Original article

Percutaneous CT guided Targeted Cryotherapy of Argon–helium Ultra–conductor Cryoablation System for 12 Patients with Hepatocellular Carcinoma.

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ABSTRACT The aim of this research is to study new therapeutic methods for primary and metastatic liver cancer by percutaneous cryotherapy of 12 patients with irresectable liver cancer.After localization of tumor by Computer Tomography (CT), the bougie of Argon-Helium-Cryocare surgical system was brought into the tumor under CT guidance. The bougie with 150℃below zero at the tip was placed in the tumor for 15 to 20 minutes and then we rose the temperature to 20℃ at the tip by Helium ablation. The treatment was repeated again under CT guidance.12 patients with liver cancer who received the cryotherapy. The frozen scopes were monitored by real-time CT. The values of AFP, CEA and CA199 decreased significantly after cryotherapy in major patients. Temporary low-grade fever in majority of patients and dysfunction of liver in few patients appeared and then regressed without any treatments. Chest pain appeared only in one patient after cryotherapy. All the patients got improvements in quality of life and of subjective symptoms within 30 days after cryotherapy. Argon-helium targeted cryocare surgical system has the advantages of minimally invasion, fewer side-effects and high safety. The cryotherapy shows significant therapeutic effect in short-term observation and is a new treatment of choice for patients with unresectable liver cancers to increase prognosis.

Key Words: Hepatocellular carcinoma; cryotherapy; argon-helium cryoablation system.

INTRODUCTION

Argon-helium cryoablation system is a new ultra-low temperature medical therapy transformed from American space technology. The technology destroys solid tumors by ultra-low temperature and rapid freezing with advantages of simple-operation, minimal invasion, safety and high-efficiency. This technology has already been applied in treatment of lung cancer, liver cancer, kidney cancer, prostate cancer and other solid tumors after being introduced to China in 1999[1-5]. Multiple methods are available, but type-B ultrasonic and CT which is most commonly used, were applied to guide the cryotherapy bougie into solid tumors after percutaneous puncture.[6-8] The treatments for primary and secondary advanced liver cancer of 12 patients by targeted

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percutaneous cryotherapy of argon-helium ultra-conductor cryoablation system were concluded and reported since 2006.

MATERIALS AND METHODS

Patient population and data collection

Our study was a retrospective analysis of patients who had been diagnosed pathologically as Hepatocellular carcinoma by the Department of Pathology in Zouping Traditional Chinese Medicine Hospital, between January 2006 and June 2014.12 patients including 8 males and 4 females with a median age of 58.5 years and an age range of 37-80 years accepted the therapy. Among those,there were 7 primary liver cancers and 5 metastatic liver cancers in which, 2 derived from ascending colon cancers, 1 from rectal cancer, 1 cardia cancer and 1 intestinal mesothelioma in total 12 patients. There were 8 cancers in right hepatic lobe and 4 cancers in left. Most of cases were diagnosed as multiple lesions except 3 case of single lesion with major diameters of 3cm to 10cm. The mutiple lesions with major diameter of 0.2cm to 8cm of 2 cases were distributed all over the diseased liver. The study protocol was approved by the Ethics Committee of Zouping Traditional Chinese Medicine Hospital. Informed consent was obtained from each patient prior to study enrollment at the time of hospital admission. The demographic, clinical, laboratory, and radiological data for all patients admitted or transferred to our hospital with a diagnosis of hepatocellular carcinoma were reviewed retrospectively for this study.

Diagnostic basis

The metastatic tumors were all diagnosed by pathological diagnosis after resection. The primary tumors were diagnosed by CT, Magnetic Resonance Imaging (MRI) and AFP.

Inclusion criteria

1. Secondary hepatic carcinomas with definite pathological diagnosis and primary hepatic carcinomas with definite Imaging and Hematology changes as determined by CT, MRI and AFP. 2. Diagnoses of all the 12 patients were confirmed by authentic surgeons and pathologists. After overall evaluation on lesion location, tumor size, dispersion and systemic conditions, the patients are not suggested to undergo a surgery or cannot afford to pay the cost of surgery. 3.Two patients had evident extra-hepatic metastasis. 4. Patients with large lesions in livers which can be cryoablated completely or partly to reduce tumor burden were selected.

Refrigeratory equipment: Cryocare Surgical System made by ENDOCARE co. America.

Technology and methods

1. The amount, specifications and models of cryocare surgical system bougies were selected according to the size of lesions. 2. CT localization were applied to confirm the insertion point, direction and depth of bougies. 3. The guiding steel wires and dilated tube were used for bougies whose diameters were less than 3mm to keep the catheter sheaths at preset positions in tumors. 4. The bougies were inserted along the catheters. The catheter sheaths were pulled back after that. 5. Cryocare surgical system was turned on and kept on for 8 to 15 minutes so that the temperature of bougie decreased to 150℃ below zero. 6. Argon input was stopped when frozen range expanded 0.1 to 0.3cm over the tumor margin under CT monitoring. After that helium ultra-conduction system was turned on to recover temperature to 20℃. Then the freeze-thawing cycle was repeated once. 7. The bougies were pulled back and hemostatic adhesives were used to stuff the needle tracks.

RESULTS

Special changes appeared at CT imaging after cryotherapy. A new arch enhanced zone followed by a dense mass of black shadow appeared at CT imaging between frozen tissues and non-frozen tissues along formation of the frozen ball at bougie tip. An expanding rounded frozen zone centred around the bougie of cryocare surgical system appeared with freezing going on and was well defined compared to non-frozen zone (Fig.1-1~3). Under the monitoring for black shadow expansion, we can confirm the size and coverage of frozen ball and then judge that if the tumor is embraced by frozen ball.(Fig.1-3)l The liver CT imaging of our cases showed low density shadows whose densities were lower than that before cryotherapy in lesion, 1 week after the cryotherapy. No changes of tumor size were shown according to liver CT imaging 1 month after cryotherapy. For example, A woman with severe liver cancer, after argon-helium cryoablation surgery was followed up for 3 years, still lives a normal life. (Fig.2-1~2) The values of AFP in 3 cases of primary liver cancers changed from 490ng/ml, 389ng/ml and 267ng/ ml to 138ng/ml, 126ng/ml and 87ng/ml respectively 15 days after cryotherapy. As shown above, the decreases of AFP values are very significant. The values of AFP in 2 cases of prime liver cancer decreased slightly from 128ng/ml and 109ng/ml to 106ng/ml and 89ng/ml respectively 1 month after cryotherapy while no evident changes of the other 2 cases were shown. The CEA values of 9 cases decreased after cryotherapy compared with high CEA values before cryotherapy. The CEA values of 3 cases showed no significant changes between before and after cryotherapy. Other changes: temperatures of most patients usually rose up to 37 to 38

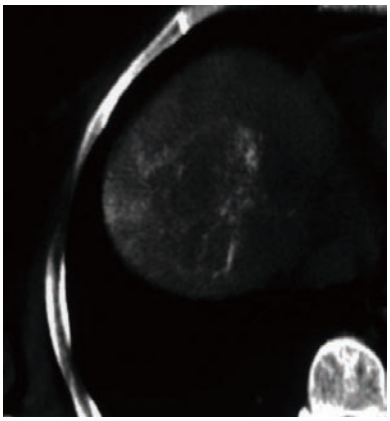

Fig.1.1Tumor image of liver before surgery.

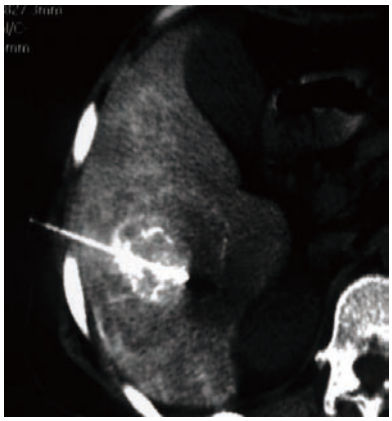

Fig.1.2 The image in the argon–helium cryoablation surgery.

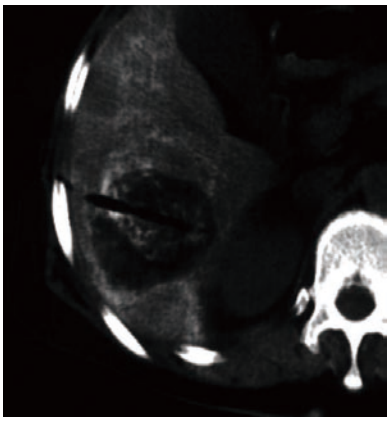

Fig.1.3The image after the argon–helium cryoablation surgery.

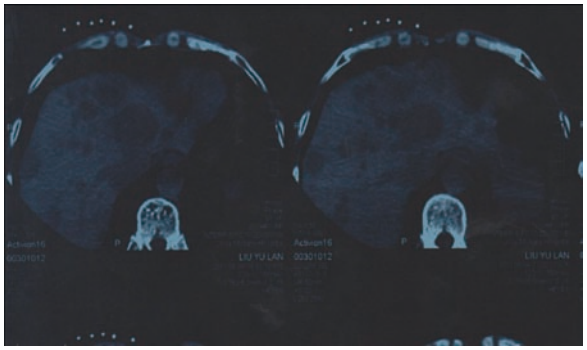

Fig. 2.1. Whole liver occupied by a cancer invasion, and a number of tumor mass distribution in the left lobe is very obvious.

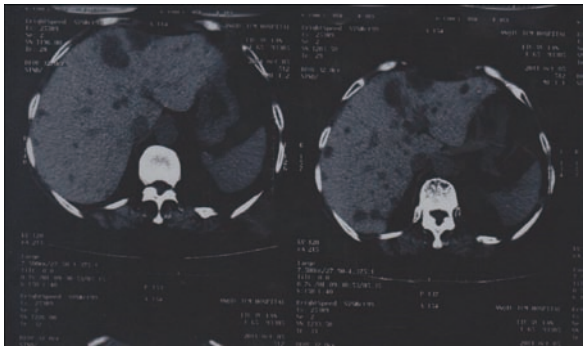

Fig. 2.2. After 2 years of Cryotherapy and traditional Chinese medicine treatment, strengthen CT showed that hepatic tumor, the former has improved markedly. And survival with tumor, with follow–up 3 years, patients have a normal life.

℃, with some to 38.5℃ 1 days after cryotherapy, and lasted for 3 to 5 days and spontaneously regressed. Some of patients suffered transient liver dysfunction and recovered spontaneously after 1 to 2 weeks. 2 patients suffered hematochezia on the 5th and 7th day respectively after cryotherapy and recovered after hemostasis treatments. The symptoms of most patients, such as asthenia and inappetence, improved more or less after cryotherapy and the quality of life improved significantly as compared with that before cryotherapy.

DISCUSSION

Occurrence and development of tumor in human are closely related to the immune function of the patients. The anti-tumor immunity is mainly depended on cellular immunity, among which T cells and NK cells are extremely important [1]. CD4+ and CD8+ represent two main subsets of T cells, both of which maintain a dynamic balance in normal circumstances. If this balance is broken because of changes in quantity, the cellular immune function would be disrupted. The patients with malignant tumors usually have different degrees of immune dysfunction. Various immune functions keep interaction each other during the development of tumor, and influence the development and prognosis of the disease[2]. The decreases in CD3+ T cells, CD4+ T cells and CD4+/CD8+ and the increase of CD8+ in our study were the significant characteristics in patients with endometrial cancer, which suggested that there is a relation between T cell subsets and endometrial cancer, which is consistent with the study of Yin FB [3]. The reasons of CD4+/CD8+ decreased is the reduction of CD4+cells or increase of CD8+cells, which maybe due to the reduction of TH cells and increase of TS cells. The negative regulatory effect is greater than the positive regulatory, which maybe lead to the reduction of lymphocyte immune function in patients with endometrial cancer.

NK cells have the following characteristics of immunology: dissolving target cells without allergy; abundant immunoglobulin fragments receptor; appearing in monocytes around; a large number of azurophilic granules in the cytoplasm. These characteristics make it have an important function of immune

surveillance, which play an important role in the human anti-tumor immunity and prevent tumorigenesis [4]. Our data showed that the activity of NK cells in patients with endometrial cancer is significantly lower than that in healthy control, which is the same as that in other tumor reported. The reasons are possibly related with the following factors: consumption of a large number of NK cells during killing tumor cells; secreting some kind of inhibition or a closed agent from tumor cells; redistribution of NK cell in the blood.

CONCLUSSION

The argon-helium ultra-conductor cryoablation system manufactured by ENCOCARE Co. makes use of abrupt argon explosion at the bougie point to freeze lesion to -150℃ in 90 seconds. It can also make use of helium to unfreeze and heat the frozen bougie. The ultra-conductor cryoablation system can freeze liver cancer tissue via percutaneous puncture without hurting tissue around the bougie passage. It has the advantages of minimally invasion, simple operation, non -toxic and side-effect free, and is beneficial to clinical promotion for its acceptance among patients. Real-time CT is used to monitor operation progress, and thus the argon-helium ultra-conductor cryoablation system has reached a new therapeutic level in liver cancer treatment. Obviously, the new therapy has changed the desperate status of advanced-stage liver cancer, and has become the prime therapy for middle-stage and advanced-stage liver cancer, and of-course for early stage as well, As for patients that can be operated on, the argon-helium ultra-conductor cryoablation system is a choice with better effects and higher survival rate. The cryotherapy for liver cancer uses rapid ultralow temperature freezing and ablation to damage and apoptosis of cancer cells. It involves three steps, ultra-low temperature, freezing, and ablation. The lowest temperature, freezing speed, freezing time and freezing-ablation repetition are 4 factors to decide the damage and apoptosis of cancer cells. The basic factor of cell apoptosis is tissue temperature. Cell damages often occur at -20℃ to -30℃, and some cancer cell apoptosis occur at -40℃ to -50℃. The ultralow temperature causes ice crystals in cytoplasm, and the freezing process crystallizes tissue cells. Then the rapid ablation causes abrupt explosion of the crystals in cancer cells, and leads to apoptosis of cells with broken cell membranes [9], which stay in the tissue to form antigens, which can further induce antibodies to cooperate with T lymphocyte to further kill cancer cell residue. This is the so-called "after-treatment immunity effect"[10, 11]. The advantages of ultra-temperature cryotherapy include clear tissue damage edge, even and total apoptosis of cancer cells within freezing area, and real-time CT or type-B ultrasonic monitor for the location of bougie and size of frozen area. In accordance with our experiment, blood vessels with diameter larger and 4.0 mm are rarely damaged by freezing because of blood pool effect, and thus it can be applied to cases in which tumors cannot be resected because of nearby great vessels. The liver cancer therapy of argon-helium ultra-conductor cryoablation system via percutaneous puncture causes smaller trauma and less bleeding to patients, who are then able to leave hospital earlier because of quicker recovery, so that the medical expenses of patients are reduced relatively. Therefore, it is widely applied to primary and secondary liver cancers which cannot be operated on [12]. We believe that the complicating disease rate of argon-helium ultra-conductor cryoablation system in liver cancer treatment has already become very low with the development of the therapy. It is reported that most researches show that the cryotherapy of liver cancer has higher safety performance and lower complicating disease rate. Complications are mostly related to over-freezing, and mainly involve pleural effusion, myoglobinuria, bleeding, bile leak, and liver abscess [13,14]. The 7 patients in this article all suffered from transient fever, which is considered as reactive fever caused by the stimulation or absorption of frozen tissue. 3 patients suffered from short-term liver function dysfunction, which can be found in similar reports [15], so that liver treatment should be undertaken after cryotherapy of liver cancer. The 2 cases with bleeding after treatment are both patients with cirrhosis and portal vein high pressure, and selection of such patients should be cautious. According to our experience in freezing-ablation treatment, the ultralow freezing treatment of liver cancer is not only applied to some middle and advanced-stage cases which cannot be resected by operation, but also considered as the prime therapy for patients unwilling to take operations [16].

In Conclusion, the argon-helium ultra-conductor cryoablation system for liver cancer has the advantages of minimally invasion, easy operation, radiation and toxic free procedure. It can be better accepted by patients, and is beneficial to clinical promotion. It has better treatment effects, longer survival period, higher safety performance and lower complicating disease rate comparing with surgical operation. It is believed that the ultralow temperature treatment of liver cancer is not only applied to some middle and advanced-stage cases which cannot be resected by operation, but also considered as the prime therapy for patients unwilling to take operations.

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