Clinical Case Report

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# High-intensity focused ultrasound combined with transcatheter arterial chemoembolization and radiotherapy for advanced hepatocellular carcinoma

## A case report

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**Abstract**

**Introduction:** Primary hepatocellular carcinoma (HCC) is one of the most common malignancies, only 10% to 20% of HCC patients are surgically resectable as most of the patients are diagnosed at advanced stages at presentation. The efficiencies of transcatheter arterial chemoembolization (TACE), high-intensity focused ultrasound (HIFU), and three-dimensional conformal radiation therapy (3D-CRT) in patients with advanced HCC have been clinically confirmed. We here report a patient with HCC accompanied by venous tumor thrombus, who was treated with the combination of these 3 therapies. The patient survived for 16 months with good quality of life.

**Patient concerns:** The patient was a 72-year-old male with a primary multicentric HCC accompanied by tumor thrombus in the right hepatic vein. The patient had the symptoms of abdominal distention and liver pain. He refused sorafenib treatment because of personal reason.

**Diagnosis:** Primary multicentric HCC stage IIIB cT4N0M0, accompanied by tumor thrombus in the right hepatic vein; chronic viral hepatitis B; and hepatitis B virus-related decompensated liver cirrhosis.

**Interventions:** TACE + HIFU + 3D-CRT.

**Outcomes:** The patient had an overall survival of 16 months with good quality of life. Compared with monotherapy, the combined therapy significantly prolonged patient survival time with improved clinical benefits.

**Conclusion:** The combination of TACE, HIFU, and 3D-CRT is safe and effective in the treatment of advanced HCC, which provides a possible comprehensive treatment strategy for advanced HCC.

**Abbreviations:** 3D-CRT = three-dimensional conformal radiation therapy, HCC = hepatocellular carcinoma, HIFU = high Intensity focused ultrasound, PVTT = portal vein tumor thrombus, TACE = transcatheter arterial chemoembolization.

**Keywords:** comprehensive strategy, high-intensity focused ultrasound, portal vein tumor thrombus, primary hepatocellular carcinoma, transcatheter arterial chemoembolization, three-dimensional conformal radiotherapy

## 1. Introduction

Primary hepatocellular carcinoma (HCC) is one of the most common malignancies. Surgical resection and liver transplantation are considered the radical treatment for HCC. However, most HCC patients are diagnosed at advanced stages, losing the chance of radical surgery. In China, 85% to 90% of HCC cases occur following hepatitis-related cirrhosis. Over 90% of blood supply to the tumor is derived from the hepatic artery.[1] Transcatheter arterial chemoembolization (TACE) is a technique that embolizes the tumor-feeding artery with embolic agents added with chemotherapeutic drugs. By TACE, the blood supply of the tumor is blocked, resulting in tumor ischemia, anoxia, and necrosis. Meanwhile, highly concentrated chemotherapeutic agents accumulate in the tumor, thus exerting its maximum killing effect on tumor cells.[2]

As a novel non-invasive technique for malignant solid tumors, high-intensity focused ultrasound (HIFU) can precisely focus ultrasound energy in a focal area of the tumor to produce transient high-temperature (60–100°C) thermal effect, mechanical effect, and transient cavitation effect,[3,4] causing irreversible damage to tumor cells. HIFU can also significantly enhance the viability of NK cells, increase the number of T cell subsets, and enhance the cellular immune function. HIFU can maximally protect liver function, causing no or little damage to the tissues

*Editor: N/A.*

*The authors have no conflicts of interest to disclose.*

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*Medicine (2019) 98:31(e16660)*

*Received: 10 January 2019 / Received in final form: 25 May 2019 / Accepted: 8 July 2019*

*http://dx.doi.org/10.1097/MD.0000000000016660*

outside the focal area. It is safe and effective in patients with HCC complicated with severe cirrhosis who are unsuitable for surgery.[5]

Three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy, as highly mature techniques, can effectively protect normal liver tissues while delivering a high dose of radiation to the target area of HCC, so as to improve the efficacy of radiotherapy in the treatment of HCC.[6,7]

## 2. Case report

A 72-year-old man had an over 40-year history of chronic viral hepatitis B and a 10-year history of post-hepatitis B cirrhosis. He had no family history of HCC. There was no obvious cause for abdominal distension and liver pain since June 2013. In November 2013, upper abdominal CT revealed liver cirrhosis, a space-occupying lesion in the upper right lobe of the liver suggestive of HCC, intrahepatic multiple nodular lesions suggestive of multicentric HCC; the possibility of metastasis could not be ruled out. On December 6, 2013, contrast-enhanced abdominal MRI revealed liver cirrhosis, a space-occupying lesion sized 5.0 cm × 3.8 cm in the superior parietal lobule of the right liver lobe suggestive of HCC, and intrahepatic multiple nodular space-occupying lesions suggestive of multicentric HCC. Blood alpha-fetoprotein was >1000 IU/L. The patient refused the pathological examination. Clinical diagnoses included: primary HCC stage IIIA cT3N0M0 (multicentric); chronic viral hepatitis B; and decompensated hepatitis B virus-related cirrhosis. The patient refused sorafenib treatment due to economic reasons. After adequate disease assessment, an HIFU-based comprehensive treatment plan was made. TACE was performed once on December 18, 2013 followed by HIFU for tumor ablation on December 27, 2013. More specifically, under general anesthesia, the patient lay in a supine position. Normal saline (750 mL) was injected into the pleural cavity through the 7th or 8th intercostal space, with the patient being placed in a right lateral recumbent position. According to the preoperative contrast-enhanced liver MRI, plain CT, and ultrasound findings (a lesion of about 30 mm × 40 mm × 40 mm in the hepatic dome area and a lesion of about 10 mm × 8 mm × 8 mm near the gallbladder), and to avoid any possible damage to the gallbladder, ribs, diaphragm, and other tissues, the HIFU treatment parameters were selected as follows: frequency, 0.91 MHz; focal length, 140 mm; diameter of transducer, 220 mm, $\alpha = 90°$, $\gamma = -15°$, $\Psi = 0°$; and layer thickness, 5 mm. The ultrasound on the transducer revealed the lesions in the liver, and the images in the therapeutic zone were acquired layer by layer. The treatment began at 11:08 AM. Lesions in segments V and VIII were treated separately by spot scan. The average power was 323 W, the total treatment time was 606 seconds, and the treatment energy was 195,840.0 J. Obvious enhancement was visible inside the lesion during the treatment. The treatment was finished at 13:01 PM, and the process was uneventful. The patient was sent back to the ward after recovering from anesthesia.

After HIFU treatment, liver-protecting agents were administered. The patient presented no symptoms such as cough, chest tightness, or shortness of breath, but had abdominal distention accompanied by mild pain in the right liver region, which was relieved 1 day later. The patient had a good recovery after HIFU. He could walk and started eating 12 and 24 hours after the treatment, respectively. His general condition returned to normal, and he could completely take care of himself. On January 16, 2014, after positioning for 3D-CRT, radiotherapy was administered with a total dose of 5400 cGy/18 f. Meanwhile, 3 cycles of capecitabine monotherapy (1.5 g, b.i.d, d1–14) were also given. The patient had stable disease status and good physical condition after the treatment. Symptoms of abdominal distention and pain of hepatic region disappeared. The Karnofsky score was 80. In March 2014, metastasis to both lungs was found, and the patient agreed to take oral sorafenib. However, he stopped sorafenib treatment due to severe gastrointestinal reactions. On November 4, 2014, a follow-up upper abdominal CT revealed a tumor thrombus arising from the right hepatic vein. Digital subtraction angiography showed a fistula between hepatic artery and portal vein and a fistula between hepatic artery and hepatic vein. Fistula occlusion and chemoembolization were then performed. After 3 weeks, CT scan showed that Lipiodol was well deposited in the diseased area of the right lobe of the liver, and the outcome was satisfactory. New bone metastases were detected in February 2015, along with increased metastases in both lungs. On April 4, 2015, the patient died of respiratory failure. This study was approved by the Ethics Committee of the North China Petroleum Bureau General Hospital. Informed written consent was obtained from the relatives of patient for publication of this case report.

## 3. Discussion

Sorafenib remains one of the standard treatments for advanced HCC, but leading to a median overall survival of only 6.5 months.[8] TACE is still one of the mainstay treatments for unresectable advanced HCC. However, it is difficult for TACE alone to kill tumor cells completely, especially the cells at the edge of tumor. Research has shown that the tumor necrosis rate after TACE was not more than 44% when a tumor diameter was greater than 3 cm.[9] Moreover, TACE cannot achieve complete necrosis for tumors with incomplete capsule or showing invasive growth. Since HCC is often accompanied by cirrhosis and hepatic reserve malfunction, multiple sessions of TACE may aggravate liver function damage. In addition, HCC cells are prone to invade the liver envelope, adjacent organs, and blood vessels, and multiple blood vessels are involved in feeding the tumor, making it extremely difficult to achieve complete embolism. The 5-year survival rate in patients with unresectable primary HCC treated by TACE is 7% to 8%. Therefore, TACE alone is not an optimal treatment option for HCC.[10] The combination of HIFU with TACE can compensate for this shortcoming. The embolic agents carrying chemotherapy drugs can block the blood vessels of the tumor, reducing the blood flow that feeds the tumor. Thus, the energy generated during HIFU treatment will not be easily carried away by the blood flow, greatly enhancing the curative effect of HIFU. Furthermore, the local aggregation of iodine oil in the tumor changes the difference in acoustic impedance and the sound absorption coefficient of the target area during HIFU, enabling the high-energy ultrasound to effectively focus on the tumor target area in vivo, so as to destroy the tumor and prolong patient survival. Kim et al[11] found that in patients with <5 cm primary HCC without vascular cancer embolus (90 cases in BCLC stage B and 30 in BCLC stage C), the median survival was 57 months in HIFU + TACE group, which was significantly superior to that (36 months) in TACE group. Via its thermal effect, HIFU can block tumor-feeding blood vessels, thus achieving the therapeutic effect on the tumor. It allows a real-

time display of the lesion and its relationships with adjacent tissues and observation of the changes in the tumor acoustic images of the target area before and after treatment, which enables timely adjustment of treatment dose and accurate in vitro in situ "noninvasive" resection of the tumor. HIFU can also significantly enhance the viability of NK cells, increase the number of T cell subsets, and enhance the cellular immune function.

In recent years, an increasing number of reports have described the application of radiotherapy in the comprehensive treatment of HCC. Radiotherapy can compensate for the shortcomings of TACE. Radiotherapy has the advantages of precise positioning, low set-up error and accurate treatment. By increasing the radiation dose in the target area, reducing the radiation dose in adjacent normal tissues, and giving further treatment for the tumors with ineffective embolism or the edge of tumor, radiotherapy can improve the therapeutic effects in unresectable primary HCCs. In addition, when the dose is well controlled on the normal liver tissue, 3D-CRT can markedly reduce liver function damage, increase local treatment effectiveness, protect normal liver tissue, increase survival rate, and improve the prognosis.[6] Studies have shown that radiotherapy combined with TACE can be a safe and feasible treatment option for advanced HCC accompanied by portal vein tumor thrombus (PVTT), and compared with TACE monotherapy, the combined therapy can significantly improve the median survival.[12,13]

As is well known, hypoxic cells and cells in S-phase are not sensitive to radiotherapy but are highly sensitive to hyperthermia. Proportion of hypoxic cells is high in the central area of tumors and the cells are more tolerable to the radiotherapy. However, hypoperfusion facilitates heat accumulation, which helps to accomplish thermal ablation of tumors. On the contrary, as the adjacent area of a tumor has rich blood supply, with an increased proportion of hypoxic cells, the effectiveness of radiotherapy gradually improved, while the abundant blood flow can carry away the surrounding heat, protecting the adjacent tissues from being injured. In addition, hyperthermia can inhibit DNA damage repair in tumor cells after radiotherapy. Therefore, the combination of radiotherapy and HIFU can theoretically enhance the efficacy of radiotherapy. Jin et al[14] applied HIFU combined with stereotactic radiotherapy to treat 34 lesions in 21 patients with malignant liver tumors. Two weeks after stereotactic radiotherapy followed by HIFU, MRI showed that 23 lesions (67.6%) were completely ablated, among which 7 had an ablation volume ratio of ≥80%. The median survival was 18 months, and the 1-year survival rate was 74.1%. These results indicated that the combination of radiotherapy and HIFU may have a synergistic effect in the treatment of liver tumors.

HCC can easily invade portal vein, forming PVTT. The incidence of PVTT is 44% to 62.8%.[15] As a leading cause of HCC-related death, PVTT has a poor prognosis, and the median survival time of untreated patients was only 2.7 months.[16] No effective treatment has been available for PVTT. According to Chung et al,[17] the 1 and 2-year survival rates were only 30% and 18% in 110 HCC patients with portal vein involvement treated by conventional TACE. Ishikura et al[18] treated 20 PVTT patients by TACE followed by radiotherapy and found that the response rate reached 50%, the 1-year survival rate was 25%, and the median survival time was 5.3 months. HCC patients complicated with PVTT have poor response to monotherapy, suggesting that the combined therapy may improve the outcomes.

In a retrospective study, Ni et al[19] found that for patients with unresectable advanced HCC, the median survival time was 26 months and the 1, 3, and 5-year survival rates were 70%, 35%, and 15%, respectively, after TACE + 3D-CRT + adjuvant HIFU. Among these patients, 117 were in Child grade A and only 3 in Child grade B. Notably, Ni et al's study did not include HCC patients with vascular tumor thrombus and thus the prognoses were relatively good. In Ni et al's study, TACE and 3D-CRT were the main treatments, and HIFU was used as a supplementary technique. In our study, however, a comprehensive treatment strategy was designed before treatment, and HIFU was the dominant treatment. Child stage and total radiotherapy dosage were found to be independent factors for the survival of patients. Therefore, the combination of these 3 methods is safe and effective in the treatment of advanced HCC.

## 4. Conclusions

TACE is firstly performed to embolize the main tumor-feeding vessels to reduce their blood supply. The HIFU thermal ablation technique is then applied to destroy the central area of the tumor, where there are more hypoxic cells. For the adjacent area of the tumor, where there is rich blood supply and residual tumor may exist after HIFU treatment, local radiotherapy with 3D-CRT is administered to kill the tumor cells. Theoretically, TACE, HIFU, and 3D-CRT can exert synergistic effects when used in combination. Although the present case was accompanied by a venous tumor thrombus, the patient still achieved a 16-month survival. This may be attributed to the rational use of a variety of treatments. The shortcomings of this treatment regimen included that the patients did not receive sorafenib targeted therapy when first diagnosed, and did not receive ablation treatment. In short, advanced HCC cannot be cured by any single treatment. It is generally accepted that a comprehensive strategy may improve the outcome of the HCC patients. HIFU combined with TACE and 3D-CRT provides a possible mode of comprehensive treatment for unresectable advanced HCC accompanied by vascular tumor thrombus, increases patient survival, and improves quality of life. This combination protocol deserves further verification in future prospective clinical trials.

## Author contributions

**Conceptualization:** Yue-E Liu, Jie Zong, Xiao-Cang Ren, Qiang Lin.
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