J Cancer Res Clin Oncol (1993) 120:100–102

Journal of Cancer Research and Clinical Oncology

The role of cryosurgery in the treatment of hepatic cancer: a report of 113 cases

Xin-Da Zhou[1], Zhao-You Tang[1], Ye-Qin Yu[1], Jian-Mao Weng[2], Zeng-Chen Ma[1], Bo-Heng Zhang[1], Ya-Xin Zheng[1]

[1] Liver Cancer Institute, Shanghai Medical University, China
[2] Shanghai Institute of Technical Physics of the Academic Sinica, Shanghai, China

Received: 4 December 1992/Accepted: 27 May 1993

Abstract. From November 1973 to June 1992, cryosurgery with liquid nitrogen (–196° C) was performed on 113 patients with hepatic cancer, including 107 patients with primary liver cancer (PLC) and 6 patients with secondary liver cancer (SLC). Of the 107 PLC patients, the subclinical stage constituted 30.8% (33/107), the moderate stage 61.7% (66/107), and the late stage 7.5% (8/107). There were 32 cases with small PLC (up to 5 cm). Liver cirrhosis was observed in 86.0% (92/107). We designed flat cryoprobes for freezing surface tumors, and single and multiple trocar cryoprobes for freezing tumors deep within the hepatic parenchyma. Intraoperative ultrasound was used for monitoring hepatic cryolesions. There were no operative mortalities and complications, such as rupture of a tumor, delayed bleeding, or bile leakage. The 5-year and 10-year survival rates were 22.0% and 8.2%, respectively, for the 107 PLC patients and 48.8% and 17.1%, respectively, for the 32 patients with small PLC. Of the 6 SLC patients, survival ranged from 2 months to 90 months (average, 23.2 months). One SLC patient has been well for 7 years and 6 months after cryosurgery. These results indicate that cryosurgery, the in situ freezing of cancer, is a safe and effective treatment for unresectable hepatic cancer.

Key words: Liver cancer – Cryosurgery

Introduction

Modern cryosurgery for the treatment of malignant neoplasms has been applied for more than three decades; however, it has mostly been limited to easily accessible areas of the body, such as skin, rectal, prostatic, gynecological, head, and neck cancers (Gage 1992). With visceral tumors, apart from the need to expose the tumor by laparotomy, the major problem is that destruction of large tumors by freezing is difficult. Recently, encouraging trials using cryosurgery in the treatment of lung and hepatic metastases have been reported (Charnley et al. 1989; Kuramoto and Kamegai 1978; Onik et al. 1991; Ravikumar et al. 1991; Xie et al. 1983), but the techniques are not yet well developed and the long-term benefits are not known. In this article we report on the long-term results of cryosurgery in the treatment of 113 patients with hepatic cancer, including 107 patients with primary liver cancer (PLC), and 6 patients with secondary liver cancer (SLC). The role of cryosurgery in the treatment of hepatic cancer is discussed.

Presented in part at the 4th World Congress of Hepato-Pancreato-Biliary Surgery, 7–11 June 1992, Hong Kong

Correspondence to: X. D. Zhou, Liver Cancer Institute, Shanghai Medical University, Zhong Shan Hospital, Shanghai 200032, P. R. China

Abbreviations: PLC, primary liver cancer; SLC, secondary liver cancer, IOUS, intraoperative ultrasound; AFP, α-fetoprotein

Materials and methods

Patients. From November 1973 to June 1992, 113 patients with hepatic cancer were treated by cryosurgery wth liquid nitrogen (–196° C) at the Liver Cancer Institute of Shanghai Medical University. Histological examinations revealed that 107 were PLC (hepatocellular carcinoma 104, cholangiocarcinoma 1, and mixed type 2), and 6 were SLC (from colon cancer 4, stomach cancer 1, and gall bladder cancer 1). The patients' ages ranged from 26 years to 69 years (median, 48 years), and the male to female ratio was 6.1:1. The criteria for clinical staging of PLC were defined as follows: subclinical, without obvious PLC symptoms or signs; moderate, with obvious PLC symptoms or signs, but without obvious jaundice, ascites, or distant metastasis; and late, with obvious jaundice, ascites or distant metastasis. In this series, the subclinical stage constituted 30.8% (33/107), the moderate stage 61.7% (66/107), and the late stage 7.5% (8/107). There were 32 cases (29.9%) with small PLC (up to 5 cm). Liver cirrhosis was present in 86.0% (92/107). Preoperative serum α-fetoprotein (AFP) was abnormal (more than 20 ng/ml) in 72.0% (77/107).

Cryosurgery for PLC was mainly indicated for (a) patients with severe liver cirrhosis in whom hepatic resection would be contraindicated, (b) residual tumor at the cut surface or in the rest of the liver after resection of the main tumor and (c) unresectable recurrent PLC after major hepatic resection (Zhou et al. 1992).

Cryosurgery modalities employed in the 107 PLC cases were as follows: (a) cryosurgery only in 49 cases (45.8%); (b) cryosurgery plus hepatic artery ligation and/or perfusion in 30 cases (28.0%); (c) cryosurgery for residual tumor plus resection of the main tumor in 18 cases (16.8%); (d) cryosurgery plus resection of the frozen area in 10 cases (9.3%).

In the 6 patients with SLC, 4 were considered unsuitable for surgical resection because of multiple lesions. In the remaining 2 patients, cryosurgery was carried out for residual tumor at the cut surface of the liver after resection of the main tumor. None of the 6 patients had associated liver cirrhosis.

Technique. A right subcostal incision was used for liver exposure. Liver was examined by intraoperative ultrasound (IOUS). Cryoprobes of various sizes and shapes were used depending on the size and location of the tumor. Flat probes 3.5 cm and 5 cm in diameter were used for surface lesions. A trocar probe 8 mm in width and 7 cm in length was used for deeper lesions. Multiple penetrations (three to six needles, each needle being 2.5 mm wide, 5 cm long) with a single cryoprobe (4 cm in diameter) were sometimes used for deeper lesions (Zhou et al. 1992). The probe and its handle were connected with a particular angle connector for treating tumors located in the right upper lobe of the liver. The probe was driven by a cryosurgical system (LD-2, Shanghai Institute of Technical Physics of the Academic Sinica) that circulated liquid nitrogen at –196° C through an insulated metal sheath. A probe temperature of –180° C was achieved by this system. Freezing was accomplished by placing the flat probe on the tumor surface with minimal pressure, or by placing the trocar probe into the tumor under ultrasound guidance with continuous monitoring of the freeze/thaw process by ultrasound. If a flat probe was used, care had to be taken to ensure good contact between the probe and the tissue to facilitate exchange of heat. A few millimeters of the normal liver around the tumor was also frozen to ensure the completeness of cryofreezing. The time for each freezing was 15 min. After the tissue was visibly thawed the freezing and thawing cycle was repeated. Lesions that were too large to be frozen in a single application of the cryoprobe were treated by application of the probe to multiple sites, overlapping frozen areas or by the simultaneous use of two freezing units. After cryosurgery, the tract made by the cryoprobe was packed with Gelfoam or sutured surgically.

Routine perioperative medication was given (Zhou et al. 1980). Liver function, serum AFP levels and ultrasound examination and/or computed tomographic scan were monitored preoperatively and postoperatively.

Survival rates were calculated by the life-table method.

Results

The cryosurgical techniques provided a controllable and predictable area of necrosis. During the process of freezing, the white frosted appearance of the tissue gradully extended away from the side of the probe. The largest surface diameter of the frozen area was 7 cm when a 3.5-cm-diameter flat probe was used. Freezing with the flat probe produced a roughly hemispherical lesion. The freezing depth relative to the surface diameter was approximately 1:2. The largest ice ball generated using the 8-mm trocar probe was 6–7 cm in diameter (Fig. 1). IOUS was useful to guide the cryoprobe to the correct position and to monitor the freeze/thaw process. The margin of the frozen area, as the border advanced through the tumor during freezing, had a hyperechoic rim that permitted correlation of the tumor with the cryosurgical treatment. The disadvantages of the flat-probe systems were related to the fixing of the probe to the tissue during freezing. Occasionally it was difficult to obtain a good fit of the flat probe over irregular liver cancers. In addition, tumors deep within the hepatic parenchyma were impossible to freeze with surface probes that had limited-depth penetration. A single trocar cryoprobe and multiple penetrations with a single cryoprobe can solve the above problems.

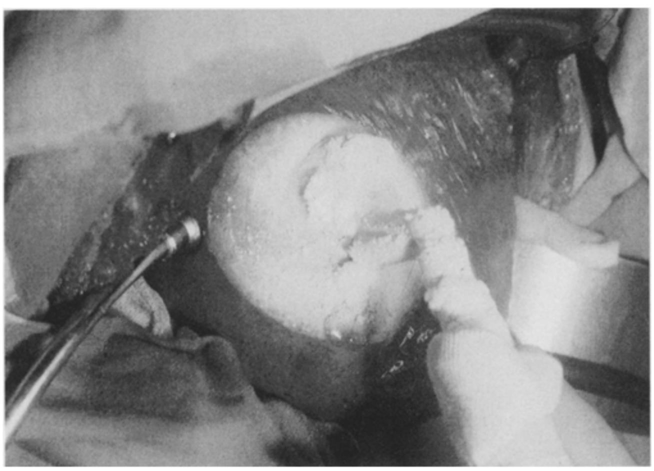

Fig. 1. The largest ice ball generated using an 8-mm-wide trocar cryoprobe is 6–7 cm in diameter

There were no operative mortalities or severe complications such as rupture of tumor, delayed bleeding or bike leakage, except one case of abscess formation after cryosurgery requiring drainage before closure. The patients had a raised temperature for several days postoperatively, but it rarely exceeded 39° C. Liver function changes after cryosurgery were not unlike those following any other minor liver procedure (Zhou et al. 1980). AFP dropped gradually postoperatively in 79.2% (61/77) of the PLC cases with abnormal preoperative AFP (above 20 ng/ml).

By the end of July 1992, the 1-, 3-, 5-, 8-, and 10-year survival rates were 65.5%, 34.9%, 22.0%, 16.4%, and 8.2%, respectively, for the 107 PLC patients, 93.3%, 66.5%, 48.8%, 34.2%, and 17.1%, respectively, for the 32 patients with PLC up to 5 cm, and 53.3%, 18.2%, 7.3%, 0%, and 0%, respectively, for the 75 patients with PLC above 5 cm. When analyzed with respect to treatment modalities without considering the size of the tumor, the 1-, 3-, 5-, 8-, and 10-year survival rates were 52.7%, 27.7%, 15.1%, 7.6%, and 0%, respectively, for the 49 PLC patients treated by cryosurgery only, 68.4%, 26.7%, 16.0%, 0%, and 0%, respectively, for the 30 PLC patients treated by cryosurgery plus hepatic artery ligation and/or perfusion, 77.8%, 33.0%, 33.0%, 33.0%, and 0%, respectively, for the 18 PLC patients treated by cryosurgery for residual tumor plus resection of the main tumor, and 100%, 80.0%, 60.0%, 40.0% and 40.0%, respectively, for the 10 PLC patients treated by cryosurgery plus resection of the frozen area.

Of the 6 patients with SLC, survival ranged from 2 months to 90 months (average, 23.2 months); 3 patients are still alive. One patient had SLC 1 year and 6 months after resection of descending colon cancer. The second operation was performed on 30 January 1985, and three tumor nodules (3 cm, 2.5 cm, and 1.5 cm in diameter respectively) were found in the bilateral lobes of the liver. Aspiration biopsy demonstrated SLC. Cryosurgery plus hepatic artery ligation and perfusion were carried out. The patients is still alive and has been well for 7 years and 6 months after cryosurgery.

Discussion

The optimal treatment of primary or metastatic liver cancer is complete surgical excision of the tumors. At present, however, the resectability is low because of multiple tumor nodules involving both hepatic lobes, coexisting advanced liver disease, or the anatomical location of the tumor close to major vessels. Conservative treatments for hepatic cancer, such as chemotherapy or radiation therapy, appear to be of limited efficacy. Therefore, we applied cryosurgery for treating unresectable hepatic cancer (Zhou et al. 1979, 1985, 1988, 1992). Cryosurgery is a treatment in which tumors are frozen and then left in situ to be reabsorbed. Cryosurgery's advantage is that it is a focal treatment, sparing more normal liver tissue than resection, thus allowing multiple lesions affecting both lobes of the liver to be treated. By piercing the liver with a trocar probe under IOUS guidance, even tumors deep within the hepatic parenchyma can be destroyed. In addition, there is some evidence that cryosurgery of a tumor has an added immunological bennefit by possibly sensitizing the patient to tumor antigens. Some reports have suggested that the distant metastases from cancer of the prostate might shrink in size in some individuals following cryosurgery (Soanes et al 1970). Regression of metastatic disease in the contralateral location has also been noted in some patients with lung cancer treated by cryosurgery (Uhlschmid et al. 1979).

Hepatic cryosurgery has been monitored in the past by thermocouples (Zhou et al. 1979, 1985). Since the tumor and the freezing margins may be irregular, the use of thermocouples to monitor only a few points is inadequate. With the advent of IOUS, the technical problems encountered in carrying out hepatic cryosurgery were solved. Not only can IOUS identify tumors in the liver better than any other modality, but stereotaxic capabilities can be used to monitor the freezing process. Onik et al. have shown that, once the cryoprobes are safely implanted within the tumor, IOUS is able to visualize the freezing as an easily identified hyperechoic rim with posterior acoustic shadowing as it encompasses the tumor margin (Onik et al. 1991). In addition, once normal live is frozen and then thawed, its ultrasound appearance changes in a characteristic way (i.e., becoming hypoechoic compared with normal unfrozen liver, documenting that the cryosurgical margin has fully encompassed the tumor) (Onik et al. 1991).

The current study suggested that cryosurgery could be safely applied to treat hepatic tumors, without any deaths or severe complications. Major vascular structures are known to be resistant to freezing injury. The common bile duct, however, probably does not fare as well. Initially, edema of the wall caused partial luminal occlusion and, several days later, stenosis developed. Out of 13 dogs, 1 died of bile peritonitis after the development of a perforation in the duct wall (Gage et al. 1967). This problem is consistent with that of Onik et al. (1991): among the 18 patients with unresectable metastatic colon carcinoma confined to the liver who were treated by cryosurgery, there was 1 case of bile duct fistula requiring percutaneous long-term drainage before closure. This complication occurred in a patient who had a large hepatic metastasis sitting at the bifurcation of the portal vein. The treatment necessitated aggressive freezing involving the confluence of the right and left hepatic ducts. Therefore, great care should be taken in treating tumors located near the hepatic hilum. The use of IOUS may allow us to stay clear of the larger-caliber bile ducts.

The current study demonstrated that long-term control of liver cancer could be achievable by cryosurgery, the 5- and 10-year survival rates being 16.3% and 8.2%, respectively, for the 107 patients with PLC, and 34.2%, and 17.1%, respectively, for the 32 patients with PLC up to 5 cm. One patients with SLC underwent cryosurgery and survived for 7 years and 6 months afterwards. However, the results of cryosurgery for hepatic tumors are not as good as those of cryosurgery for superficial solid cancers (e.g., skin, cervix, head and neck). There are several reasons. (a) There may be inadequate freezing of a large tumor because of the difficulty in overlapping the spherical regions completely even if multiple sticks were used. Thus, the cryosurgical technique should be further improved so as to extend the frozen area, and combined treatment may be required, such as cryosurgery plus absolute ethanol injection into the bases of the frozen area and the surrounding normal liver. Hepatic cryosurgery might follow the example of surgical resection, with 1-cm margins being considered adequate (Charnley et al. 1989). (b) There may be difficulty in carrying out the reoperation for further freezing since the liver is located in the abdomen. (c) The prognosis may also be influenced by the characteristics and multicentric development of these tumors.

It is concluded that cryosurgery is a safe and effective treatment for unresectable hepatic cancers. When used in the correct way for the appropriate indications, the techniques may help solve some difficult problems in the treatment of hepatic tumors.

Acknowledgement. The authors thank Mr. Xian-Peng Jiang, Liver Cancer Institute, for invaluable assistance in preparing the manuscript.

References

Charnley RM, Doran J, Morris DL (1989) Cryotherapy for liver metastases: a new approach. Br J Surg 76:1040–1041

Gage AA (1992) Cryosurgery in the treatment of cancer. Surg Gynecol Obstet 174:73–92

Gage AA, Fazekas G, Riley EE (1967) Freezing injury to large blood vessels in dogs (with comments on the effects of experimental freezing of bile ducts). Surgery 61:748–754

Kuramoto S, Kamegai T (1978) Cryosurgery for the liver tumor (abstract) Cryobiology 15:710

Onik G, Rubinsky B, Zemel R, Weaver L, Diamond D, Cobb C, Porterfield B (1991) Ultrasound-guided hepatic cryosurgery in the treatment of metastatic colon carcinoma. Preliminary results. Cancer 67:901–907

Ravikumar TS, Kane R, Cady B, Jenkins R, Clouse M, Steele G (1991) A 5-year study of cryosurgery in the treatment of liver tumors. Arch Surg 126:1520–1524

Soanes W, Ablin R, Gonder MJ (1970) Remission of metastatic lesions following cryosurgery to prostatic cancer: immunologic considerations. Urology 104:154–159

Uhlschmid G, Kold E, Largiader F (1979) Cryosurgery of pulmonary metastases. Cryobiology 16:171–178

Xie DY, Qiu JZ, Zhuang CJ, Liu BL (1983) Cryosurgery and anaerobic *Corynebacterium* vaccine in disseminated lung cancer. Report of 50 cases. Chin Med J 96:691–694

Zhou XD, Tang ZY, Yu YQ, Lu HX, Jiang ZG, Jiang YM, Shu RT (1979) Cryosurgery for liver cancer: experimental and clinical study. Chin J Surg 17:480–483

Zhou XD, Tang ZY, Yu YQ (1980) Changes in liver function and their management after resection of primary liver cancer. Natl Med J China 60:606–611

Zhou XD, Tang ZY, Yu YQ (1985) Cryosurgery for hepatocellular carcinoma. In: Tang ZY (ed) Subclinical hepatocellular carcinoma. China Academic Publishers/Springer, Beijing/Berlin, pp 107–119

Zhou XD, Tang ZY, Yu YQ, Ma ZC (1988) Clinical evaluation of cryosurgery in the treatment of primary liver cancer. Report of 60 cases. Cancer 61:1889–1892

Zhou XD, Yu YQ, Tang ZY, Weng JM, Ma ZC, Xu DB (1992) An 18-year study of cryosurgery in the treatment of primary liver cancer. Asian J Surg 15:43–47