Eur Radiol
DOI 10.1007/s00330-008-1137-0

ONCOLOGY

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High-intensity focused ultrasound (HIFU): effective and safe therapy for hepatocellular carcinoma adjacent to major hepatic veins

Received: 31 October 2007
Revised: 16 April 2008
Accepted: 18 April 2008

Lian Zhang and Hui Zhu contributed equally to this research, which was supported by the National Natural Science Foundation of China (grant no. 30171060).

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Abstract Hepatocellular carcinoma (HCC) is an especially frequent malignancy in China. Radiofrequency ablation, percutaneous ethanol injection, transarterial chemoembolization, cryoablation, microwave coagulation, and laser-induced interstitial thermotherapy all offer potential local tumor control and occasionally achieve long-term disease-free survival. High-intensity focused ultrasound (HIFU), as a noninvasive therapy, can be applied to treat tumors that are difficult to treat with other techniques. The preliminary results of HIFU in clinical studies are encouraging. The aims of this investigation were to assess the efficacy of the system in obtaining necrosis of the target tissue and to determine whether HIFU ablation is hazardous to adjacent major blood vessels. Over 7 years, thirty-nine patients with HCC were enrolled in this investigation. The inferior vena cava (IVC), main hepatic vein branches, and the portal vein and its main branches were evaluated. The distance between tumor and main blood vessel was less than 1 cm in all these enrolled patients. Contrast-enhanced MRI was used to evaluate the perfusion of tumors and major blood vessels. We conducted HIFU ablation for the treatment of 39 patients with 42 tumors, with each tumor measuring 7.4±4.3 (1.5–22) cm in its greatest dimension. Among the 39 patients, 23 were males and 16 females. The average age was 53.2 years (range 25–77 years). Thirty-seven patients had a solitary lesion, one had two lesions, and the remaining one had three lesions. Nineteen lesions were located in the right lobe of liver, 18 in the left lobe, and 5 in both right and left lobes. Among the 42 tumors, 25 were adjacent to 1 blood vessel, 12 adjacent to 2 main vessels, 2 adjacent to 3 main vessels, and 1 adjacent to 4 main vessels. Twenty-one of the 42 tumors were completely ablated, while the rest of the tumors were ablated by more than 50% of lesion volume after one session of HIFU. No major blood vessel injury was observed in any subject after 23.8±17.2 months follow-up. HIFU can achieve complete tumor necrosis even when the lesion is located adjacent to the major hepatic blood vessels. Short-term and long-term follow-up results show that HIFU can be safely used to ablate the tumors adjacent to major vessels.

Keywords High-intensity focused ultrasound (HIFU) · Hepatocellular carcinoma · Blood vessel injury

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent life-threatening malignancies in China. Surgery is the current standard of care in selected cases, offering the chance of complete cure by tumor removal [1, 2]. Radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), cryoablation, microwave coagulation, and

laser-induced interstitial thermotherapy also offer potential local tumor control, and occasionally achieve long-term disease-free survival. However, it remains difficult to use these techniques to treat the tumors close to major blood vessels: because of the substantial risk of blood vessel injury, these techniques are all problematic. As an additional caveat, portal venous blood flow may protect adjacent tumor cells from thermal destruction [3, 4]; thus existing local therapies are unlikely to ablate tumors situated close to major blood vessels in the liver.

High-intensity focused ultrasound (HIFU) is a novel noninvasive technique that is capable of producing coagulative necrosis at a precise focal point within the body, without harming overlying and adjacent structures even within the path of the beam [5–7]. The location and extent of treatment can be monitored accurately with real-time ultrasonic imaging. The possibility that focused ultrasound therapy might be developed as a result of controlling local heating phenomena was introduced by Lynn et al. [5]. Experiments on the cat brain led to the first experimental applications of HIFU in clinical neurosurgery in the 1940s [6], but the technique was not developed at that time because of inadequate targeting methods. The advent of more sophisticated imaging has led to a resurgence of interest in HIFU. Recently, Wu et al. reported achieving large areas of coagulation necrosis with this tumor ablation technique to treat HCC [7, 8]. Can this therapy be applied to the tumors that are difficult to treat with other techniques? We aimed to assess the efficacy of the system in obtaining necrosis of the target tissue, and to determine whether HIFU ablation will cause injury to adjacent major vessels.

Materials and methods

Patients

The study was approved by the ethics committee at the Chongqing University of Medical Sciences. From January 2000 to December 2006, a total of 39 consecutive cirrhotic patients (23 male, 16 female; age range 25–77 years, mean age 53.2 years) were enrolled in this study. These subjects underwent HIFU for HCC deemed not to be surgically respectable, nor suitable for RFA or PEI, due to the location of the tumor. Among the 39 patients, 1 had RFA and 18 patients had transcatheter arterial chemoembolization (TACE) before HIFU treatment. The residual tumors were found to be close to major blood vessels by using MRI or CT. The HIFU procedure was performed between 1–2 weeks after RFA or TAE. The primary end points of the study were local tumor progression and/or injury to adjacent major blood vessels. A secondary end point was overall survival. The following inclusion criterion was further required: the distance between tumor and major blood vessels (inferior vena cava (IVC), main hepatic vein branches, and the portal vein and its main branches) was less than 1 cm. Exclusion criteria were: (1) patients with Child–Pugh grade C tumors; (2) diffuse hepatocarcinoma; (3) neoplastic thrombosis of the portal branches; (4) prothrombin time elevated < 50%; (5) platelet count less than 50,000; (6) number of foci more than three. As regards the characteristics of the HCCs, 37 patients had a solitary lesion, 1 had two lesions, and the remaining 1 had 3 lesions; a total of 42 tumors were detected in the 39 patients studied. According to the TNM classification, 16 patients were diagnosed as stage II, 12 patients were stage III, and 11 patients were stage IV. Tumor diameters were determined as the largest dimension measured by computed tomography (CT) or magnetic resonance imaging (MRI). The number of tumors was determined by ultrasound (US), hepatic arterial angiography, or MRI. Routine color Doppler US was used to detect vascular invasion and any vessels surrounding the target tumor. The characteristics of the subjects are shown in Table 1. All of these procedures were conducted with informed consent at the time of the enrollment for this study.

Pre-treatment preparation

Conventional liver biochemical tests, prothrombin time, and complete blood cell counts, chest radiography, abdominal US, ECG, and lung function were evaluated before treatment. Three-phase CT or MRI was used to detect any enhancement of the tumor image throughout the study period.

HIFU therapeutic procedure

HIFU ablation was performed by the JC HIFU system [Chongqing Haifu (HIFU) Tech Co., Ltd., Chongqing,

Table 1 Characteristics of the 39 patients with HCC close to main blood vessels treated with HIFU

Characteristics	Numbers
Total of patients	39
Sex (male/female)	23/16
Age (mean ± SD) (years)	53.2±12.3
Tumor size (mean ± SD) (cm)	7.36±4.25
Tumor number (1/2/3)	37/1/1
No. of tumors	47
AFP (+/−)	24/15
HBV infection (+/−)	20/19
Child–Pugh class (A/B/C)	39/0/0
TNM stage (II/III/IV)	16/12/11

China]. Briefly, the therapeutic procedure was guided by real-time ultrasonography (US). A DU3 US imaging device (Esaote, Genova, Italy) was used as the real-time imaging unit of the system. This 2.5- to 3.5-MHz imaging probe is situated in the center of the high-intensity focused ultrasound transducer. Therapeutic US energy was produced by a transducer with a 15-cm diameter, a focal length of 15 cm, and operating at a frequency of 0.8 MHz. HIFU therapy was performed under general anesthesia in this study. General or epidural anesthesia was necessary during HIFU treatment to prevent the patient from experiencing deep visceral-type pain and to ensure immobilization. General anesthesia with endotracheal intubation and mechanical ventilation also had the supplementary benefit of permitting provisional suspension of respiration with controlled pulmonary inflation, as necessary to ablate the lesions behind the rib cage through the intercostal space. After suitable anesthesia was induced, the patient was carefully positioned, either prone or on his or her right side, so that the skin overlaying the lesion to be treated would be easily put into contact with degassed water. A vertical ultrasound mode was chosen for the treatment. The distance between slices was 5 mm. The treatment power was increased stepwise after starting, and the ablation was terminated after the increased gray scale covered the tumor margin (Fig. 1). A treatment power of 160–250 W was used.

Evaluation of therapeutic efficacy

The short-term effects of ablation were assessed using CT or MRI, 2 weeks after initial HIFU treatment. If foci of nodular enhancement were noted in the treated tumor under CT or MRI, then another course of treatment was given. CT or MRI was repeated 2 weeks after such "booster" treatment. Tumor necrosis was considered to be complete if no enhancing areas were observed based on images obtained during early and late phases of dynamic contrast-enhanced CT or MRI. Blood vessel damage was defined as no perfusion or partial perfusion, based on images obtained during early and late phases of dynamic contrast-enhanced CT or MRI.

The long-term outcome was assessed in terms of local tumor progression, additional (new) tumor recurrence, and overall survival. The follow-up of this study ended on 31 March 2007. Follow-up examinations included monitoring serum alpha-fetoprotein level, US, and CT or MRI every 2 months. Local tumor progression was defined as the presence of an enhanced tumor on CT or MRI, corresponding to the initial target tumor area. Additional (new) tumor recurrence was defined as the development of an enhanced tumor on CT or MRI at least 2 cm away from the original tumor.

All new HCCs that emerged from either local tumor progression or additional (new) tumor recurrence were treated with the same ablation method if the tumors still met the original requirements for these therapies.

Statistical analysis

All data are reported as the mean ± standard deviation. Local tumor progression, additional (new) tumor occurrence, and overall survival were estimated using the Kaplan–Meier method, and differences were determined by the log-rank test. A P value of less than 0.05 was considered statistically significant.

The period of follow-up was defined as follows: (1) for local tumor progression rate, the time from the beginning of HIFU ablation to local tumor progression or death; (2) for overall survival rate, the time to last follow-up or death.

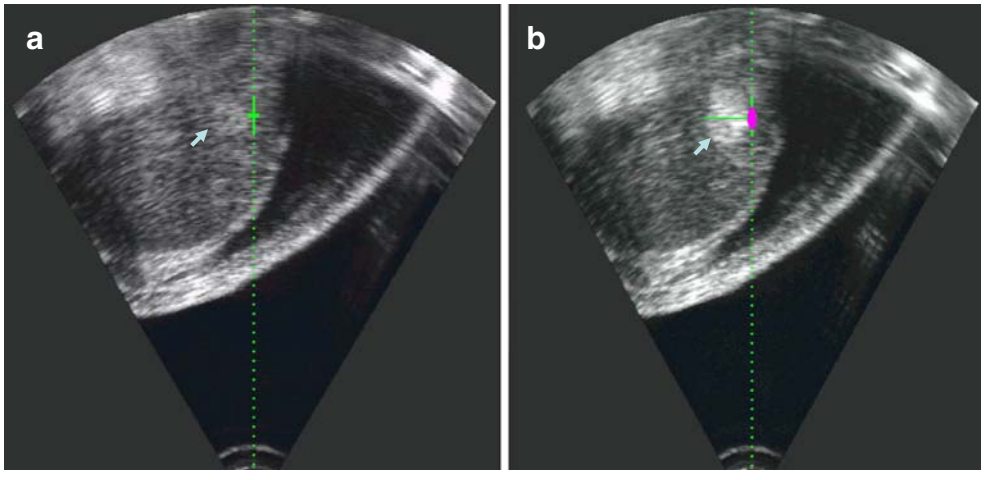

Fig. 1 Successful treatment of a small HCC (hepatocellular carcinoma) lesion. **a** Before. Sagittal US (ultrasound) image obtained at the beginning of HIFU treatment shows a small HCC lesion (*bold arrow*) close to diaphragm. **b** After. Sagittal US image obtained immediately at the end of HIFU ablation shows hyperechoic region in the treated area (*bold arrow*)

Results

Location of tumors

Among the 42 hepatic lesions, 18 lesions were located in the left lobe (segments 1–4), 19 lesions in the right lobe (segments 5–8), and 5 lesions in both left and right lobes (Table 2). Of 42 lesions 25 were near a single branch of major blood vessels, 12 of 42 lesions near 2 branches, 4 of 42 lesions near 3 branches, and 1 lesion was surrounded by 4 branches (Table 3). A total of 65 branches of major blood vessels were observed. Among these major blood vessels, there were 12 at the IVC, 7 right branches of the hepatic vein, 9 middle branches of the hepatic vein, 5 left branches of the hepatic vein, 18 portal veins, and 7 each of its left and right branches (Table 4).

Complete tumor necrosis

In these 39 patients with 42 lesions, the average tumor size was 7.36±4.25 cm (Table 1). Complete tumor necrosis was achieved in 21 patients (21/42 lesions, or 50%) after the first session of HIFU treatment. The remaining 21 of 42 lesions were ablated by more than 50% of the tumor volume (Table 5). The average size of these incomplete necrosis tumors was 9.95±4.23 cm.

Local tumor progression and additional new tumor recurrence

For the responders (i.e., those in whom complete necrosis was initially achieved), after a median of 16.5 months (mean 23.8±17.2 months) of follow-up, local tumor progression occurred (within 2 cm of the main tumor) in one of 21 patients. Additional (new) tumors in liver and spleen were found in one patient. Extrahepatic metastasis occurred in another two patients (Table 6). Of the four patients with recurrence, the previously treated HCC remained a single lesion.

Table 2 Location of the 42 tumors in the 39 patients treated with HIFU

Tumor sites	Tumor numbers	Tumor sites	Tumor numbers
S-1	2	S-5	8
S-2	7	S-6	2
S-3	7	S-7	8
S-4	7	S-8	6
Left lobe	23	Right lobe	24

Five tumors located in two segments

Table 3 Tumors and involved main blood vessels in the 39 patients treated with HIFU

Number of blood vessels near tumor	Number of tumors	Total number of blood vessels
1	25	25
2	12	24
3	4	12
4	1	4
Total	42	65

Overall survival rate

The overall survival rates at 1, 2, 3, 4, and 5 years were 75.8%, 63.6%, 49.8%, 31.8%, and 31.8% (Fig. 2). Of 39 patients 17 died during a median of 16.5 months (mean 23.8±17.2 months) of follow-up. The causes of death included progression of HCC in 2 of 39 patients, encephalopathy in 5, and variceal bleeding in 2 patients (Table 7). Figure 2 shows the survival probability of patients with HCC treated with HIFU.

Adverse effects of HIFU treatment

Mild local pain was experienced in nine (23.1%) of the 39 patients treated with HIFU. The pain was controlled by injected or oral analgesics for 2 to 3 days. Among the nine patients who had mild local pain, five patients also had mild skin burn, one patient had blisters, and another patient had mild skin burn and blisters. In 22 (56.4%) of the 39 patients with big tumors (>5 cm in diameter), serum transaminase levels increased to 2–3 times the baseline level during the first 3 days after therapy. However, these tests results returned to the baseline level within 2 weeks after therapy. No damage to bile ducts was seen.

Table 4 Information of the involved main branch of blood vessels in the 39 patients treated with HIFU

Name of blood vessels near tumor	Number of tumors
IVC	12
Right hepatic vein	7
Middle hepatic vein	9
Left hepatic vein	5
Portal vein	18
Right branch of portal vein	7
Left branch of portal vein	7
Total	65

Table 5 HIFU ablation results of 42 tumors in the 39 patients treated with HIFU

Extent of ablation (%)	Number of tumors
100	21
50–100	21
0–50	0

Discussion

For the treatment of HCC, surgical resection, PEI, or RFA are accepted as standard options [1, 2, 9–12]. RFA and PEI are already considered to be effective for the treatment of patients with relatively small, encapsulated HCC below 3 cm in the greatest dimension. However, most patients with HCC are diagnosed with large areas of liver cancer. For tumors near the main hepatic blood vessels or bile ducts, complete removal by surgical resection is not possible. Also, no matter the size, such tumors are difficult to treat by RFA or PEI, and it is very hard to achieve complete necrosis of larger tumors (Fig. 5b).

Our results indicate that HIFU can safely achieve virtually complete necrosis of tumors close to major blood vessels, without damage to vascular integrity (Figs. 3, 4, 5c). We do not precisely understand the nature of this vascular resistance to thermal damage, but it is likely that the cooling effect of rapid blood flow in a large vessel may explain the resistance of such vessels to injury. A basic understanding of factors that influence necrosis lesion size in vivo may be critical to the success of the thermoablative treatment technique; along these lines, many experiments have shown that necrosis lesion size varies directly with time of application of thermoablative techniques, and inversely with blood flow [3, 13]. But such relationships between major blood vessels and necrosis lesions have not been previously studied in the liver.

We treated tumors measuring 1.5–22 cm in diameter by HIFU. Among these tumors, 56.4% (22/39) of patients with tumors larger than 5 cm in diameter, and after a single session of HIFU treatment, the rate of complete necrosis

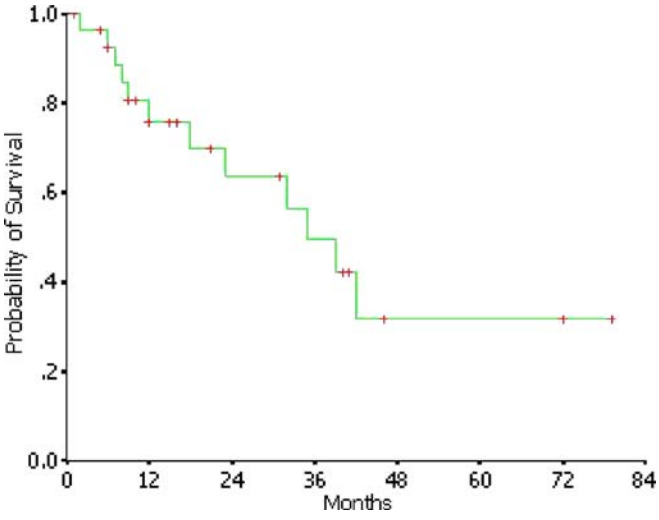

Fig. 2 Survival curve of patients with HCC treated by HIFU. The graph shows the survival probability of the 39 patients after a mean of 16.5 months (mean 23.8±13.8 months) of follow-up

was ca. 50%. While substantial, this rate of necrosis following HIFU ablation is not completely satisfactory. The lack of complete response can perhaps be explained by: (1) evolution of equipment (the newly developed HIFU therapeutic system for HCC); (2) evolving physician experience with this system; and (3) size of tumor and cooling effects from large vessels. While already effective, HIFU ablation may continue to improve as the technique evolves. With more powerful transducer development, a higher rate of complete necrosis could be reached. With technical development, therapy time could be gradually reduced in the future.

Hori [14] reported that local recurrence rates for larger tumors (>25 mm) after one session of RFA were 21.1% and 32.3% at 1 and 2 years, respectively, and at 3 years the rate was over 50% for tumors located close to the liver surface. The present results with HIFU show a lower local tumor recurrence rate as compared to that in other investigations which used different techniques, even though tumor size in this study was typically greater than in other studies. The rates of recurrence of additional (new) tumors were also similar or better than those of patients after RFA and

Table 6 Recurrence of HCC in 21 patients after 100% ablation by HIFU

Type of recurrence	Number of patients
Local recurrence	1
Different segments recurrence	1
Extrahepatic metastasis	2

All the additional lesions found in patients who had single tumors before

Table 7 Clinical findings in 17 deceased patients with HCC treated with HIFU

Cause of death	Number of patients
Variceal bleeding	2
Encephalopathy	5
Liver function failure	5
Progression of HCC	2
Others	3

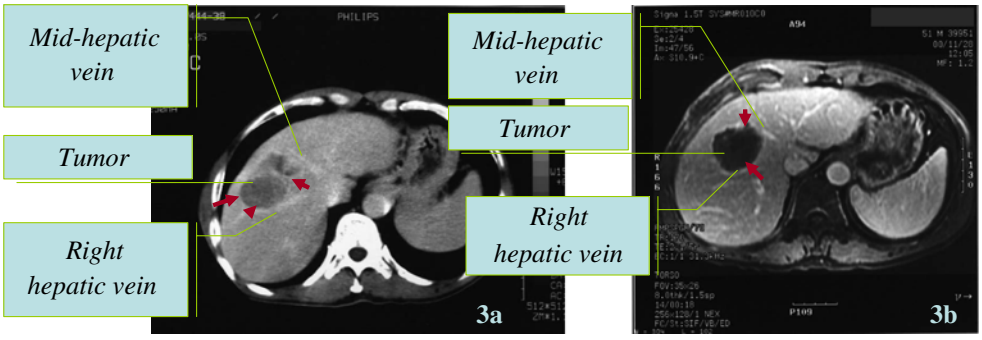

Fig. 3 Transverse contrast agent-enhanced CT and MRI of a patient (case 1) with HCC. **a** Before HIFU. CT obtained in the hepatic venous phase shows a large tumor (*bold arrows*) located between middle and right branches of the hepatic vein in segment 8. **b** After HIFU. Venous phase MRI obtained 2 weeks after HIFU treatment shows uniform hypo-attenuation (*bold arrows*) and absence of contrast enhancement, which are evidence of successful treatment. The perfusion of middle and right branches of hepatic vein was maintained

resection, perhaps because HIFU might enhance systemic anti-tumor cellular immunity in addition to local tumor destruction in patients with solid malignancies [15].

The median survival for patients with unresectable HCC and no response to therapy, such as TACE, RFA, and PEI, is considerably less than 6 months [16, 17]. Recently, Lencioni et al. reported a group of patients who had Child class A or B cirrhosis with either a single HCC less than or equal to 5 cm in diameter or multiple (as many as three) HCCs less than or equal to 3 cm in diameter, each treated

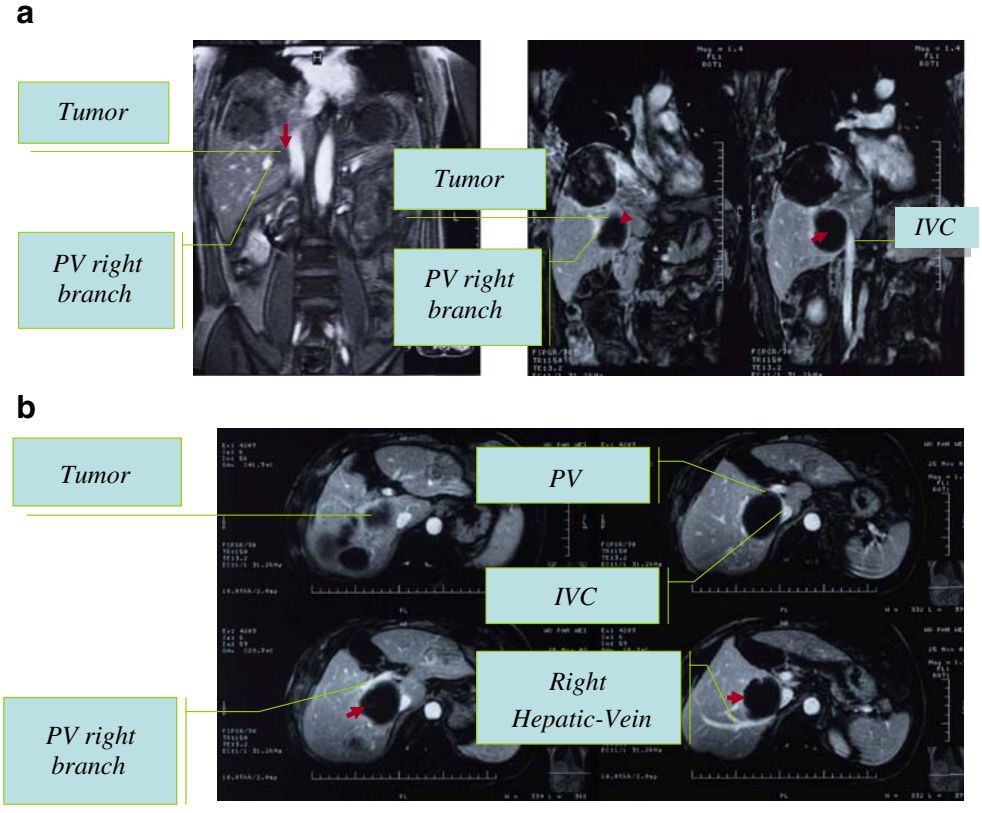

Fig. 4 Contrast agent-enhanced MR images of a 68-year-old patient (case 2) with HCC. **a** Before HIFU (*left*). Coronalenhanced MR images show a tumor (*arrow*) located between the right branch of portal vein and the inferior vena cava (*IVC*). After HIFU (*right*). There was no enhancement in the treated region (*arrow*), and no damage to inferior vena cava were observed 2 weeks after HIFU treatment. *PV* portal vein. **b** Transverse enhanced MR images obtained 2 weeks after HIFU treatment show there was no enhancement in the treated region (*arrow*) and no damage to the surrounding major blood vessels. *PV* portal vein, *IVC* inferior vena cava

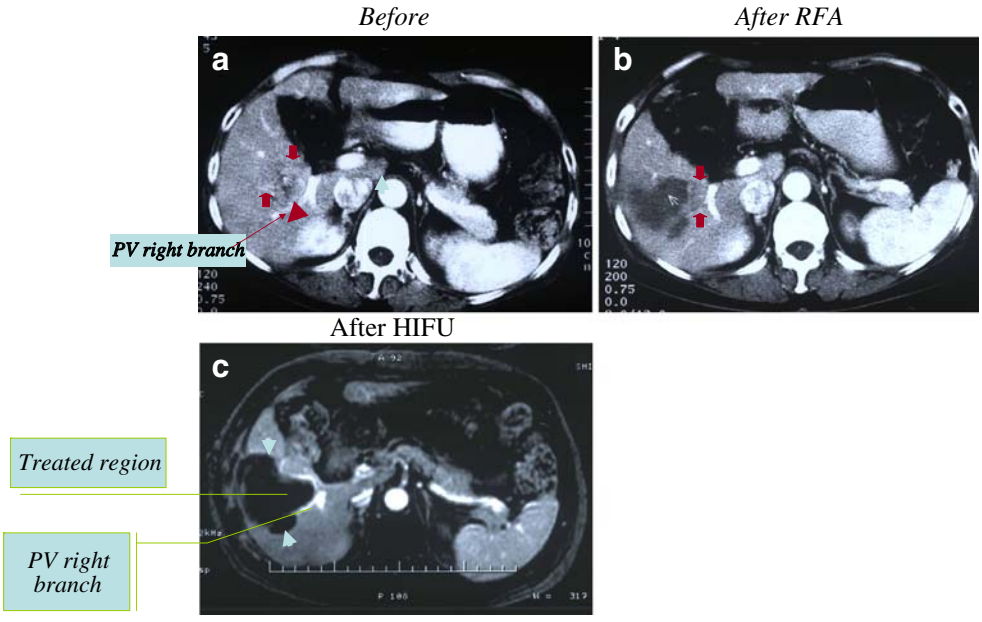

Fig. 5 Transverse contrast agent-enhanced CT and MRI of a patient (case 3) with HCC treated sequentially with RFA and then HIFU. The patient is a 64-year-old woman with HCC treated by HIFU after RFA. **a** Pre-treatment. CT obtained in the hepatic arterial phase shows a large hypervascular tumor (*bold arrows*) located close to right branch of portal vein in Couinaud segment 5. **b** Post RFA treatment. Contrast-enhanced CT obtained in the hepatic arterial phase after RF ablation shows residual HCC (*bold arrows*) close to the right branch of portal vein. **c** Post HIFU treatment. Contrast-enhanced MRI obtained 2 weeks after HIFU treatment shows uniform hypo-attenuation (*bold arrows*) and absence of contrast enhancement, which are evidence of successful treatment. The right branch of portal vein was perfused well

with RF ablation; the overall survival rates were 97% at 1 year, 67% at 3 years, and 41% at 5 years [18]. TACE is commonly used for advanced HCC. However, many randomized controlled trials failed to show a survival benefit of TACE for advanced HCC [17, 19], even though smaller studies showed positive results [20]. Are there patients who are particularly likely to benefit from HIFU? Since the hepatic artery provides at least 80% of the blood supply to HCC, and the remaining 20% of the blood supply comes from the portal vein, a small number of tumor cells remain viable after TACE. Wu et al. have shown that the combination of HIFU ablation and TACE is a promising approach in patients with advanced-stage HCC [21]. Most recently, Yamagiwa et al. [22] reported RFA with prior TACE has also shown better results; the overall survival rates in the RFA + TACE group were significantly higher (5-year, > 60%). Since the reduction of blood supply after TACE allows the use of lower levels of ultrasound energy, this will shorten treatment time with HIFU and so may reduce potential side effects. In the present study, we found the average size of the incomplete necrosis tumors was 9.95±4.23 cm. It appears that HIFU with prior TACE should be suggested for the treatment of large lesions. Our results show the average tumor size was much larger than that in other studies, so it is difficult to compare the survival rates with earlier studies. Compared with patients whose tumors were not ablated completely, those with complete ablation had higher survival rates (the survival rates at 1, 3, and 5 years were 86.3%, 62.3%, and 50.8% vs. 71.8%, 23.9%, and 0%; $p<0.05$). Additionally, the most common cause of death was progression of HCC, ultimately resulting in hepatic functional failure. Therefore, if effective local treatment can achieve a lower HCC recurrence rate, then improved survival should follow.

Our observations indicate that HIFU ablation is a relatively low-risk procedure. Mild local pain was often experienced in patients treated with HIFU, but such pain was readily controlled by injected or oral analgesics for 2 to 3 days. Another complication unique to HIFU was minor skin burn, seen in 12.8% of HCC patients after HIFU treatment. In most patients with larger tumors, transaminase levels increased to 2–3 times the baseline level during the first 3 days after HIFU, but test results returned to the baseline level within 2 weeks after therapy. There were no hemorrhagic accidents during or following treatment. No damage to bile ducts was seen.

With the development of magnetic resonance image (MRI) guidance of the ultrasound beam, MRI-guided focused ultrasound surgery (MRgFUS) has been pushed forward in oncological practice [23]. The MRI-based thermal mapping not only enhances safety but also appears to enhance efficacy because treatment parameters can be adjusted to ensure that target temperatures reach the point at which tissue necrosis is achieved. However, there are

several difficulties when treating patients with HCC or liver metastases by using MRgFUS. First, since the bore size of MRI is relatively small, it is difficult to position the patient with HCC, especially when tumors are located at the right lobe of the liver; second, it is difficult to monitor the target temperature changes because of liver movement during HIFU; third, the MRgFUS procedure will be more costly. By comparison, there is no problem to position the patient, to monitor the treated region and surrounding structures, and the cost is much lower by using ultrasonography-guided HIFU to treat patients with HCC and liver metastases.

The present study is limited because it was a feasibility study with a small number of patients. We were not able to compare the treatment effect between the patients with and without former TACE or RFA. The study is also limited because tumor size was not considered as an exclusion criterion and because of the high rate of incomplete necrosis. Future studies will need to include the treatment of more patients, with a more carefully selected group of patients. In the next prospective trial, we will use this technique as the primary treatment to treat lesions with a size smaller than 3 cm in diameter and close to major blood vessels, and this study will help to define the precise role of HIFU in the treatment of HCC.

We conclude that HIFU can achieve complete tumor necrosis even when the lesion is located adjacent to the major hepatic blood vessels. Indeed, there is no discernible damage to the major vessels, even though the adjacent lesion has been completely ablated. In the future, better patient selection, treatment repetition tailored to tumor response, and improved understanding of patient tolerance may further advance the therapeutic benefit of HIFU.

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