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ABOUT COVER

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Cryoablation combined with radiotherapy for hepatic malignancy: Five case reports

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Abstract

BACKGROUND

The survival of patients treated with monotherapy for hepatic malignancies is not ideal. A comprehensive program of cryoablation combined with radiotherapy for the treatment of hepatic malignancies results in less trauma to the patients. It may provide an option for the treatment of patients with advanced hepatic malignancies.

CASE SUMMARY

We reported 5 cases of advanced-stage hepatic malignancies treated in our hospital from 2017-2018, including 3 cases of primary hepatocellular carcinoma and 2 cases of metastatic hepatic carcinoma. They first received cryoablation therapy on their liver lesions. The procedure consisted of 2 freeze-thaw cycles, and for each session, the duration of freezing was 13-15 min, and the natural re-warming period was 2-8 min. Depending on the tumor size, the appropriate cryoprobes were selected to achieve complete tumor ablation to the greatest extent possible. After cryoablation surgery, intensity-modulated radiotherapy (IMRT) for liver lesions was performed, and the radiotherapy regimen was 5400 cGy/18f and 300 cGy/f. None of the 5 patients had adverse events above grade II, and their quality of life was significantly improved. Among them, 4 patients were free of disease progression in the liver lesions under local control, and their survival was prolonged; 3 patients are still alive.

manuscript.

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CONCLUSION

Our clinical practice demonstrated that cryoablation combined with IMRT could be implemented safely. The definitive efficacy for hepatic malignancies needs to be confirmed in larger-size sample prospective studies.

Key words: Hepatic malignancies; Primary hepatocellular carcinoma; Metastatic hepatic carcinoma; Cryoablation; Intensity-modulated radiotherapy; Case report

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Core tip: The therapeutic efficacy of monotherapy for primary hepatocellular carcinoma (HCC) and secondary HCC is usually poor, and thus, combination therapy is needed. A treatment plan of cryoablation combined with radiotherapy is safe and effective and may result in survival benefits to patients.

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INTRODUCTION

Hepatic malignancies include primary hepatocellular carcinoma (HCC) and secondary hepatocellular HCC^[1]. Primary HCC is one of the most common malignancies seen in clinical practice. Hepatic resection and orthotopic liver transplantation are considered radical treatments for HCC, while surgery is the first-line treatment for primary HCC. In China, most patients with HCC also have liver cirrhosis, and most have already reached the intermediate or advanced stages of HCC at the time of diagnosis; moreover, only approximately 20%-30% of patients have an opportunity for hepatic resection. Currently, sorafenib is one of the standard drugs used to treat advanced-stage HCC, but the median overall survival rate is only 6.5 mo^[2]. Additionally, the liver is one of the most common sites for metastatic tumors. When a tumor has metastasized to the liver, the patient is already at an advanced stage and has a poor prognosis. Currently, the treatment effect on such patients is not ideal, and new local and systemic treatments are needed. Local ablation therapy, which has been widely utilized in recent years, is associated with less trauma and definite therapeutic effect, which offers the opportunity of radical treatment to some patients with hepatic malignancies who cannot or who are unable to tolerate hepatic resection.

Local ablation therapy directly targets tumors under the guidance of medical imaging technology. This is a treatment method that directly kills tumor tissue by local adoption of physical or chemical methods. It mainly includes radiofrequency ablation (RFA), microwave ablation, cryoablation, high-intensity focused ultrasound (HIFU) ablation, and percutaneous ethanol injection, among others. Among them, cryoablation has been increasingly applied to the local ablation of hepatic malignancies due to its advantages such as causing minimal damage to the great vessels, low incidence of pain, and controllable iceball formation.

The principle of cryoablation is based on the gas throttling effect (Joule-Thomson principle)^[3], which states that after a high-pressure gas flows through a small orifice, it expands rapidly in the expansion space and absorbs the surrounding heat; this significantly reduces the surrounding temperature. Therefore, the physical destruction of tumor tissue and cells is achieved through freeze-thaw cycles. The mechanisms of cryoablation can be divided into freezing damage, thawing damage, microvascular damage, and immunomodulatory mechanisms. Generally, it is thought that the threshold temperature that induces cell death is -40 °C^[4]. After repeated freeze-thaws of tumor cells, the cells burst and the cell membrane dissolves, which promotes the release of hidden antigens in the cell and stimulates the body to produce antibodies. With the death of tumor cells, the immunosuppressive state of the tumor on the body is removed. Therefore, the body's anti-tumor immunity is enhanced, and the immune-destroying effect on the tumor cells is activated.

To achieve complete and sufficient targeted tumor destruction, the tumors were frozen until the iceball extended approximately 3-5 mm beyond the tumor margin, which can be accurately monitored by imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI)^[5-6].

The Asia-Pacific clinical practice guidelines for the treatment of primary HCC recommends the following^[7]: Local ablation is suitable for Child-Pugh class A or B patients with 3 or fewer tumors, each 3 cm or less in diameter. RFA is the first-line image-guided percutaneous ablation technique that is recommended. Many studies have shown that for the local ablation of primary HCC, cryoablation is as effective as RFA. A multicenter randomized controlled trial of 360 patients with primary HCC showed that for lesions less than or equal to 4 cm and lesions less than or equal to 2 cm, both cryoablation and RFA achieved similar therapeutic effects^[8]. The 1-, 3-, and 5-year overall survival rates were 97%, 67%, and 40% for cryoablation, respectively, and 97%, 66%, and 38% for RFA, respectively ($P = 0.747$). The 1-, 3-, and 5-year tumor-free survival rates were 89%, 54%, and 35% in the cryoablation group, respectively, and 84%, 50%, and 34% in the RFA group, respectively ($P = 0.628$). A recent meta-analysis compared the therapeutic efficacy of cryoablation and RFA in patients with hepatic malignancies and 7 articles that met the inclusion criteria were included^[9]. The meta-analysis showed an almost equal mortality of at least 6 mo, and no significant difference was observed in local tumor progression between the 2 groups. The studies discussed above showed that the therapeutic efficacy of cryoablation and RFA was similar for early-stage primary HCC.

Cryoablation is also one of the major therapies for unresectable HCC. In 2003, Xu *et al*^[10] reported the use of cryoablation in 105 masses from 65 patients with HCC. Among the 41 patients who were followed-up for more than 1 year, 32 patients (78%) were alive despite tumor recurrence, 7 patients (10.8%) died due to disease recurrence, and 3 patients (5%) died of non-cancer-related diseases. Chen *et al*^[11] applied cryoablation to treat unresectable HCC and found that the 1- and 3-year overall survival rates were 81% and 60%, respectively, while the 1- and 3-year disease-free survival rates were 68% and 21%, respectively. The 1- and 3-year overall survival rates of patients with recurrent HCC were 70% and 29%, respectively, while the 1- and 3-year disease-free survival rates were 54% and 8%, respectively.

Similarly, cryoablation is also effective for metastatic hepatic tumors. Chang *et al*^[12] reported that for the 19 patients who underwent cryoablation for liver metastases after gastrectomy for primary gastric cancer, the median overall survival was 16.0 mo, the median local tumor progression-free survival was 8.0 mo, and the 1-, 2-, and 3-year overall survival rates were 78.9%, 43.4%, and 21.7%, respectively. The patients' quality of life also improved after cryoablation therapy ($P < 0.05$) and no severe complications occurred. In summary, cryoablation is suitable for both primary and secondary HCC and is safe and effective for the treatment of advanced-stage hepatic malignancies.

Intensity-modulated radiation therapy (IMRT) technology has become increasingly advanced and can simultaneously effectively protect normal hepatic tissue and deliver a high dose of radiation to the targeted area of HCC to improve therapeutic efficacy; this confirms the status of radiotherapy in the treatment of HCC^[13,14].

The application of radiotherapy in the comprehensive treatment of HCC has gradually increased, especially for further improvement of poor efficacy after local treatment [for example, after transcatheter arterial chemoembolization (TACE)] or to target residual tumor at the margins of lesions. Radiotherapy can improve therapeutic efficacy of unresectable primary HCC treatment, improve the local control, and at the same time, effectively protect normal hepatic tissue and improve patient prognosis^[13].

Radiotherapy causes irreversible damage to the DNA of tumor cells in the irradiation field and induces tumor cell death through apoptosis, necrosis, and autophagy, among other mechanisms^[15,16]. It also promotes the release of tumor-related antigens^[17], increases the production of cytokines, alters the tumor microenvironment, and activates the body's immune system to initiate an anti-tumor immune response. Postow *et al*^[18] proposed the "Abscopal Effect", that is, a phenomenon related to local radiotherapy and the regression of metastatic cancer distant from the radiation site, which may be related to activation of the immune system. The mechanism of action may be that radiotherapy induces tumor cells to release a large amount of antigen in a short period of time; T lymphocytes are then activated after APC presentation and activated T lymphocytes (cytotoxic lymphocytes) can then act on primary and metastatic tumor cells.

Studies have shown that cryotherapy can sensitize dendritic cells to enhance their antigen presenting ability and promote their secretion of IL-4, IL-12, and other cytokines; cryoablation can also promote T and B cell proliferation and activation and can induce the body's immune system to play an anti-tumor role. Sidana *et al*^[19] proposed the model of cryoimmunotherapy, that is, cryotherapy combined with other

immunotherapy treatment to enhance the immunostimulating response. While cryoablation controls the primary tumor, it also enhances the body's anti-tumor immune response to effectively control tumor recurrence and metastasis.

The results of the study by Mu *et al*^[20] showed that the therapeutic efficacy of combination therapy of cryoablation and chemotherapy drugs for patients with advanced HCC was significantly better than that of cryoablation alone. The overall survival rate of the patients increased significantly. In addition, the overall survival rate of patients with early use of the combined multiple treatment plan was significantly better than that of patients who used monotherapy or who delayed the use of combination therapy. Studies have shown that cryoablation combined with immunotherapy could improve the median survival duration of patients and can play an anti-tumor role. This suggests that cryoablation combined with multiple other therapies can achieve fair therapeutic efficacy. Radiotherapy can activate the immune system, and hence, it has an anti-tumor function. In theory, cryoablation combined with IMRT may have a synergistic effect to enhance efficacy.

The effective freezing range of cryoablation should be 1 cm beyond the margin of the tumor^[21], that is, the surgical resection margin. In theory, all tumor tissues can be inactivated with no remaining residual tumor cells. Only through this method can significant efficacy be achieved. However, in clinical practice, cryoablation therapy may not be able to inactivate all tumor cells due to the tumor location, insertion pathway, the tumor blood supply and surrounding great vessels, and many other factors. Therefore, residual tumor cells can easily appear around the formed iceball. The postoperative supplementary treatment can effectively kill the minimal residual lesions and improve therapeutic efficacy.

IMRT can effectively solve the problem of residual tumor that forms around the iceball after cryoablation therapy. For tumor tissues with an abundant blood supply, residual tumor may be present after cryoablation. Therefore, IMRT administration at this time can effectively kill the residual tumors. IMRT is therefore a beneficial supplement after cryoablation. It is well known that hypoxic cells comprise a high proportion of tumor cells in the tumor center and that they are resistant to radiotherapy, while cryoablation can effectively kill the central area of the tumor that is relatively abundant with anaerobic cells. Therefore, cryoablation combined with IMRT may play a synergistic and complementary role, which could improve the local control rate of liver lesions. To the best of our knowledge, cryoablation combined with IMRT is rarely reported, and for the first time, we report the clinical cases of this combination therapy.

CASE PRESENTATION

Case 1

Chief complaints: We treated a 59-year-old male patient with liver metastases from colon cancer.

History of present illness: The patient underwent radical resection of colorectal cancer in December 2014. Postoperative pathology: Differentiated adenocarcinoma of the colon and liver metastasis were found after surgery. The XELOX chemotherapy regimen was administered for 4 cycles. Resection of the liver metastasis was performed on April 2, 2015. In July 2016, the carcinoembryonic antigen (CEA) level was elevated and new metastatic lesions were observed in the liver. In August 2016, TACE was performed for 1 cycle, and 8 cycles of capecitabine monotherapy were given, followed by stable efficacy evaluation. On May 25, 2017, the left hepatic lobe containing the metastatic tumor grew larger, and the disease progressed. Hepatic arteriography + chemoembolization was performed once, FOLFOX4 chemotherapy was given for 1 cycle and FOLFIR chemotherapy was given for 3 cycles, and the disease progressed again after second-line treatment. On August 29, 2017, hepatic arteriography + embolization was performed once.

History of past illness: There was no significant past medical history or family history of malignancy.

Physical examination upon admission: Physical examination of the patient showed no apparently positive signs.

Laboratory examinations: CEA 246.14 ng/mL, sugar antigen 19-9 128.02 U/mL.

Imaging examinations: The metastatic lesion in the left lobe of the liver was larger than that after the previous treatment.

Case 2

Chief complaints: We treated a 45-year-old male patient with primary HCC with hepatic metastatic and formation of a right branch of the portal vein.

History of present illness: In March 2014, the patient was diagnosed with primary HCC, which was located near the great vessels and could not be surgically resected. TACE was performed twice in March 2014 and on April 14, 2014, and HIFU ablation was performed on May 11, 2014. The third TACE treatment was performed in June 2014, and in July 2014, liver radiotherapy was performed 16 times with a total radiation dose 4800 cGy/16f. On May 17, 2017, new liver lesions were found with an increased alpha-fetoprotein (AFP) level of 888 IU/mL. The patient underwent liver CT on July 24, 2017, which revealed right hepatic cancer and right portal vein thrombi formation. Therapeutic efficacy evaluation: Disease progression.

History of past illness: This patient had a history of hepatitis B-associated cirrhosis for 20 years and was untreated. A history of hypertension for 5 years.

Physical examination upon admission: The patient had hepatic tenderness.

Laboratory examinations: On May 17, 2017, Alpha fetoprotein increased to 1000IU/mL (upper limit of detection value in our hospital).

Imaging examinations: On July 24, 2017, liver enhanced CT scan: Right HCC, right portal vein thrombus formation.

Case 3

Chief complaints: A 41-year-old female diagnosed with primary HCC.

History of present illness: On March 16, 2017, right lobe liver cancer was diagnosed by both liver MRI and CT with an AFP level of 259IU/mL. Two TACE treatments were performed on April 1, 2017, and May 11, 2017.

History of past illness: This patient had a history of hepatitis B-associated cirrhosis for 10 years and was untreated.

Physical examination upon admission: Physical examination of the patient showed no apparently positive signs.

Laboratory examinations: On July 25 2017, Alpha fetoprotein was 22.34 IU/mL.

Imaging examinations: Enhanced abdominal CT suggested that the lesion at the top of the right lobe of HCC changed after interventional surgery.

Case 4

Chief complaints: A 61-year-old male diagnosed with primary HCC, with multiple liver metastases, cirrhosis, and ascites.

History of present illness: On December 20, 2015, he diagnosed with primary HCC by MRI and CT, with multiple liver metastases, cirrhosis, and ascites. TACE was performed 4 times on December 9, 2015, January 18, 2016, February 14, 2016, and May 17, 2016. Hepatic encephalopathy occurred on November 11, 2016, and improved after treatment. TACE was given 4 times successively on February 9, 2017, May 4, 2017, June 14, 2017, and August 21, 2017.

History of past illness: This patient had a history of hepatitis B-associated cirrhosis for more than 20 years and was untreated.

Physical examination upon admission: Physical examination of the patient showed no apparently positive signs.

Laboratory examinations: On August 17, 2017, Alpha fetoprotein increased to 376.47 IU/mL and saccharide antigen 19-9 was 62.38 U/mL.

Imaging examinations: Abdominal CT showed postoperative changes of lesions in the right lobe of the liver, cirrhosis, portal hypertension, and open abdominal collateral vessels.

Case 5

Chief complaints: A 61-year-old female was diagnosed with Spinal canal invasion after thoracolumbar fibrosarcoma surgery (T12L1) multiple intrahepatic metastasis.

History of present illness: On December 13, 2014, the patient underwent posterior

lumbar laminectomy for intraspinal tumors (extramedullary subdural) and adnexal tumors. Local tumor recurrence occurred 3 mo after surgery, and the tumor at the recurrence site was controlled after three-dimensional conformal radiotherapy and HIFU ablation. MRI findings on May 15, 2017: New metastatic lesions in the liver. Ultrasound-guided liver space occupying biopsy pathology (May 26, 2017, pathology no. 1901664): Consistent with fibrosarcoma metastasis to the liver; the disease had progressed again. Three TACE treatments and HIFU ablation of the metastatic liver lesions were given. Therapeutic efficacy evaluation: Stable. On January 5, 2018, the patient was reexamined by enhanced CT: A rich blood supply was observed around the liver metastatic lesions, which was indicative of tumor recurrence. TACE treatment was performed once on January 17, 2018. However, no further treatment was given due to personal reasons. Reexamination of upper abdominal MRI + enhancement in June 2018: Progression of liver metastasis.

History of past illness: This patient had a history of hypertension for 12 years.

Physical examination upon admission: Physical examination of the patient showed no apparently positive signs.

Laboratory examinations: The serum chemistries and complete blood count was normal.

Imaging examinations: MRI scan of liver suggested the progression of liver metastases.

FINAL DIAGNOSIS

Case 1

Radical resection of colon cancer with multiple hepatic metastases.

Case 2

(1) Primary HCC with hepatic metastasis of portal vein thrombus formation; (2) Decompensated period of cirrhosis after chronic viral hepatitis Band; and (3) Hypertension.

Case 3

(1) Primary HCC; and (2) Chronic viral hepatitis band liver cirrhosis with an enlarged spleen.

Case 4

(1) Primary HCC with multiple intrahepatic metastasis; and (2) Decompensated period of cirrhosis after chronic viral hepatitis Band, Celiac effusion, hepatic encephalopathy.

Case 5

(1) Spinal canal invasion after thoracolumbar fibrosarcoma surgery (T12L1) multiple intrahepatic metastasis; and (2) Hypertension.

TREATMENT

Case 1

On September 19, 2017, hepatic metastatic tumor cryoablation was performed. Before the procedure, a raster and spiral CT was used for guidance and localization. After determining the insertion point and insertion angle, routine sterilized drape was used in the operative area. Two cryoprobes 2.4 mm in diameter were selected and inserted at the predetermined location on the lesion under CT guidance, and then cryotherapy was initiated. Two freeze-thaw cycles were used in the cryotherapy process. Freezing occurred for 15 min during the first cycle, which was followed by natural rewarming for 2 min; freezing occurred for 15 min during the second cycle. No adverse events (AEs) such as pneumothorax and hemorrhage were encountered during the surgery. From October 25, 2017, IMRT for metastatic liver tumors was performed. Radiotherapy regimen: 5400 cGy/18f and 300 cGy/f.

Case 2

On July 25, cryoablation for the hepatic liver lesion was performed: 2 cryoprobes 1.7 mm and 2.4 mm in diameter were selected and inserted at the predetermined location

on the lesion under CT guidance, and then cryotherapy was initiated. Two freeze-thaw cycles were performed in the cryotherapy process. Freezing occurred for 15 min during the first cycle, which was followed by natural rewarming for 8 min; freezing occurred for 15 min during the second cycle. The surgery went well and only a small degree of pneumothorax occurred. On September 24, 2017, HIFU ablation of the right portal vein thrombi was performed. On October 17, 2017, liver lesion radiotherapy was initiated with a total dose of radiotherapy of 5400 cGy/18f and 300 cGy/f.

Case 3

On July 25, 2017, cryoablation of the hepatic lesions was performed under local anesthesia: 2 cryoprobes 1.7 mm and 2.4 mm in diameter were selected and inserted at the predetermined location on the lesion under CT guidance, and then cryotherapy was initiated. Two freeze-thaw cycles were used in the cryotherapy process. Freezing occurred for 15 min during the first cycle, which was followed by natural thawing for 8 min; freezing occurred for 15 min during the second cycle. The surgery went smoothly, and only a small degree of pneumothorax occurred. On September 5, 2017, she began radiotherapy for the lesion in the right lobe of the liver. Radiotherapy regimen: 5400 cGy/18f and 300 cGy/f. The radiotherapy was completed on September 28, 2017.

Case 4

Cryoablation of hepatic lesions was performed on September 3, 2017: 4 cryoprobes 2.4 mm in diameter were selected and inserted at the predetermined location on the lesion under CT guidance, and then cryotherapy was initiated. Two freeze-thaw cycles were used in the cryotherapy process. Freezing occurred for 15 min during the first cycle, which was followed by natural thawing for 8 min; freezing occurred for 15 min during the second cycle. The surgery went smoothly, and a small degree of pleural effusion was observed on the right side. On October 24, 2017, this patient began radiotherapy for the hepatic lesion. Radiotherapy regimen: 5400 cGy/18f and 300 cGy/f. The radiotherapy was completed on November 26, 2017.

Case 5

Cryoablation of the hepatic tumor was performed on July 5, 2018: 2 cryoprobes 1.7 mm in diameter were selected and inserted at the predetermined location on the lesion under CT guidance, and then cryotherapy was initiated. Two freeze-thaw cycles were used in the cryotherapy process. Freezing occurred for 13 min during the first cycle, which was followed by natural rewarming for 5 min; freezing occurred for 13 min during the second cycle. The surgery was performed without incident. On August 6, 2018, radiotherapy of the liver lesions was initiated. Radiotherapy regimen: 5400 cGy/18f and 300 cGy/f; radiotherapy ended on August 30, 2018.

OUTCOME AND FOLLOW-UP

Case 1

CEA decreased to 126.63 ng/mL, and carbohydrate antigen 19-9 decreased to 76.62 U/mL. Postoperative oral monotherapy (tegafur chemotherapy) was administered for 1 cycle. Reexamination on June 2018: The lesions treated by cryoablation had no blood supply, but new liver lesions were observed. Overall evaluation: Disease progression.

On June 29, 2017, radioactive iodine-131 seed implantation was performed. On October 29, 2018, a new bone metastasis was found, and on November 6, 2018, TACE was performed. Clinical death occurred on March 13, 2019. The local control duration of the hepatic lesions was 17 mo and clinical death occurred 18 mo after cryoablation therapy.

Case 2

On April 14, 2018, a new pulmonary metastasis was found at reexamination and the disease was in progression. On April 25, 2018, pulmonary interventional perfusion chemotherapy (TAE) was performed once, and on June 10, 2018, cryoablation was performed on the lesion in the right lung. On June 22, 2018, new lesions were found in the periphery of the hepatic lesion treated with cryoablation. Evaluation: Disease progression. Death occurred on September 16, 2018. The local control time of the hepatic lesion was 11 mo, and clinical death occurred 14 mo after cryoablation therapy.

Case 3

AFP dropped to normal and she began treatment with oral entecavir (an anti-viral treatment) from September 28, 2017. She now lives a normal life and is still alive. The

liver lesion has been under control for 20 mo.

Case 4

Alphafetoprotein decreased during follow-up. He began treatment with oral entecavir (an anti-viral treatment) from November 26, 2017. After treatment, he lived completely independently and is still alive. The liver lesion has been controlled for 19 mo.

Case 5

Reexamination in October 2018: Liver cryoablation lesions were stable, but lesions in both lungs were increased. Overall evaluation: Disease progression. Oral treatment of anlotinib was given, and the Karnofsky Performance Score (KPS) was 80. After cryoablation therapy, the patient lived independently and is still alive. The liver lesion treated with cryoablation has been controlled for 9 mo.

A summary of each patient was shown on [Table 1](#).

DISCUSSION

Most patients have already reached the intermediate or advanced stages of HCC at the time of diagnosis, and therefore, they lose the opportunity for radical surgery. In China, 85%-90% of liver cancer occurs as a result of post-hepatitis cirrhosis, and many patients cannot tolerate surgery. At the same time, the liver is also a common target organ for metastasis of some malignant tumors, such as colorectal cancer, breast cancer, pancreatic cancer, melanoma, and renal cancer, among others. Due to multiple metastatic lesions, the surgical resection rate is low, and the therapeutic effect is dismal.

Cryoablation has the characteristics of rapid rewarming, cold temperature freezing, and reversal of hot and cold. It can rapidly reduce the temperature of lesioned tissue to $-140\text{ }^{\circ}\text{C}$ with argon gas, which causes rapid freezing of the lesion site^[1]. Then, it eliminates the lesion using heat *via* rapid thawing with helium gas. This type of therapy has advantages in destroying cancer cells while effectively preserving normal hepatic tissues; this therapy is also associated with a quick recovery, minimal trauma, and high reproducibility and is also simple to perform^[3].

Rong *et al*^[22] selected 866 patients with primary HCC who met the Milan criteria (single lesions less than or equal to 5 cm, multiple lesions less than or equal to 3 cm, and each lesion was less than or equal to 3 cm) for cryoablation. The complete ablation rate reached 96.1%, and the postoperative 1-, 3-, and 5- year survival rates were 98.6%, 80.6%, and 60.3%, respectively, but the corresponding local recurrence rates were 10.7%, 22.1%, and 24.2%, respectively. Yang *et al*^[23] treated 300 primary HCC patients with cryoablation therapy, after which the therapeutic efficacy, safety, and complications were evaluated. In all, 165 of the patients had incomplete ablation, while 135 had complete ablation. The median follow-up time was 36.7 mo. For the patients with early-, intermediate-, and advanced-stage HCC, the postoperative 1-, 2-, and 3-year survival rates were 91%, 85%, and 65%, respectively, for early-stage HCC, while the rates were 87%, 62%, and 45%, respectively, for intermediate-stage HCC; the rates were 73%, 25%, and 12%, respectively, for advanced-stage HCC. The median survival duration for patients with early-, intermediate-, and advanced-stage disease was 45.7 ± 3.8 mo, 28.4 ± 1.2 mo and 17.7 ± 0.6 mo, respectively. One study included 124 primary HCC patients treated with cryoablation^[24], including 16 with early-stage disease, 42 with intermediate-stage disease, and 66 with advanced stage disease. After cryoablation of the tumors, the serum level of AFP was reduced in 76 (82.6%) patients, and 205 (92.3%) of the 222 tumor lesions were diminished or unchanged. The median survival time was 31.3, 17.4, and 6.8 mo for those in the early, intermediate, and progressive stages, respectively. The above studies indicate that cryoablation is an effective treatment for both early-, intermediate-, and advanced-stage primary HCC.

Qian *et al*^[25] reported 1-year survival rates of 80% and 46% for 34 patients with secondary and recurrent HCC, respectively, treated with cryoablation therapy. Littrup *et al*^[26] performed cryoablation on a total of 370 tumors in 176 patients with metastatic liver cancer, with an average follow-up time of 1.8 years. The local tumor recurrence rates of colorectal cancer and non-colorectal cancer with liver metastasis were 11.1% and 9.4%, respectively. The average time to local recurrence of liver metastasis was 9.5 mo for colorectal cancer and 7.9 mo for non-colorectal cancer. Another study^[27] with the results of long-term follow-up also confirmed that cryoablation was a safe and effective ablation technique for patients with liver metastases from colorectal cancer. In this study, 304 patients with liver metastases from advanced colorectal cancer were treated with cryoablation. 293 of them were analyzed. The median overall survival time was 29 mo, and the survival rates of 1, 3, 5 and 10 years were 87% 41.8%, 24.2%,

Table 1 Summary of patients

Case	Sex	Age (yr)	Final diagnosis	Treatment options before cryoablation	Cryoablation + radiotherapy		Continue treatment	Follow-up time (mo)	Local control time (mo)	Survival
					Cryoablation	Radiotherapy				
1	M	59	Radical resection of colon cancer with multiple hepatic metastases	Disease was progressive after third-line treatment for liver metastasis after colon cancer surgery	2 cryoprobes, total treatment time: 31 min	5400 cGy /18f, 300 cGy/f	Chemotherapy, radioactive iodine-131 seed implantation	18	17	No, died on March 13, 2019
2	M	45	Primary hepatocellular carcinoma with hepatic metastasis of portal vein thrombus formation	Disease was progressive after first line treatment	2 cryoprobes, total treatment time: 38 min	5400 cGy /18f, 300 cGy/f	TACE, Cryoablation for metastatic lung lesion	14	11	No, died on September 16, 2018
3	F	41	Primary hepatocellular carcinoma	Disease was stable after first-line treatment	2 cryoprobes, total treatment time: 38 min	5400 cGy /18f, 300 cGy/f	Entecavir	20	20	Yes
4	M	61	Primary liver cancer with multiple intrahepatic metastasis	Disease was progressive after TACE first-line treatment	4 cryoprobes, total treatment time: 35 min	5400 cGy /18f, 300 cGy/f	Entecavir	19	19	Yes
5	F	61	Spinal canal invasion after thoracolumbar fibrosarcoma surgery (T12L1) multiple intrahepatic metastasis	Disease was progressive after fifth-line treatment after palliative surgery	2 cryoprobes, total treatment time: 31 min	5400 cGy /18f, 300 cGy/f	The liver lesion was stable; anlotinib was taken orally	9	9	Yes

TACE: Transcatheter arterial chemoembolization.

13.3%, respectively. The median disease-free survival was 9 mo.

In summary, experimental and clinical applications show that cryoablation is safe and effective for the treatment of hepatic malignancies. Cryoablation is an effective and acceptable new local therapy for metastatic liver cancer. Moreover, iceball formation can be observed by the naked eye. Cryoablation has a very small effect on the surrounding great vessels and can be performed alone or in combination with other methods such as radiotherapy, chemotherapy, immunology, or surgery to better control the lesions.

Our clinical practice also demonstrated that cryoablation combined with IMRT for primary and secondary HCC is safe and effective and is well tolerated with minor AEs. Some patients had a small degree of pneumothorax and pleural effusion, but none had AEs above Grade II. The local control time of liver lesions ranged from 9-20 mo (we continued to follow-up patients who already had 9 mo of local control). Three patients are still alive, and the KPS scores are all 80 points or above. For these 5 patients with liver malignancies, as planned, we adopted the combination treatment strategy by using cryoablation followed by local radiotherapy. Serious complications did not occur and good clinical efficacy was achieved.

CONCLUSION

Our clinical practice demonstrated that cryoablation combined with IMRT could be implemented safely. The definitive efficacy for hepatic malignancies needs to be confirmed in larger-size sample prospective studies.

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