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Short and long term efficacy of high intensity focused ultrasound therapy for advanced hepatocellular carcinoma

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Abstract

Background: The aim of this study was to investigate the short and long term efficacy of high intensity focused ultrasound therapy (HIFU) in patients with advanced hepatocellular carcinoma (HCC).

Methods: Patients with surgically unresectable HCC received either HIFU plus supportive treatment (HIFU group, $n = 151$) or supportive treatment only (control group, $n = 30$), according to their willingness. Short term efficacy, including improvement in tumor imaging parameters, decrease in serum α -fetoprotein (AFP) levels, symptom relief (i.e. Karnofsky Performance Status and numerical rating scales) and response rates, and long term efficacy, including an increase in survival rates and improvement of quality of life (QOL), was monitored.

Results: Tumor imaging parameters, serum AFP levels and symptom scores improved significantly in the HIFU group compared with the control group (all $P < 0.05$). In the HIFU group, a complete and a partial response were achieved in 28.5% ($n = 43$) and 60.3% ($n = 91$) of cases, respectively, while the rates were 0% and 16.7% ($n = 5$), respectively, in the control group. The overall response rate (88.8%) was significantly greater in the HIFU group (16.7%) than in the control group ($P < 0.01$). In addition, the 1- and 2-year survival rates were 50.0% and 30.9%, respectively, in the HIFU group, which were significantly greater than those (3.4% and 0%, respectively) in the control group (both $P < 0.01$). The QOL score was 83.1 ± 8.0 at 3 months after HIFU, which was significantly greater than the pre-HIFU score (67.7 ± 5.9) and the score at 3 months after treatment (69.0 ± 8.5) in the control group (both $P < 0.05$). No severe complications occurred during and after HIFU.

Conclusion: HIFU is an effective and safe ablation therapy with satisfactory short and long term efficacy for patients with advanced HCC.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world. China ranks among the highest risk areas with an incidence of 20–60/100 000 persons.¹ Surgical intervention have so far been the only curative therapy. However, the majority of patients with HCC are not suitable for surgical resection or liver transplantation because of either the advanced stage of the lesions or the presence of underlying cirrhosis. Several ultrasound (US)-guided regional ablation techniques, such as percutaneous ethanol injection (PEI), radiofrequency (RF), interstitial laser coagulation (ILC) and cryotherapy, have been developed for the treatment of HCC.^{2,3} However, all these techniques require percutaneous insertion of an instrument and they are generally indicated for patients with less than two tumors and a maximal tumor diameter of less than 3 cm. High intensity focused ultrasound (HIFU) therapy has been developed for the treatment of tumors of solid organs clinically, and was first

approved for the treatment of HCC in China in 1999.⁴ HIFU is a non-invasive treatment method, which precisely targets the tumor tissues without skin incision. HIFU focuses an extracorporeal source of US to a specific target tissue inside the body. The US energy passes harmlessly through overlying tissues en route to a tightly focused target area. The rapid rate of energy deposition generates a rapid rise in temperature (65°C – 100°C), which results in irreversible cell death with a defined region of tissue necrosis. The ability to accurately target a lesion with HIFU by using a real-time US guide allows precise ablation of lesions of any shape without damage to surrounding structures. Its non-invasive characteristics allow HIFU to treat large tumors and multinodular tumors, which is unachievable with other conventional ablation therapies.^{5,6} Despite several reports on the application of HIFU in HCC therapy worldwide,^{7–14} the systemic evaluation of the clinical efficacy, especially the long-term efficacy of HIFU for advanced HCC, has not been well documented. Therefore, the aim of this study was to determine the short and long term

efficacy and possible adverse events of HIFU in the treatment of advanced stage HCC in China.

Methods

Patients

From January 2001 to January 2005, a total of 322 consecutive patients with advanced HCC were admitted to the Department of Gastroenterology and Hepatology, First Municipal People's Hospital of Guangzhou. All were unsuitable for surgical resection. The diagnosis was made by clinical manifestations with confirmation from laboratory examinations, including elevation of serum levels of α -fetoprotein (AFP) and an imaging technique including computed tomography (CT) or magnetic resonance imaging (MRI), according to the standard criteria issued by the Chinese Association of Cancer Prevention.¹⁵ In addition, liver biopsy specimens were taken from 21 patients for pathological confirmation. Each patient was initially evaluated by a group of senior surgeons and physicians working together to determine the patient's suitability for surgery. Patients with surgically unresectable HCC were included in this trial if the Child-Pugh score was less than 10 and if there were only limited extrahepatic metastases with only sparse lymph node involvement. Patients who had the following conditions were excluded: (i) end-stage HCC, that is, lesions involving over 70% of the liver, more than five tumors and diffuse infiltrative lesions in more than one lobe; (ii) liver failure; (iii) hepato-renal syndrome; (iv) severe concomitant diseases; (v) a history of surgical resection of liver cancer; (vi) a history of receiving liver transplantation or any other kind of regional ablation therapies (e.g. transcatheter arterial chemoembolization [TACE], PEI or RF) within 3 months of this study; (vii) unwillingness to attend this study.

A total of 249 patients met the inclusion criteria. For ethical reasons we were unable to perform a randomized study on HCC patients. We could not estimate the sample size in each group before the study. At the beginning of this study, we believed that HIFU was the optimal choice and, accordingly, we recommended it to all patients after we explained to them the nature of HCC and the characteristics of all other available therapeutic options in the hospital. Patients made the decision by themselves according to their willingness and preference. Eventually 151 patients accepted our recommendation and entered the HIFU study arm while 30 patients who decided to try traditional Chinese medicine or did not want any therapeutic modalities were enrolled in the control arm. The other 68 patients who chose other therapeutic methods (15 with RF, 22 with PEI and 31 with TACE) were excluded from this study.

The study protocol was approved by the Ethics Committee of the First Municipal People's Hospital of Guangzhou, an affiliated hospital of Guangzhou Medical College. Written consent was obtained from each patient.

Instrument

HIFU tumor therapy equipment was provided by Chongqing HIFU Technology (Chongqing, China). The instrument is composed of three parts: a firing system located in a tank filled with degassed water; an imaging system consisting of an US scanner

coupled with a stereotaxic localizing arm; and a computer controlling system for the firing sequence and the movement of the firing head in three directions.

Focused US was produced with a 12 cm diameter piezoelectric ceramic transducer. The system was operated by using one of several therapeutic transducers with focal lengths that varied from 90 to 160 mm. For each focal length there was a choice between two transducers; one that operated at 0.8 MHz and the other that operated at 1.6 MHz. The choice of transducer depended on the depth of the target lesion, with the most commonly used parameters in this study being an operating frequency of 0.8 MHz and a focal length of 135 mm. An US imaging device was used as the real-time imaging unit of the system. A 3.5–5.0 MHz imaging probe was connected to the center of the HIFU transducer. The integrated transducer could be moved smoothly by electric motors in six directions: three orthogonal directions (X, Y and Z), rotation along the US beam axis, and rotation along the long or short axis of the bed. Controlled by a computer, the imaging probe was placed either against the skin or at a distance from the skin in water for pretreatment imaging. The integrated transducer was mounted in a water reservoir with the US beam directed upward. The water bag was filled with degassed water. The US beam of the therapeutic transducer and the imaging probe completely overlapped so that the longitudinal axis of the HIFU beam was in the two-dimensional US imaging plane. A calibrated polyvinylidene fluoride membrane hydrophone with a spot diameter of 0.5 mm was used to map the acoustic pressure field of the focused transducer at the focal peak intensities from 200–300 W/cm². The focal region was cigar shaped, with dimensions of 9.8 mm along the beam axis and 1.3 mm in the transverse direction. The absorbing target method was used to measure the total acoustic power output in degassed water at 21°C.^{6,14}

Treatment procedures

US and CT/MRI were performed before HIFU therapy to image the tumors. The number, size, location and morphology of the lesions were then determined. Special attention was paid to reveal the anatomical structures near the tumors. A variety of US beam deliveries were customized according to each patient's anatomic structure, tumor location and size. If the ribs obstructed the therapeutic US beam from targeting the whole lesions, they were removed 2 weeks before HIFU. In this study of 151 cases, 28 patients (18.5%) underwent rib resections.

Routine examinations and preoperative preparations were conducted according to the principle of surgery. The patients were fasted overnight, a nasogastric tube was inserted into the stomach for decompression, and the local skin for the HIFU operation area was shaved and cleaned with degassed water beforehand. During the operation, patients were fixed properly on the table. For patients undergoing long-term therapy, general anesthesia was used to ensure patients' comfort and immobility. The positions, sizes and morphological aspects of tumors were determined with an US diagnostic probe. Next, the monitoring system of the therapeutic transducer was switched on and the treatment range was defined according to the image parameters. The treatment focus was moved following the planned procedures from spot to line, from line to slice, from slice to volume. Eventually the entire targeted region was covered by HIFU, leading the whole tumors to

coagulation necrosis. During the therapeutic process, the real-time estimate of the therapeutic effect by the computer system was carried out through the graphic changes of the targeted field and the echo of the tissue. The therapeutic dosage, which was controlled by the computer, was adjusted with the feedback parameters.

After HIFU, patients received supportive therapy. No chemotherapy or any other kind of ablation therapy was given. Patients received additional HIFU sessions during the follow-up period if cancer relapsed or recurred. In total, 23 patients received more than one HIFU session. The patients in the control group received supportive therapy in addition to traditional Chinese medicines ($n = 26$) if they wished.

Follow-up of patients

Patients in both groups stayed in the hospital for at least 2 weeks and were then discharged if the general conditions allowed. When patients stayed in the hospital they were monitored weekly by means of physical examinations, complete blood counts, and renal (serum blood urea nitrogen [BUN] and creatinine) and hepatic function (serum aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin and bilirubin) tests. All patients were followed up for determination of the long term efficacy and complications related to the therapy. Patients were arranged to visit the hospital at month 1, 2, 3 and then at an interval of 3 months after HIFU for physical examinations, complete blood counts, and renal and hepatic function tests. The symptom scores, physical signs, methods of medical care and supportive treatment, status of family support, hepatic and renal functions, findings of image examinations (US and CT/MRI) and any possible adverse events of HIFU were recorded at each visit. In addition, a blood sample was taken for the measurement of serum levels of AFP, carcinogenic embryonic antigen (CEA) and CA19-9. Furthermore, the Karnofsky Performance Status (KPS) scales for general health and numerical rating scales (NRS) for pain at months 0, 1, 3, 6 and 12, and quality of life (QOL) scales at month 0, 3 and 12 were obtained. Briefly, three rating scales in the Chinese version were used to measure patients' conditions in general health and severity of symptoms. KPS scales (scores from 0 to 100) were based on the following items: severity of symptoms rated by patients themselves, activities of daily life and levels of nursing evaluated by medical staff. High KPS scores suggest good health.¹⁶ NRS for the evaluation of the severity of abdominal pain ranging from no pain (score 0) to severe pain (score 10) was rated by the patients themselves.¹⁷ QOL scales were estimated with a questionnaire form of QOL for liver cancer (QOL-LC) issued by Sun Yat-Sen University of Medical Sciences, China.¹⁸ This form was a modified version of the World Health Organization QOL for cancer patients (WHOQOL-BREF)¹⁹ and validated in Chinese patients. The form included 22 questions. Patients answered each question by self-rating the degree of severity on a scale from 0 to 9. A total score (from 0 to 100) was obtained by summarizing all questions.¹⁸

Evaluation of short and long term efficacy and complications of HIFU

Short term therapeutic effectiveness was estimated with the following items: (i) improvement in tumor imaging parameters

including a decrease in tumor size, decrease of tumor blood supply and change of imaging signals, suggesting coagulation necrosis in tumor areas; (ii) symptom relief including increase in KPS scores and/or decrease in NRS scores; and (iii) decrease of serum levels of AFP by more than 50%. Complete response (CR) was defined when all three items were reached, and partial response (PR) was defined when item 1 plus 2 or 1 plus 3 were reached. No response (NR) was defined when CR or PR was not achieved.

Long term effectiveness was determined with the increase of the survival rates and improvement of QOL-LC scores during the follow-up periods.

Complications of HIFU were considered if there was instability in vital signs (e.g. blood pressure, heart rate, respiratory rate and blood oxygen saturation) during and shortly after HIFU, or if there was any adverse event (e.g. injury of splanchnic organs and the impairment of renal or hepatic function) within 2 weeks after HIFU.

Statistical analysis

Values for the continuous variables were presented as the mean $\pm$ standard deviation (SD). Student's *t*-test and the χ^2 -test were used for evaluations of continuous and categorical variables, respectively. SPSS software 12.5 for Windows (SPSS, Chicago, IL, USA) was used for data analysis. Difference was considered statistically significant when the *P* level was less than 0.05.

Results

Demographic and clinical data at entry to the study

At entry to the study, all patients enrolled had symptoms such as upper abdominal pain, bloating, fatigue and loss of appetite. The majority (72.4%) had underlying cirrhosis. All patients had damaged hepatic function with elevated serum ALT levels. All variables including age, gender, duration and severity of the disease, hepatic function, renal function and tumor metastases were normally distributed and were not significantly different between the HIFU group and the control group (Table 1). The maximal diameter of tumors ranged from 3–20 cm (7.6 ± 3.4 cm) in the HIFU group and from 5–18 cm (6.9 ± 4.1 cm) in the control group. Number of tumor lesions were between one and five (1.3 ± 1.8) in the HIFU group and between one and four (1.4 ± 1.2) in the control group. Hepatitis B surface antigen (HBsAg) was detected in most patients (95 in the HIFU group and 24 in the control group; all $P < 0.05$).

Because results obtained from non-randomized studies are likely to be confounded by some biases, we attempted to minimize the selection bias by recruiting consecutive patients, and to minimize the control group bias by conducting a pre- and post-treatment comparison, in addition to the test- and control-group comparison for all variables, except the response rate and the survival rate.

Short term efficacy

Symptom relief was observed 1–2 days after HIFU and became more obvious at 1 month. The investigated variables before

Table 1 Demographic and clinical data of high intensity focused ultrasound (HIFU) and control groups at entry to the study

Variable	HIFU group (<i>n</i> = 151)	Control group [†] (<i>n</i> = 30)
Age (years, mean $\pm$ SD)	29–78 (54 $\pm$ 23)	39–68 (61 $\pm$ 18)
Sex (male/female)	122/29	24/6
Disease duration (months, mean $\pm$ SD)	3.9 $\pm$ 5.8	2.8 $\pm$ 2.6
With cirrhosis (<i>n</i> , %)	106 (70.2%)	25 (83.3%)
TNM stages (IIb/III/IV)	7/81/63	1/15/14
Child-Pugh degree (A/B/C)	76/65/10	5/18/7
Total bilirubin level	35.5 $\pm$ 30.3	37.2 $\pm$ 32.3
ALT level	92.5 $\pm$ 33.6	97.7 $\pm$ 31.6
BUN level	6.5 $\pm$ 3.3	7.1 $\pm$ 3.8
AFP elevation (<i>n</i> , %)	137 (90.7%)	27 (90.0%)
CA19-9 elevation (<i>n</i> , %)	53 (35.1%)	11 (36.6%)
Number of lesions (mean $\pm$ SD)	1.3 $\pm$ 1.8	1.4 $\pm$ 2.1
Maximal diameter of lesion (cm, mean $\pm$ SD)	7.6 $\pm$ 3.4	6.9 $\pm$ 4.1
With portal vein embolism (<i>n</i> , %)	79 (52.3%)	16 (53.3%)

[†]There was no significant difference between the two groups for all variables. AFP, α -fetoprotein; ALT, alanine aminotransferase; BUN, blood urea nitrogen; TNM, tumor stage.

Table 2 Changes in the Karnofsky Performance Status (KPS) scores, numerical rating scale (NRS) scores, and serum levels of α -fetoprotein (AFP) and CA19-9 at month 1 in the high intensity focused ultrasound (HIFU) and control groups

Variable	HIFU group (<i>n</i> = 151)		Control group (<i>n</i> = 30)	
	Month 0	Month 1	Month 0	Month 1
KPS score	47.7 $\pm$ 13.9	68.9 $\pm$ 13.5*	48.8 $\pm$ 18.3	51.9 $\pm$ 24.5
NRS score	5.3 $\pm$ 2.5	4.5 $\pm$ 1.9	5.1 $\pm$ 2.9	4.8 $\pm$ 3.1
AFP (ng/mL)	738 $\pm$ 312	457 $\pm$ 198*	754 $\pm$ 328	763 $\pm$ 319
CA19-9 (u/L)	108 $\pm$ 65	99 $\pm$ 56	95 $\pm$ 54	111 $\pm$ 63

**P* < 0.05 compared with preoperation (month 0) and controls (both months 0 and 1).

(month 0) and 1 month after HIFU (month 1) are shown in Table 2. Both KPS and NRS scores improved after HIFU, but only KPS scores reached the significant level (*P* < 0.05). Post-HIFU serum AFP levels decreased significantly compared with levels before HIFU (*P* < 0.05). Serum levels of CA19-9 also decreased, but did not reach significant levels compared with the control group. Besides the evidence of imaging improvement, both relief of symptoms and decrease of laboratory tumor makers were observed at month 1 in the HIFU group compared to the control group. Although not all parameters reached significant levels, a trend in improvements was definitely observed.

Improvement of tumor MRI imaging parameters in a typical case is shown in Figure 1. After HIFU treatment, the decrease in tumor size, decrease of tumor blood supply and change of imaging signals (cavitation) suggested coagulation necrosis in tumor areas.

In the HIFU group comprising 151 patients, CR and PR were achieved in 28.5% (*n* = 43) and 60.3% (*n* = 91) of patients, respectively, while the rates were 0% (*n* = 0) and 16.7% (*n* = 5), respectively, in the control group comprising 30 patients. Thus, the total response rate (CR + PR) in the HIFU group was 88.8%, which was significantly greater than that (16.7%) in the control group (*P* < 0.01).

Long term efficacy

The overall mean duration of follow-up was 12.5 $\pm$ 13.9 months (range: 3–34 months), with the duration being longer in the

HIFU group (14.3 $\pm$ 13.8 months) than in the control group (7.6 $\pm$ 7.5 months) (*P* < 0.05). In the HIFU group, 15 patients (10.0%) dropped out of the follow-up. Among these patients, 10 dropped out within 6 months, three between 6 months and 1 year, and two after 1 year. In the control group, two patients dropped out between 6 months and 1 year. The reason for drop out from the two groups was due to the patients' unwillingness to be disturbed with follow-up programs. The crude survival rates at 6 months, 1 year and 2 years were significantly higher in the HIFU group than in the control group (*P* < 0.01) (Table 3).

In the HIFU group, the QOL scores at month 3 and month 12 in surviving patients were 83.1 $\pm$ 8.0 and 74.2 $\pm$ 6.9, respectively. The score at month 3 was significantly increased compared with the pre-HIFU scores (68.9 $\pm$ 7.5) (*P* < 0.05). In the control group, the QOL scores at month 0, 3 and 12 were 67.7 $\pm$ 5.9, 69.0 $\pm$ 8.5 and 66.7 $\pm$ 7.2, respectively. The QOL scores at month 3 in the HIFU group (83.1 $\pm$ 8.0) were also significantly higher than those (69.0 $\pm$ 8.5) in the control group (*P* < 0.05).

Complications

During and shortly after HIFU, vital signs including blood pressure, pulse, respiratory rates and blood oxygen saturation were stable in all patients. Slight fever (<38.5°C) and transient local pain occurred and lasted for 2–5 days in almost all cases after HIFU. Impairment of hepatic functions (i.e. elevation of serum

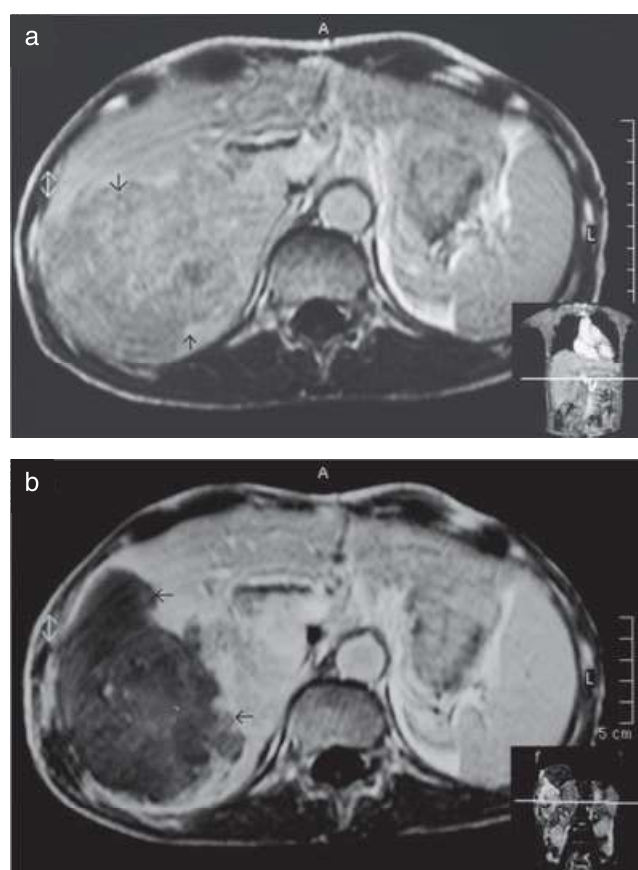


Figure 1 Magnetic resonance imaging (MRI) on T1-weighted images showing improvement in hepatocellular carcinoma (HCC) in a typical case (male, aged 58 years) after high intensity focused ultrasound (HIFU). (a) Tumor (18.2 cm × 13.8 cm × 9.2 cm) located in the right posterior lobe (arrow); (b) after HIFU, the tumor shrinks and cavitation with obvious necrosis and decreased blood supply is seen (arrow).

Table 3 Crude survival rates in the high intensity focused ultrasound (HIFU) group and the control group

Follow-up duration	HIFU group (n = 151) [†]	Control group (n = 30) [‡]
6 months	109/141 (77.3%)*	8/30 (26.7%)
1 year	69/138 (50.0%)*	1/29 (3.4%)
2 years	42/136 (30.9%)*	0/28 (0%)

* $P < 0.01$ compared with the control group. [†]Ten patients dropped out within 6 months, three between 6 months and 1 year, and two patients after 1 year. [‡]Two patients dropped out between 6 months and 1 year.

ALT and/or bilirubin levels) lasted for 2–3 weeks. The severity of the impairment was related to the size of the targeted area and the dosage of HIFU. No severe complications, such as liver failure or bleeding, took place in all patients, including 55 patients with portal vein cancer embolisms. Minor skin burns at operation spots occurred in 38 (2.5%) patients. Reactive effusion from the right pleural cavity was observed in seven patients, but all of the above patients recovered within 2 weeks. There were no other severe adverse events throughout the study.

Discussion

The first work to consider potential applications of HIFU was published in 1942. During the 1950s and 1960s most studies were performed in neurosurgery. In 1956, HIFU was suggested as a treatment for cancer for the first time and then the specific properties of HIFU conduction and its effect on experimental tumors were thoughtfully investigated. The thresholds for liver tissue destruction with varying exposure parameters were established from the 1970s to the 1990s.^{7,8} Tumor models were used to predict the effect of HIFU on HCC or liver metastases in humans. HIFU as an ablative technique has been applied to the treatment of prostate cancer and benign prostatic hyperplasia in Europe.^{8,9} A number of phase II trials for HIFU to treat a variety of benign and malignant diseases of solid organs have been going on in many countries for decades.^{7–9} The mechanisms of tissue destruction with HIFU ablation are mainly related to hyperthermia and cavitation. HIFU can also activate body immunity and decrease tumor growth.^{20,21} HIFU is a new ablation technique with several advantages, including non-invasiveness, accuracy, real-time targeting process and shape suitability. Therefore, HIFU provides patients with a new therapeutic option with less pain, less damage to splanchnic functions, faster recovery and no risk of tumor seeding from the inserted instrument tract. China is the first country to approve HIFU for the treatment of HCC.⁴ After clinical trials in more than 1000 patients with tumors of solid organs, including liver, kidney, bone, breast, uterus and prostate, the clinical guidelines for HIFU for tumors issued by the Chinese Medical Association was published in 2005.²²

The short term efficacy of HIFU for patients with HCC has been reported in some studies.^{10–12} So far, only two papers from the same team reported the long term survival rates of HIFU.^{13,14} However, these studies were based on either small sample sizes or were conducted in a non-controlled nature. In the present controlled studies with a relatively larger sample size, we observed improvement of both short and long term efficacy of HIFU in patients with advanced HCC, which was in agreement with previous observations.^{10–12} The most important point was that HIFU resulted in a significant increase in survival rates. Although our findings were consistent with the observations reported by others using HIFU^{13,14} or other regional ablation techniques, such as PEI and RF therapies,^{2,3} our results appear to be more exciting, because all patients included in this study had advanced (late stage) HCC. QOL scores have not been well evaluated in previous studies to determine the efficacy of HIFU for HCC. In the present study, we chose month 3 after HIFU as the earliest time to measure the QOL scores, in order to ensure the accuracy of QOL assessment. At that time almost all patients were discharged from the hospital. The significant improvement of QOL also supports the clinical benefit of HIFU.

For ethical reasons, it was impossible to perform a randomized study on patients with HCC. However, the patients in this study and control arms originated from the same unit during the same period of time, and the demographic and clinical data at entry to the study between the two groups were parallel and comparable statistically. The bias may be unavoidable as they were in a non-randomized study. As mentioned, we tried to minimize the selection bias and the control group bias. We also tried to minimize the detection bias by blinding the staff involved in the imaging and laboratory examinations. Both short and long term comparisons in

favor of the HIFU group made the conclusion more convincing. However, the outcomes for the long term survival rates are vulnerable to being confounded by many factors, such as a less active attitude towards the disease and poorer nutritional maintenance in the control group than in the HIFU group. The survival rates of HIFU being similar to but not superior to those of other regional ablation therapies in the literature indicates that our findings are reliable.^{2,3} It seems that careful ablation of the tumors by HIFU is not sufficient to further prolong the survival time.

Owing to its non-invasive nature, HIFU can be applied to multinodular and large tumors, and even lesions located nearby the hepatic hilus and the cancer embolisms in the portal vein. Therefore, many patients with late stage HCC unsuitable for other ablation therapies were enrolled in the present study. We successfully treated 55 patients with portal vein cancer embolisms without severe adverse effects and major complications, which suggested the safety of HIFU for these patients. Therefore, HIFU extends the indications of conventional ablation therapies. However, some disadvantages of HIFU were observed in the present study. First, it was a time-consuming procedure, taking on average 3–4 h for one operation. In some difficult cases, more than 7 h were needed. In these cases general anesthesia was given to ensure patients received the treatment in a calm state. It is impossible and not advisable to increase the HIFU intensity to shorten the therapeutic time, due to the limitation of the HIFU device or due to the avoidance of damage to overlying structures, especially burns to the skin. Second, it was a labor intense work, usually needing five medical staff including an operation doctor, an US doctor, an anesthetist, a nurse and an engineer working together. Third, in patients whose tumor was located behind a rib, which makes the US beam unable to penetrate the narrow inter-rib space to target the whole lesion at an accurate angle, the rib had to be removed to obtain a proper window for the therapy. Under these circumstances HIFU is even more invasive than the other ablation therapies. In the present study of 151 patients, 28 patients (18.5%) underwent rib resections. At the beginning of this study, we believed that HIFU was the best choice for most patients with HCC. We referred the patients who needed a rib resection to HIFU. However, after 4-years of observation, we failed to observe any advantage of HIFU over other ablation techniques (PEI and RF) in terms of survival rates.¹⁶ After having balanced the benefit of HIFU and the damage of rib resections, we suggest that patients with tumors behind a rib should be referred to other ablative therapies, instead of HIFU. In this way, rib resection can be avoided and HIFU maintains its non-invasive nature. Therefore, we recommend the following indications for HIFU in HCC treatment: (i) advanced HCC, which is unsuitable for surgical resection; (ii) tumor involvement less than 70% volume of the liver; (iii) the number of lesions less than five; (iv) not in the end-stage of liver disease (liver failure, hepato–renal syndrome); (v) no severe concomitant diseases; and (vi) no lesion behind the rib.

The scope of the combination of HIFU with other treatment modalities is likely to expand. Combination of HIFU and TACE increases the effectiveness of both techniques and shortens the HIFU therapeutic time, because the reduction of the blood supply and deposition of contrast in tumor areas after TACE enables HIFU to effectively and precisely destroy target lesions.^{14,23} Intravenous injection of microbubble contrast agent might also increase the effect of HIFU treatment.^{24,25}

In conclusion, HIFU achieved satisfactory short and long term efficacy and is safe for the treatment of advanced HCC. Therefore, HIFU offers a new therapeutic option with less invasion and wider indications than the conventional ablation techniques. More studies, especially ones with large scale randomized clinical trials, are needed to confirm our observations and to further determine the role of HIFU in HCC treatment.

References

- Bosh FX, Ribes J, Charies R, Diaz M. Epidemiology of hepatocellular carcinoma. *Clin. Liver Dis.* 2005; **9**: 191–211.
- Jansen MC, van Hillegersberg R, Chamuleau RA *et al.* Outcome of regional and local ablative therapies for hepatocellular carcinoma: a collective review. *Eur. J. Surg. Oncol.* 2005; **31**: 331–47.
- Beaugrand M, N'kontchou G, Seror O *et al.* Local/regional and systemic treatment of hepatocellular carcinoma. *Semin. Liver Dis.* 2005; **25**: 201–11.
- Wu F, Chen WZ, Bai J. A preliminary study of high intensity focused ultrasound in the treatment of hepatocellular carcinoma. *Chin. J. Ultrasound (Zhonghua Chao Sheng Za Zhi)* 1999; **8**: 213–16.
- Wang Z, Bai J, Li F *et al.* Study of 'biologic focal region' of high-intensity focused ultrasound. *Ultrasound Med. Biol.* 2003; **29**: 749–54.
- Kennedy JE, Ter Haar GR, Cranston D. High intensity focused ultrasound: surgery of the future? *Br. J. Radiol.* 2003; **76**: 590–9.
- Jolesz FA, Hynynen K, McDannold N, Freundlich D, Kopelmam D. Non-invasive thermal ablation of hepatocellular carcinoma by using magnetic resonance-guided focused ultrasound. *Gastroenterology* 2004; **127** (Suppl. 5): s242–7.
- Kennedy JE, ter Haar GR, Cranston D. High intensity focused ultrasound: surgery of future? *Br. J. Radiol.* 2003; **76**: 590–9.
- Illing RO, Kennedy JE, Wu F *et al.* The safety and feasibility of extracorporeal high-intensity focused ultrasound (HIFU) for the treatment of liver and kidney tumours in western population. *Br. J. Cancer* 2005; **93**: 890–5.
- Wu F, Wang ZB, Chen WZ *et al.* Extracorporeal high intensity focused ultrasound ablation in the treatment of 1038 patients with solid carcinoma in China: an overview. *Ultrason. Sonochem.* 2004; **11**: 149–54.
- Kennedy JE, Wu F, ter Haar GR, Gleeson FV *et al.* High-intensity focused ultrasound for the treatment of liver tumors. *Ultrasonics* 2004; **42**: 931–5.
- Li CX, Xu GL, Jiang ZY *et al.* Analysis of clinical effect of high-intensity focused ultrasound on liver cancer. *World J. Gastroenterol.* 2004; **10**: 2201–4.
- Wu F, Wang ZB, Chen WZ *et al.* Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma. *Ann. Surg. Oncol.* 2004; **11**: 1061–9.
- Wu F, Wang ZB, Chen WZ *et al.* Advanced hepatocellular carcinoma: treatment with high intensity focused ultrasound ablation combined with transcatheter arterial embolization. *Radiology* 2005; **235**: 659–67.
- Ren ZG. Diagnostic criteria for primary liver cancer: guideline of Chinese Association for cancer prevention. *Chin. J. Hepatol. (Zhonghua Gan Zang Bing Za Zhi)* 2000; **8**: 135 (in Chinese).
- Karnofsky DA. The use of nitrogen mustards in palliative treatment of carcinoma. *Cancer* 1948; **1**: 634–56.
- Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain* 1994; **56**: 217–26.

- 18 Fan ZG. Quality of life for patients with liver cancer. In: Fan ZG, ed. *Measurement and Application of Quality of Life*. Beijing: Beijing Medical University Publication, 2000; 298–303 (in Chinese).
- 19 Ferrell BR, Dow KH, Grent M. Measurement of quality of life in cancer survivors. *Qual. Life Res.* 1995; **4**: 523–31.
- 20 Wu F, Wang ZB, Lu P *et al.* Activated anti-tumor immunity in cancer patients after high intensity focused ultrasound ablation. *Ultrasound Med. Biol.* 2004; **39**: 1217–22.
- 21 Miller DL, Song J. Tumor growth reduction and DNA transfer by cavitation-enhanced high intensity focused ultrasound in vivo. *Ultrasound Med. Biol.* 2003; **29**: 887–93.
- 22 Chinese Medical Association. Guideline for clinical application of high intensity focused ultrasound to treat tumors. *Natl. Med. J. China (Zhonghua Yi Xue Za Zhi)* 2005; **85**: 796–7 (in Chinese).
- 23 Jin CB, Wu F, Wang ZB *et al.* High intensity focused ultrasound therapy combined with transcatheter arterial chemoembolization for advanced hepatocellular carcinoma. *Chin. J. Tumor (Zhonghua Zhong Liu Za Zhi)* 2003; **25**: 401–3 (in Chinese).
- 24 Kaneko Y, Maruyama T, Takegami K *et al.* Use of a microbubble agent to increase the effect of high intensity focused ultrasound on liver tissue. *Eur. Radiol.* 2005; **15**: 1415–20.
- 25 Kennedy JE, ter Heer GR, Wu F *et al.* Contrast-enhanced ultrasound assessment of tissue response to high intensity focused ultrasound. *Ultrasound Med. Biol.* 2004; **30**: 851–4.