunately, only about 10 % of newly diagnosed HCC patients are eligible candidates for resection[1]. Therefore, alternative treatment modalities have been developed, including localized ablative techniques involving either freezing (cryoablation) or chemical desiccation (ethanol ablation)[2].

Cryoablation uses extremely low temperature to destroy tumor tissues, and has been shown to be as effective as surgical resection for treatment of primary or metastatic liver cancer[3]. Percutaneous ethanol injection (PEI) has been reported to be effective against small HCC, but is not eligible for advanced HCC[4]. We employed percutaneous cryoablation in combination with ethanol injection following cryoablation for treatment of unresectable HCC and yielded better results. This paper reports our experience using the combined therapy in 65 HCC patients and evaluates the effectiveness and safety.

MATERIALS AND METHODS

Subjects

Between March 2001 and January 2003, 65 HCC patients underwent combined treatment of percutaneous hepatic cryoablation and PEI. There were 47 men and 18 women. Their ages ranged from 32 to 78 years, with a mean age of 51 years. Sixty patients had histories of heapatitis B infection, and 4 had hepatitis C infection. Informed consents were obtained from all patients undergoing combined therapy.

The diagnosis of HCC in 43 patients was proven by liver pathology, and the remaining cases had HCC diagnosed by classical imagings, including computed tomography (CT), magnetic resonance and ultrasonography, and biochemical markers, such as increased alpha-fetoprotein (AFP). Forty-four patients had only one mass in the liver, being 4.8 cm to 15 cm in diameter with an average of 7.3 cm. Twenty-one patients had 2-4 masses from 6 cm to 14 cm in diameter. There were a total of 105 masses in 65 patients and the average number of masses per patient was 2.6.No patient had evidence of extrahepatic metastases.

All except 2 cases had cirrhosis. Using Child-Pugh' s score in assessing the severity of cirrhosis, 39 patients were classified as class A, and 25 as class B.

Cryoablation procedure

The cryoablation was performed with the Cryocare system (Endocare, Irvine, CA, USA) using argon gas as a cryogen.

Cryoprobes (3, 5 or 8 mm) were inserted into the center of tumor mass under ultrasonographic guidance, and two freeze-thaw cycles were performed, each reaching a temperature of -180 ℃ at the tip of the probe. The time of freezing was dependent on the achievement of an "ice ball", visible as a hypoechoic region by ultrasonography. Generally, the tumor was frozen at a maximum flow rate for about 15 minutes, thawed for 5 minutes and then refrozen for another 15 minutes. A margin of at least 1 cm normal hepatic tissue was frozen circumferentially around the tumor. For the mass larger than 5 cm in diameter, two or three cryoprobes were placed within the center and periphery of tumor respectively, to insure freezing of the entire tumor. Finally, the cryoprobe was removed when the tip temperature reached above 0 ℃, and the tract formed was sealed off with fibrin glue immediately after removal of the cryoprobe to ensure haemostasis.

Alcohol ablation

PEI was administered in 36 patients with tumor masses larger than 6 cm in diameter and was given 1-2 weeks after cryoablation and then once a week for up to 4-6 sessions. Absolute alcohol (100 %) was slowly injected into the peripheral zone of cancerous tissues in liver through a 20-gauge needle under ultrasonographic guidance. The goal of this procedure was to achieve a "black stain" shown by ultrasonography in the tumor tissues. A maximum of 5 ml alcohol was injected per site, with a maximum of 20 ml per session.

Postoperative follow-up

All patients were followed up at monthly intervals. The serum α-fetoprotein (AFP) levels were assayed during each visit. The first CT scanning was performed within one month after cryoablation to detect residual tumor, and then CT scan study was done every 3 months in the initial six months and every 6 months subsequently to detect recurrence.

RESULTS

Disease status and survival

All patients were followed up for a median duration of 14 months with a range of 5-21 months. The disease status of the patients is shown in Table 1. Thirty-three patients (50.8 %) were currently free of tumor with an average follow-up of 13.8 months. Twenty-two patients (33.8 %) were alive with disease recurrence: two had bone metastases, three were found to have lung metastases, and the remaining 17 had recurrences in the liver, of whom only 3 developed a cryosite recurrence. Among the 41 patients who were followed up for more than one year, 32 (78 %) were alive despite of tumor recurrence. Seven patients (10.8 %) died from their tumors, and had recurrence of tumor in the liver remnant at a mean of 7.8 months with an overall survival of 13.2 months. Three patients (4.6 %) died of noncancer-related causes. One died of myocardial infarction,1 died of pneumonia, and 1 died of liver failure,respectively.

Table 1 Disease status

	Number of patients	Percent of patients	Follow-up (months)
Alive free of tumor	33	50.8	16.8
Alive with tumor recurrence	22	33.8	17.2
Died of tumor recurrence	7	10.8	13
Died of noncancer-related diseases	3	4.6	4

Tumor size

Among the forty-three patients who had a CT scan available for review, 38 (88.4 %) had a shrinkage of tumor mass, with an average size of the dominant tumor changing from a preablative size of 7.9 cm (3.7-13.2 cm) to a 3-month postablative size of 5.6 cm (2.1-8 cm). Twenty-two received biopsies of their cryoablated tumor mass under ultrasonography guidance. All biopsies except one, showed only dead or scar tissues.

Serum AFP levels

An increased serum AFP, with a median level of 367 ng/L, ranging from 68 to 1 210 ng/L, was detected in 46 patients preablatively. The AFP levels were lowered to normal or nearly normal range in 42 patients (91.3%) during postablative 3-6 months, and the median AFP level was 59 ng/L with a range of 12-365 ng/L.

Complications

Complications of cryoablation included liver capsular cracking in one patient and recovered after blood transfusion. Transient thrombocytopenia occurred in 4 patients within 1 week following cryoablation, 2 of whom received platelet transfusion. Two patients developed asymptomatic right-sided pleural effusions, both had cancer in the right lobe which was close to the dome of the diaphragm. The pleural effusions disappeared spontaneously within 2-3 weeks. Two patients developed liver abscess at the previous cryoablation site 2 and 4 months respectively following cryoablation, and were recovered after antibiotics and drainage treatment.

The majority of patients receiving PEI had pain at injection site, fever and a feeling of alcohol intoxication, which were transient and subsided with conservative management. No patient experienced an appreciable risk.

DISCUSSION

Prognosis of unresectable HCC is very poor. In Japan, the median survival for 229 patients receiving no specific treatment was 1.6 months[5]. Although chemoembolization is associated with good objective responses in the tumor, a recent controlled trial showed that by itself, chemoembolization offered no improvement in survival compared with supportive therapy alone[6]. During the past years, great efforts have been made to improve the survival of patients with this disease[7]. In this trial, percutaneous cryoablation in combination with PEI showed more satisfactory therapeutic efficacy. Among the 65 HCC patients receiving this combined therapy and followed up for a median duration of 14 months, 50.8 % of the patients are currently free of tumor and 33.8 % are alive with tumor recurrences. Among the 41 patients who were followed up for more than one year, 78 % are alive despite of tumor recurrence. Only 10.8 % died from tumor recurrence with an overall survival for 13.2 months. Of the patients who had CT scan available for review, 88.4 % had a shrinkage of tumor masses. Of the 22 patients who received biopsies of their cryoablated tumor masses, all but one showed only dead tumor cells or scar. Of the patients who had an increased AFP preablatively, 91.3 % had a decrease of AFP to normal or nearly normal levels during postablative 3-6 months.

The present result is comparable with those by other authors. Crews *et al*[8] reported that forty patients with hepatic malignancy underwent cryoablation and the estimated 18-month survival was 60 % and 30 % for patients with HCC and with colorectal metastasis, respectively. Lam *et al*[9] treated 4 patients with recurrent HCC after previous curative hepatectomy with cryoablation. All their patients are still alive with a survival after cryoablation ranging from 12 to 23 months. Sheen *et al*[10] have demonstrated that the median survival for HCC patients after cryoablation was 36 months. Zhou *et al*[11,12]

reported 1-, 3- and 5-year survival rates of 78 %, 54 % and 40 %, respectively in 235 HCC patients who received cryoablation. It should be noted that the cryoablation reported by these authors was mainly performed through intraoperative approach with a large invasion, while in the present trial, cryoablation was performed percutaneously, being minimally invasive and allowing for a rapid recovery.

Cryoablation is a method of *in situ* tumor ablation. A circulated cryogen is used to target tumors to induce irreversible tissue destruction at a temperature below 40 ℃. Tumor cell death is caused by both direct and indirect mechanisms. The direct cellular damage is a result of intra- and extra-cellular ice crystal formation and solute-solvent shifts, which induce cell dehydration and rupture. The indirect effect was found to be resulted from the vessel obliteration which would result in ischemic hypoxia[13,14].

As a local therapy, cryoablation has been found to carry certain advantages over other forms of HCC treatment[15]. First, it is able to destroy only the tumor tissue in liver sparing more noninvolved tissues, which is of important significance to HCC patients, because the majority of these patients would been found to have cirrhosis and decreased reserve of liver function[16]. Second, because of the warming effect of flowing blood, large blood vessels, such as inferior vena cava and portal vein, are somewhat imperious to the effect of freezing. Therefore, tumors close to these venous systems could safely undergo cryoablation, whereas resection of tumors close to large vascular structures would be very difficult[17].Third, it is known that liver cirrhosis is a basis of HCC development, if the entire liver is cirrhotic, any part of the liver can develop new tumors. Liver cryoablation has been found to be more effective than surgical resection in treating multiple new tumors[13]. Forth,in contrast with other local ablations, such as radiofrequency, which are difficult to reliably destroy tumors greater than 5 cm in diameter, cryoablation would be a promising means for the treatment of this larger form of tumor[2]. Lastly, the rapid freeze-thaw process could enhance necrosis and help induce an immune response against the surviving tumor cells[18].

During cryoablation, freezing would occur in three main areas: (1) The center of iceball near the cryoprobe, where freezing would be rapid and the temperature would be lowest. (2) The middle of the iceball, where the tissue experienced intermediate cooling rate. (3) The periphery of the iceball, where slow rates of cooling would occur[18]. The cytotoxic effect from rapid cooling was the greatest in the center of the iceball, while cells at the periphery of the iceball might survive, particularly if the tumor abutted a large intrahepatic blood vessel that abrogated the effects of tissue cooling. The surviving tumor cells would result in recurrence of the disease. PEI has been used extensively for treatment of HCC. Ethanol could diffuse into the tumor cells and cause nonselective protein denaturation and cellular dehydration, leading to coagulated necrosis. Subsequent fibrosis and small vessel thrombosis would also contribute to cellular death. Therefore, after cryoablation which could destroy the majority of tumors, PEI used at periphery of tumor could destroy residue tumor tissues. It is obvious that cryoablation in combination with PEI had a complementary effects on preventing recurrence[18]. In this series, PEI was given to 36 patients with tumor masses larger than 6 cm in diameter 1-2 weeks after cryoablation, that might be contributory to a better outcome. Moreover, among the 17 patients who had recurrent tumors, only 3 had recurrence at the original cryosite, suggesting that the effectiveness of this combined therapy was good.

Cryoablation has been considered as a safe modality[10]. Transient intra-ablative hypothermia is the most common side effects. The use of warming blankets and fluid warmers has been proven beneficial. Transient thrombocytopenia and hypoglycemia have been observed. Patients should be observed for possible coagulopathy when large tumor (greater than 5 cm) has been frozen. Pleural effusions may occur in tumor mass treated close to the dome of the diaphragm. Cracking of the hepatic capsule might occur during the thawing process[13,17,19], which was seen in one patient in this series. It is one of the most serious complications of hepatic cryoablation, and could be controlled with conservative therapies for most of the cases. Cryoshock manifested as varying degrees of acute renal failure, disseminated intravascular coagulation and adult respiratory distress syndrome, was reported[15]. It has been shown that cryoshock occurred in greater than 40 % of the volume of tissue treated, and lesions over 6 cm were associated with a greater risk[17]. However, lesions up to 10 cm in size were treated safely in the present series. This complication might be related more to the total duration of cryoablation than to the volume of tumor tissue treated[10]. Nevertheless, it is necessary to prevent the disastrous complication. Diuresis with mannitol and alkalinization of urine should be used in all patients to avoid myoglobinuria and subsequent renal damage[8]. PEI has been proven safe, and no significant complication was associated with this modality in the present series.

In conclusion, this technique offers the curative treatment option for HCC that cannot be surgically removed due to the anatomic location of the tumor, and the presence of other comorbid conditions that would otherwise preclude a major liver resection. Percutaneous approach has the advantage of a minimal invasion and allows for a rapid recovery and does not produce appreciable complications. The integration of this technique with other adjuvant regional modalities, especially PEI, may be used as an alternative to resection, so as to improve a long-term disease-free survival in selected patients.

REFERENCES

1 **Staley CA.** Surgical therapy of hepatic tumors. In: Zakim D and Boyer TD, eds. Hepatology. A Textbook of Liver Disease. *Philadelphia: Saunders* 2003: 1371-1381

2 **Adam R**, Hagopian EJ, Linhares M, Krissat J, Savier E, Azoulay D, Kunstlinger F, Castaing D, Bismuth H. A comparison of percutaneous cryosurgery and percutaneous radiofrequency for unresectable hepatic malignancies. *Arch Surg* 2002; **137**: 1332-1339

3 **Onik GM**, Atkinson D, Zemel R, Weaver ML. Cryosurgery of liver cancer. *Semin Surg Oncol* 1993; **9**: 309-317

4 **Gournay J**, Tchuenbou J, Richou C, Masliah C, Lerat F, Dupas B, Martin T, Nouel JF, Schnee M, Montigny P, D'Alincourt A, Hamy A, Paineau J, Le Neel JC, Le Borgne J, Galmiche JP. Percutaneous ethanol injection vs. resection in patients with small single hepatocellular carcinoma: a retrospective case-control study with cost analysis. *Aliment Pharmacol Ther* 2002; **16**: 1529-1538

5 **Okuda K**, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985; **56**: 918-928

6 **Groupe d'Etude et de Traitement du Carcimome Hepatocelltaire**. A comparison of lipiodol, chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995; **332**: 1256-1261

7 **Lau WY,** Leung TW, Yu SC, Ho SK. Percutaneous local ablative therapy for hepatocellular carcinoma: a review and look into the future. *Ann Surg* 2003; **237**: 171-179

8 **Crews KA**, Kuhn JA, McCarty TM, Fisher TL, Goldstein RM, Preskitt JT. Cryosurgical ablation of hepatic tumors. *Am J Surg* 1997; **174**: 614-618

9 **Lam CM**, Yuen WK, Fan ST. Hepatic cryoablation for recurrent hepatocellular carcinoma after hepatectomy:a preliminary report.

J Surg Oncol 1998; **68**: 104-106
10 **Sheen AJ**, Poston GJ, Sherlock DJ. Cryotherapeutic ablation of liver tumours. *Br J Surg* 2002; **89**: 1396-1401
11 **Zhou XD**, Tang ZY, Yu YQ, Ma ZC. Clinical evaluation of cryosurgery in the treatment of primary liver cancer. Report of 60 cases. *Cancer* 1988; **61**: 1889-1892
12 **Zhou XD**, Tang ZY, Yu YQ, Weng JW, Ma ZC, Zhang BH, Zheng YX. The role of cryosurgery in the treatment of hepatic cancer: areport of 113 cases. *J Cancer Res Clin Oncol* 1993; **120**: 100-102
13 **Ross WB**, Horton M, Bertolino P, Morris DL. Cryotherapy of liver tumours-a practical guide. *HPB Surg* 1995; **8**: 167-173
14 **Erce C**, Parks RW. Interstitial ablative techniques for hepatic tumours. *Br J Surg* 2003; **90**: 272-289
15 **Shafir M**, Shapiro R, Sung M, Warner R, Sicular A, Klipfel A. Cryoablation of unresectable malignant liver tumors. *Am J Surg* 1996; **171**: 27-31
16 **Bilchik AJ**, Sarantou T, Wardlaw JC, Ramming KP. Cryosurgery causes a profound reduction in tumor markers in hepatoma and noncolorectal hepatic metastases. *Am Surg* 1997; **63**: 796-800
17 **Seifert JK**, Morris DL. Indicators of recurrence following cryotherapy for hepatic metastases from colorectal cancer.*Br J Surg* 1999; **86**: 234-240
18 **Wong WS**, Patel SC, Cruz FS, Gala KV, Turner AF. Cryosurgery as a treatment for advanced stage hepatocellular carcinoma: results, complication, and alcohol ablation. *Cancer* 1998; **82**: 1268-1278
19 **Dwerryhouse SJ**, Seifert JK, McCall JL, Iqbal J, Ross WB, Morris DL. Hepatic resection with cryotherapy to involved or inadequate resection margin (edge freeze) for metastases from colorectal cancer. *Br J Surg* 1998; **85**: 185-187

Edited by Ma JY and Wang XL