High-intensity focused ultrasound for hepatocellular carcinoma — a single-center experience

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Mini-Abstract

High-intensity focused ultrasound (HIFU) is a totally non-invasive ablation treatment for hepatocellular carcinoma. The complete tumor ablation rate was 79.5%. The 1-year survival rate was 87.7%.

Abstract

Objective: This study aims to evaluate the outcome of patients with hepatocellular carcinoma (HCC) treated by high-intensity focused ultrasound (HIFU) in a single tertiary referral center.

Summary Background data: HIFU is the latest developed local ablation technique for unresectable HCC. The initial experience on its efficacy is promising, but the survival benefit of patients undergoing HIFU for HCC is poorly defined.

Methods: From October 2006 to December 2008, 49 patients received HIFU for unresectable HCC. Each patient underwent a single session of HIFU with a curative intent. Treatment efficacy and survival outcome were evaluated. Clinicopathologic factors affecting the primary technique effectiveness and overall survival rates were investigated by univariate analysis.

Results: The median size of the treated tumors was 2.2 cm, ranging from 0.9 cm to 8 cm. The majority of patients had single tumors (n = 41, 83.6%). Thirty one patients (63.2%) had artificial right pleural effusion during HIFU treatment to reduce damage to the lung and diaphragm. The hospital mortality rate was 2% (n = 1) and the complication rate was 8.1% (n = 4). The primary technique effectiveness rate was 79.5% (39 out of 49 patients). It increased from 66.6% in the initial series to 89.2% in the last 28 patients. Tumor size (≥ 3.0 cm) was the significant risk factor affecting the

complete ablation rate. The 1- and 3-year overall survival rates were 87.7% and 62.4%, respectively. Child-Pugh liver function grading was the significant prognostic factor influencing the overall survival rate.

Conclusions: HIFU is an effective treatment modality for unresectable HCC with a high technique effectiveness rate and favorable survival outcome.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, with a high prevalence in Asia and an increasing incidence in Western countries. With advancement in technologies, local ablation therapies have emerged as effective treatment options for unresectable HCC. These include cryoablation therapy, interstitial laser therapy, microwave coagulation, radiofrequency ablation (RFA), and high-intensity focused ultrasound (HIFU). Among these treatment options, HIFU is the only treatment modality that is completely extracorporeal.

HIFU is based on the unique characteristic of ultrasound beams (0.8 – 3.5 MHz), which can be focused at a distance from the radiating transducer. The accumulated energy at the focal region induces tissue necrosis of the targeted lesion without causing damage to the surrounding vital structures. The ability of inducing immediate cell death at a distance from the ultrasound source without the need of surgery or insertion of ablation instruments makes HIFU an attractive treatment option for HCC. While data on the efficacy of HIFU in treating HCC remain scarce, initial clinical results obtained from pioneer researchers in China have been encouraging.[1-7] The reported complete ablation rates ranged from 28.5% to 68%.[1,6,7] The short-term survival (one-year) rates ranged from 42.9% to 61.5%.[1,4] However, there is no report on identification of the possible risk factor affecting the complete ablation rate and the possible prognostic factor influencing the overall survival. Such information is crucial in

establishing the role of HIFU in the management of patients with HCC. The present study aims to evaluate the clinical outcome of patients with HCC treated by HIFU, and investigate the clinicopathologic factors affecting the complete ablation rate of HIFU and patient survival.

Methods

Selection of patients

From October 2006 to December 2008, 49 patients with unresectable HCC received HIFU treatment. Patients with advanced diseases due to tumor invasion to major intrahepatic blood vessels or extrahepatic metastasis were not selected for the treatment. Patients with HCC that could not be visualized by diagnostic ultrasound of the HIFU system were also excluded. Diagnosis of HCC was based on radiological features shown by computed tomography scan or magnetic resonance imaging (MRI) scan and/or raised serum α-fetoprotein concentration (over 400 ηg/ml). A tumor was considered unresectable if the patient had unsatisfactory liver function or if there was a high medical risk for the patient to undergo hepatic resection. The selection criteria for HIFU were as follows: (1) The maximal tumor diameter was less than 8 cm. (2) The number of tumor nodules was less than 3. (3) The tumor could be detected by ultrasound imaging and there were no bowel adjacent to the tumor. Each selected patient underwent a single session of HIFU aiming at complete ablation of all

detected tumors. A total of 57 tumors were ablated. During the initial phase of the study period (from October 2006 to May 2007), 21 patients had transarterial injection of iodized poppyseed oil (Lipiodol) into their tumors about two weeks before HIFU treatment because previous researchers suggested that Lipiodol could reduce tumor blood supply and increase the deposition of ultrasonic energy in the tumor. In the later phase of the study (from June 2007 to December 2008), 28 patients received HIFU only.

Treatment procedures

The JC HIFU system (Chongqing Haifu Technology, Chongqing, China) was used in this study. The ablation process was guided by real-time ultrasound imaging. This system is composed of a real-time diagnostic ultrasound device, an integrated ultrasound therapy transducer (12 cm in diameter), a six-directional therapeutic planning system, an ultrasound generator, a degassed water circulation unit, and a computer unit for automated master control. The focused ultrasound was produced by the transducer operating at 0.8 MHz (aperture 120 mm, focal length 150 mm). The target lesion was identified using a central 3.5-MHz diagnostic ultrasound probe, which was integrated in the center of the therapeutic transducer. Both diagnostic and therapeutic ultrasound beams were emitted simultaneously in the same direction.

In patients receiving pre-HIFU Lipiodol deposition into their tumors, hepatic angiography was performed two weeks before HIFU treatment. Lipiodol was delivered via selective cannulation of the feeding artery of the target tumor.

HIFU treatment was performed under general anesthesia to alleviate deep visceral pain caused by HIFU and to ensure immobilization of patients. Temporary inspiratory or expiratory control by the anesthesiologist helped to minimize liver movement caused by ventilation during the treatment.[8] In selected patients with a tumor at the dome of the liver, artificial right pleural effusion was induced before treatment. Detailed planning was carried out according to the tumor size and location as detected by the diagnostic ultrasound transducer. Parallel slides of the target tumor with 5-mm separation were obtained. Using provisional therapeutic parameters based on the depth and vascular supply of the target tumor, tissue of each tumor slide was completely ablated from deep to superficial region by successful sweeps of the HIFU head. The ablation process was repeated slide by slide to achieve entire tumor ablation. During the ablation process, grey-scale changes were noted in the ablation zone, signifying the effectiveness of ablation.

Data collection and outcome measures

Clinical details of all 49 patients were prospectively collected in a database. Clinical parameters included patient demographics, tumor characteristics, and treatment parameters (total treatment duration and acoustic power). Short-term outcome measures were post-HIFU complication rate, hospital mortality, and tumor responses. A complication was defined as any adverse event after HIFU, and hospital mortality was defined as any death in the same admission for the procedure. Tumor responses were classified as the primary technique effectiveness rate and secondary technique effectiveness rate, according to the recommendation by the international Working Group on Image-guided Tumor Ablation[9]. The primary technique effectiveness rate was defined as the percentage of tumors that were successfully eradicated following the initial course of HIFU, whereas the secondary technique effectiveness rate was defined as the percentage of tumors that have undergone successful repeat ablation following identification of local tumor progression. Tumor response to HIFU was assessed by MRI, which was performed one month after the procedure. Successful tumor ablation was defined as complete absence of hyperintensity signal in T2W images and absence of contrast enhancement within the original tumor region (Figure 1). Any contrast-enhancing area within the original tumor region on post-ablation MRI scan indicated a residual tumor. RFA or chemoembolization was performed in selected patients to treat

residual tumors. All patients had monitoring of serum α-fetoprotein concentration, chest radiograph and MRI scan every three months to detect tumor recurrence.

Statistical analysis

Continuous data were expressed as medians with ranges and were compared using the Mann-Whitney *U* test. Categorical data were compared using the χ^2 test with Yates correction or Fisher exact test where appropriate. The overall and disease-free survival rates were calculated by the Kaplan-Meier method and compared between the groups using the log-rank test. The end-point of disease-free survival was recurrence of HCC at or outside of the ablation site or death of the patient, but excluding hospital mortality. Clinicopathologic variables were analyzed for their effects on the primary technique effectiveness and overall survival rates. Host factors included age, gender, hepatitis B surface antigen status, anti-hepatitis C antibody status, Child-Pugh liver function grading[10], serum bilirubin level, serum albumin level, platelet count, and previous treatment (hepatectomy, RFA or transarterial chemoembolization). Tumor factors included maximum tumor size, number of tumors (solitary vs. multiple) and serum α-fetoprotein level. Finally, the practice of pre-HIFU Lipiodol deposition, the use of artificial right pleural effusion, and the primary and secondary technique effectiveness were included in the analysis of overall survival. For the significant continuous variables identified by the univariate analysis, the cut-off value was determined

using the discriminant analysis. All statistical analyses were performed using the statistical software SPSS 11.0 for Windows (SPSS Inc., Chicago, IL). A *P*-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

The demographic and clinicopathologic data of all 49 patients treated by HIFU are shown in Table 1. Among the 49 patients, 37 patients (76%) were hepatitis B carriers and 7 patients (14%) were hepatitis C carriers. The majority of patients (n = 41, 83.6%) had preserved liver function (Child-Pugh class A). These patients had high medical risks (presence of co-morbidities) to undergo hepatic resection for HCC. Another 8 patients had marginal liver function (Child-Pugh class B) that prohibited major hepatic resection of tumors. Liver transplantation was not offered to them because of the local policy of offering scarce deceased organs to patients with Child-Pugh class C liver function only. HIFU was performed for intrahepatic recurrent tumors in 17 patients and 14 patients following hepatectomy and RFA, respectively. Eighteen patients (36%) received HIFU for tumors that failed previous transarterial chemoembolization. Twenty-eight patients (57.1%) received HIFU as the primary treatment for their newly diagnosed HCC. The median tumor size was 2.2 cm (range, 0.9 – 8 cm). The majority of patients (n = 41, 83.6%) had solitary tumors. Artificial right

pleural effusion was induced before HIFU treatment in 31 patients (63%) with tumors near to the diaphragm to reduce damage to the lung and diaphragm by heat generated during the treatment. The median HIFU treatment duration was 26 minutes (range, 3 – 124 minutes).

Short-term outcome

One patient in the early part of the series died of myocardial infarction one day after HIFU treatment. This patient had underlying ischemic heart disease, which was not diagnosed before the HIFU treatment. The hospital mortality rate was 2%. The treatment-related complication rate was 8.1% (n = 4). The complications included first-degree and second-degree skin burn around the treatment zone in 2 patients and 1 patient, respectively. These complications were due to an error of using high acoustic power. One patient developed bruising over the right chest wall, extending to the right loin region. This was caused by bleeding from intercostal vessels that were injured during induction of artificial pleural effusion. The median hospital stay was 4 days (range, 2 – 16 days) (Table 2).

Ten patients (20.4%) had residual tumors detected by MRI one month after the treatment. The primary technique effectiveness rate was 79.5% (39 of 49 patients). Taking into consideration the total number of ablated tumor nodules, the primary technique effectiveness rate was 82.4% (47 out of 57 nodules). Four patients received percutaneous RFA treatment for residual tumors and three of them were rendered tumor-free after RFA. Another 4 patients

having residual tumors underwent transarterial chemoembolization but tumor control was incomplete. The overall secondary technique effectiveness rate after HIFU and RFA was 85.7% (42 out of 49 patients).

Table 3 showed the results of univariate analysis on the possible risk factors for incomplete ablation after HIFU treatment. Tumor size was the only significant risk factor affecting the primary technique effectiveness rate of HIFU. Patients with primary technique effectiveness had significantly smaller tumors than those with residual tumors after HIFU treatment (median tumor size: 2.29 cm vs. 3.75 cm, $P = 0.013$). The cut-off value of tumor size as the significant risk factor for incomplete ablation by HIFU was 3.0 cm. The primary technique effectiveness for tumors < 3.0 cm was 90.6% (29 out of 32 patients), whereas that for tumors ≥ 3.0 cm was 58.8% (10 out of 17 patients). The primary technique effectiveness rate of patients with HIFU alone (89.2%) was higher than that of those with HIFU and pre-treatment Lipiodol deposition (66.6%), although the difference was not significant statistically.

Tumor recurrence and survival outcome

The median follow-up period was 24 months (range, 3 – 38 months). Among the 42 patients with tumors completely ablated by primary and secondary techniques, 9 patients (21.4%) developed local recurrence at the HIFU treatment zone. The long-term local tumor

control rate is 67%. All the 9 patients with local tumor recurrence belonged to the group in which HIFU treatment was preceded by Lipiodol deposition. On the other hand, all patients treated by HFIU alone did not develop local tumor recurrence at the site of HIFU treatment. Seventeen patients (40.4%) had intrahepatic tumor recurrence (away from the ablation site). Four patients (9.5%) developed extrahepatic metastasis. The overall recurrence rate was 61.9% (26 out of 42 patients). The 1- and 3-year overall survival rates were 87.7% and 62.4%, respectively (Figure 2). The 1- and 3-year disease-free survival rates were 40.7% and 0%, respectively (Figure 3). Among the clinicopathologic factors, Child-Pugh grade was the only significant prognostic factors influencing overall survival. The overall 1- and 3-year survival rates of the patients with Child-Pugh class A were 90.2% and 68.5%, respectively, whereas those of the patients with Child-Pugh class B were 75% and 33.3%, respectively ($P = 0.028$). The overall survival rates of patients with secondary technique effectiveness (1-year survival rate: 92.9%; 3-year survival rate: 66.8%) were better than those of the patients with residual tumors after sequential local ablation (1-year survival rate: 53.6%; 3-year survival rate: 35.7%) (P=0.06) (Table 4).

Discussion

HIFU is a newly developed non-invasive treatment modality for liver tumors. Compared with other local ablation therapies, HIFU treatment has the major advantage of being totally

extracorporeal without the need of insertion of any ablation needle in the target lesion. With high acoustic intensities (up to 10,000 Watt/cm^2), HIFU induces instantaneous cell death by two major mechanisms, namely, thermal effect and mechanical effect.[11] The thermal effect of HIFU features heat generation due to absorption of acoustic energy by the target tissue. A lethal temperature of up to 60°C causes coagulative necrosis within a few seconds. Since high-intensity energy is focused at a small volume, damage to tissues between the transducer and the target lesion is minimized. The mechanical effect involves cavitation[12], microstreaming[13] and radiation forces[14]. With these destructive mechanisms, irreversible cell death occurs through coagulative necrosis and apoptosis.

The application of HIFU technology in the management of patients with HCC is still in its infancy period. The feasibility and safety of HIFU for liver tumors were initially demonstrated in the early 1990s.[11] However, this technology has not gained much enthusiasm, primarily because of the difficulties in tumor targeting and monitoring of the ablation process. However, with recent advances in the ultrasound technology, the accuracy of targeting of HIFU has improved considerably.

The initial experience of HIFU for HCC was obtained from researchers in China using the JC HIFU system, which was also used in the present study. In a study by Wu et al[1] in which 55 patients with large HCC (with a mean diameter of 8.14 cm) and cirrhosis received HIFU treatment, no major complications were recorded. Completeness of ablation was

assessed in 26 patients and the complete ablation rate was 69.2%. The overall survival rates were 61.5% at 12 months and 35.3% at 18 months. In another study by the same group[4], the efficacy of HIFU combined with chemoembolization was compared with that of chemoembolization alone in 50 patients with advanced HCC. Patients who underwent combined treatment had significantly better survival than those who received chemoembolization alone. In the Western population, the efficacy of this HIFU system in treating liver tumors has also been validated.[15] In this study, the effectiveness of HIFU was confirmed and a higher primary technique effectiveness rate (79.5%) was achieved.

Although the treatment efficacy and survival benefits of HIFU for patients with liver cancer were well documented in the previous studies[1-7], clinicopathologic factors influencing the completeness of tumor ablation and patient survival were not studied in detail. We found that tumor size (≥ 3.0 cm) was a significant risk factor accounting for incomplete tumor ablation after HIFU. Although HIFU has the merit of being extracorporeal in nature, the portion of skin and subcutaneous tissue along the pathway of focused ultrasound was frequently affected, causing tissue edema. As large tumors require longer ablation time by the HIFU machine, the resulting cutaneous and subcutaneous tissue edema will reduce the targeting ability of the diagnostic ultrasound of the HIFU machine. Hence, the precision of the deposition of focused ultrasound onto the target lesion will be negatively affected. As shown in our study, patients with residual tumors after a single session of HIFU treatment had

significantly larger tumors (median tumor size: 3.75 cm vs. 2.29 cm). Large tumors may, therefore, need "planned" repeated HIFU treatment or a second treatment once a residual lesion is detected by imaging.

Apart from tumor size, the use of pre-treatment Lipiodol deposition was another possible factor affecting the completeness of tumor ablation. In the treatment protocol of HIFU designed by researchers in China, Lipiodol deposition via hepatic angiography is usually combined with this ablation technique.[1,4] Theoretically, Lipiodol deposition in the tumor can increase the ablation volume of HIFU by two possible mechanisms. First, tumor blood flow decreases after Lipiodol occlusion of tumor microvasculatures, resulting in reduced heat loss during thermal treatment by HIFU. Second, Lipiodol deposition in the tumor causes increased deposition of ultrasonic energy.[16] Nevertheless, the administration of Lipiodol shortly before HIFU is not without disadvantages. In fact, non-specific deposition of Lipiodol within the same liver segment as the target tumor invariably affected ultrasound localization of the tumor and hence the targeting accuracy of HIFU because the affected liver segment was also filled with Lipiodol (Figure 4). In such instance, tumor margins could only be poorly defined by the diagnostic ultrasound. Moreover, the non-tumorous liver parenchyma within the acoustic window might be involved in the HIFU ablation process because non-specific deposits of Lipiodol could absorb high-intensity ultrasonic energy. It could be disastrous if any vital vasculatures or the biliary system were within this acoustic window.

We postulated that HIFU without Lipiodol deposition might be more effective than the combined-treatment approach in terms of completeness of ablation, provided that tumor margins could be clearly defined by the HIFU system. With this assumption, we modified the treatment protocol of HIFU in the later phase of our study by adopting the HIFU-alone treatment. The effectiveness of HIFU-alone approach was supported by the finding of our study. The primary technique effectiveness rate of patients with HIFU alone (89.2%) was higher than that of those with HIFU and pre-treatment Lipiodol deposition (66.6%, $P = 0.076$). Such high complete ablation rate is comparable with that achieved by RFA[17-21], the most commonly used local ablation technique for HCC at present. It should be emphasized that meticulous techniques are necessary to ensure complete ablation of the tumor in the HIFU-alone approach. It is important to carry out pre-HIFU planning using diagnostic ultrasound to ensure that the liver tumor is clearly visible before administering HIFU. We believe that complete tumor ablation can be achieved by ultrasonic energy using the HIFU system alone as long as tumor margins can be clearly defined during the procedure.

We identified that the Child-Pugh grade was the prognostic factors influencing the overall patient survival. This is compatible with the natural course of disease and the patients' suboptimal liver function may not allow them to receive further treatments. Meanwhile, patients with secondary technique effectiveness tended to have better overall survival than those with residual tumors after sequential local ablation. The assessment of completeness of

ablation after HIFU was an important step in our series. Every patient had MRI scan after treatment to document the completeness of tumor ablation.[22] The advantage of MRI over computed tomography scan is that assessment of tumor viability will not be influenced by the deposition of Lipiodol in the case that pre-treatment Lipiodol deposition has been performed. With accurate assessment, aggressive treatment for any residual tumors after HIFU can be carried out without any delay as long as their liver function is optimal. In our study, percutaneous RFA was performed in 4 of 10 patients with residual tumors after HIFU, making the overall secondary technique effectiveness rate 85.7%. Repeated HIFU treatment to residual tumors was not performed in this series. In the future, with accumulation of experience, repeated HIFU for residual tumors may be the treatment of choice. Although HIFU for HCC is still not widely accepted in many centers, the high treatment efficacy of the HIFU-alone approach should not be underestimated. Hence, HIFU treatment can be considered as one of the effective treatment options in the setting of current tumor ablation technology. In particular, a multidisciplinary approach using different tumor ablation techniques might be the future direction of management of HCC patients.

Our study has confirmed the efficacy of HIFU for patients with HCC. However, HIFU is not without complications. Compared with a recent reported series[23], the complication rate of the present series is lower (8.1%). First and second degree skin burn is especially disturbing. Further refinement of the technique, such as artificial ascites[24] and intermittent delivery of

acoustic energy to allow skin cooling, has been introduced in our recent practice. Their efficacy will be evaluated in future reports.

This study, a retrospective data analysis, has two limitations, namely, a relatively short follow-up period and a small patient number. Nevertheless, it has provided an insight into a new direction for ablation treatment for HCC. The protocol of HIFU without prior Lipiodol deposition can benefit patients with a higher rate of tumor control, making HIFU a favorable non-invasive treatment option. In this study, we used the JC HIFU system, which relies on ultrasound for tumor targeting and ablation monitoring. The problem of reduction in targeting ability of diagnostic ultrasound of this system by cutaneous and subcutaneous tissue edema can be overcome by using MRI guidance, which relies on the temperature change of the ablated area as the targeting index. As the MRI-guided HIFU system is coming into clinical practice,[25] comparison of these two systems on efficacy of ablation will be another future goal in the evaluation of HIFU for HCC patients.

In conclusion, HIFU is an effective treatment modality for unresectable HCC with a high technique effectiveness rate and favorable survival outcome. Further studies to compare its effectiveness with other ablation modalities are warranted.

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We declare that we have no conflict of interest in the present study.

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Figure legends

Figure 1 MRI scan shows a 2.7-cm segment VIII HCC before (a) and after (b) HIFU treatment. Arrow indicates the tumor impinging on the middle hepatic vein before HIFU treatment. Complete ablation was achieved after a single session of HIFU treatment without pre-treatment Lipiodol deposition.

Figure 2 Overall survival rate of 49 patients after HIFU treatment.

Figure 3 Disease-free survival rate of 48 patients after HIFU treatment.

Figure 4 CT scan shows non-specific deposition of Lipiodol in the left liver after transarterial administration. Arrow indicates the target tumor.

Table 1. Demographic and clinicopathologic data of 49 patients treated by HIFU.

Characteristics	Values
Age, years, median (range)	65 (44 – 84)
Sex ratio, M : F	40 : 9
Hepatitis B surface antigen positive	37 (76)
Hepatitis C virus antibody positive	7 (14)
Child-Pugh liver function classification	
Class A	41 (84)
Class B	8 (16)
Serum bilirubin, μmol/L, median (range)	16 (4 – 46)
Serum albumin, g/L, median (range)	38 (24 – 45)
Platelet count ($\times 10^9$/L), median (range)	103 (26 – 268)
Previous hepatic resection	17 (35)
Previous transarterial chemoembolization	18 (36)
Previous radiofrequency ablation	14 (29)
Serum α-fetoprotein, ηg/ml, median (range)	11 (2 – 8840)
Size of largest tumor, cm, median (range)	2.2 (0.9 – 8)
Number of tumors treated (solitary / 2 lesions)	41 / 8
Pre-HIFU Lipiodol deposition in tumor	21 (43)
Artificial right pleural effusion during HIFU	31 (63)
Total treatment duration, min, median (range)	26 (3 – 124)
Average acoustic power, watt, median (range)	376 (155 – 473)

Values are numbers of patients (percentage) unless stated otherwise.

Table 2. Short-term results after HIFU treatment in 49 patients with HCC.

Characteristics	Values
Hospital mortality	1 (2)
Treatment-related complications	4 (8.1)
First-degree skin burn	2
Second-degree skin burn	1
Chest wall bruising	1
Hospital stay, days, median (range)	4 (2 – 16)
Primary technique effectiveness rate[a]	39 (79.5)
Primary technique effectiveness rate[b]	47 (82.4)

Values are numbers of patients (percentage) unless stated otherwise.

a. Complete tumor ablation in number of patients (percentage)

b. Complete tumor ablation in number of tumor nodules (percentage)

Table 3. Univariate analysis on possible risk factors for incomplete ablation after HIFU.

Factors	**Complete ablation**		***P* value**
	Yes (n=39)	**No (n=10)**	
Age, years, median (range)	65 (44 – 81)	68.5 (48 – 84)	0.275
Sex ratio, M : F	31 : 8	9 : 1	0.663
Hepatitis B infection	28 (71.7)	9 (90)	0.414
Hepatitis C infection	6 (15.3)	1 (10)	1.000
Child-Pugh liver function class A : class B	34 : 5	7 : 3	0.333
Serum bilirubin, μmol/L, median (range)	16 (4 – 44)	14 (8 – 46)	0.673
Serum albumin, g/L, median (range)	39 (24 – 45)	37 (27 – 45)	0.456
Platelet count, ($\times 10^9$/L), median (range)	103 (46 – 268)	123 (26 – 192)	0.775
Serum α-fetoprotein, ηg/ml, median (range)	15 (2 – 3951)	9 (5 – 8840)	0.813
Previous hepatectomy	13 (33.3)	4 (40)	0.721
Previous radiofrequency ablation	9 (23)	5 (50)	0.093
Previous chemoembolization	22 (56.4)	8 (80)	0.278
Tumor size, cm, median (range)	2.29 (0.9 – 8)	3.75 (1.1 – 5.7)	0.013*
Number of tumors, median (range)	1 (1 – 2)	1 (1 – 2)	0.727
Pre-HIFU Lipiodol deposition	14 (35.8)	7 (70)	0.076
Use of artificial pleural effusion	25 (64.1)	6 (60)	1.000

Values are numbers of patients (percentage) unless stated otherwise.

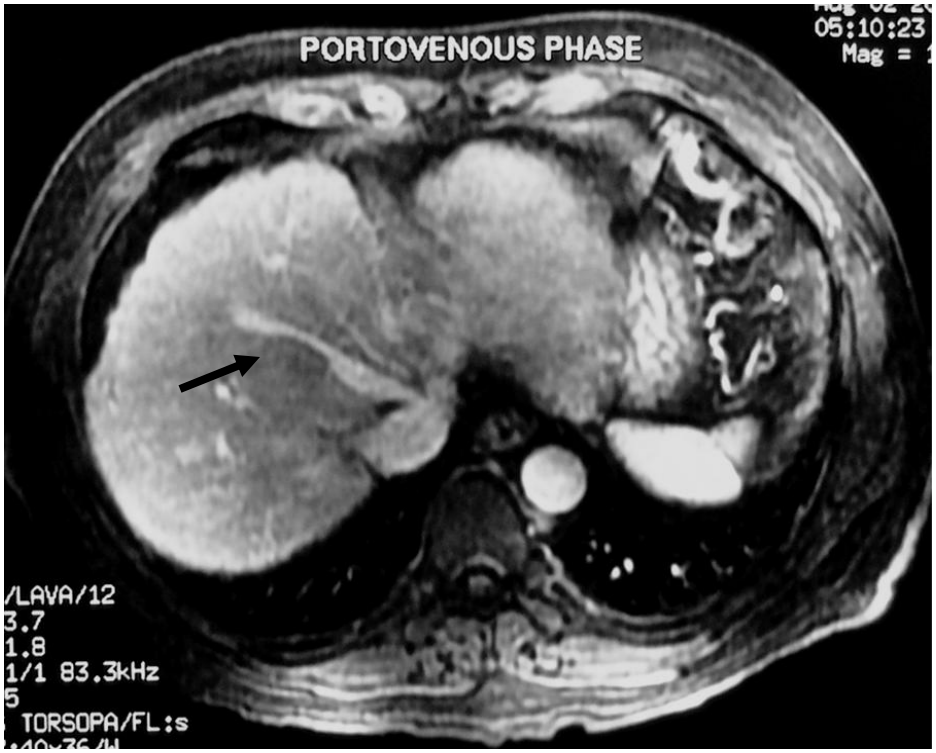
*Statistically significant.

Table 4. Univariate analysis on possible prognostic factors affecting the overall survival after HIFU.

Factors		1-year survival rate, %	3-year survival rate, %	*P* value
Age	≤ 60 (n = 15)	100	67.9	0.222
	> 60 (n = 34)	82.1	60.8	
Sex	Male (n = 40)	89.9	64.3	0.244
	Female (n = 9)	77.8	50	
Hepatitis B infection	Yes (n = 37)	91.7	66.9	0.698
	No (n = 12)	75	56.3	
Hepatitis C infection	Yes (n = 7)	71.4	47.6	0.512
	No (n = 42)	90.3	68.3	
Child-Pugh liver function	class A (n = 41)	90.2	68.5	0.028*
	class B (n = 8)	75	33.3	
Serum bilirubin	≤ 23 μmol/L (n = 35)	88.6	71.8	0.741
	> 23 μmol/L (n = 14)	85.7	49.6	
Serum albumin	≤ 30 g/L (n = 5)	80	30	0.102
	> 30 g/L (n = 44)	88.5	66.7	
Platelet count	≤ 150 $\times 10^9$/L (n = 35)	85.5	61.8	0.888
	> 150 $\times 10^9$/L (n = 14)	92.9	66.8	
Serum α-fetoprotein	≤ 200 ηg/ml (n = 37)	91.7	57.5	0.831
	> 200 ηg/ml (n = 12)	75	75	
Previous hepatectomy	Yes (n = 17)	100	72.5	0.103
	No (n = 32)	81.1	57.9	
Previous RFA	Yes (n = 14)	85.7	77.9	0.543
	No (n = 35)	79	56.2	
Previous TACE	Yes (n = 30)	86.5	61.6	0.891
	No (n = 19)	89.5	77.4	
Tumor size	< 3.0 cm (n = 32)	96.9	57.9	0.474
	≥ 3.0 cm (n = 17)	70.1	61.3	
No. of tumors	Solitary (n = 41)	90.1	63.4	0.352
	Multiple (n = 8)	75	62.5	
Pre-HIFU Lipiodol deposition	Yes (n = 21)	85.7	60	0.744
	No (n = 28)	89.3	76.9	
Use of artificial pleural effusion	Yes (n = 31)	87	60.5	0.971
	No (n = 18)	88.9	70	
Primary technique effectiveness	Yes (n = 39)	92.3	68.1	0.249
	No (n = 10)	68.6	45.7	
Secondary technique effectiveness	Yes (n = 42)	92.9	66.8	0.060
	No (n = 7)	53.6	35.7	

*Statistically significant. RFA, radiofrequency ablation. TACE, transarterial chemoembolization

Figure 1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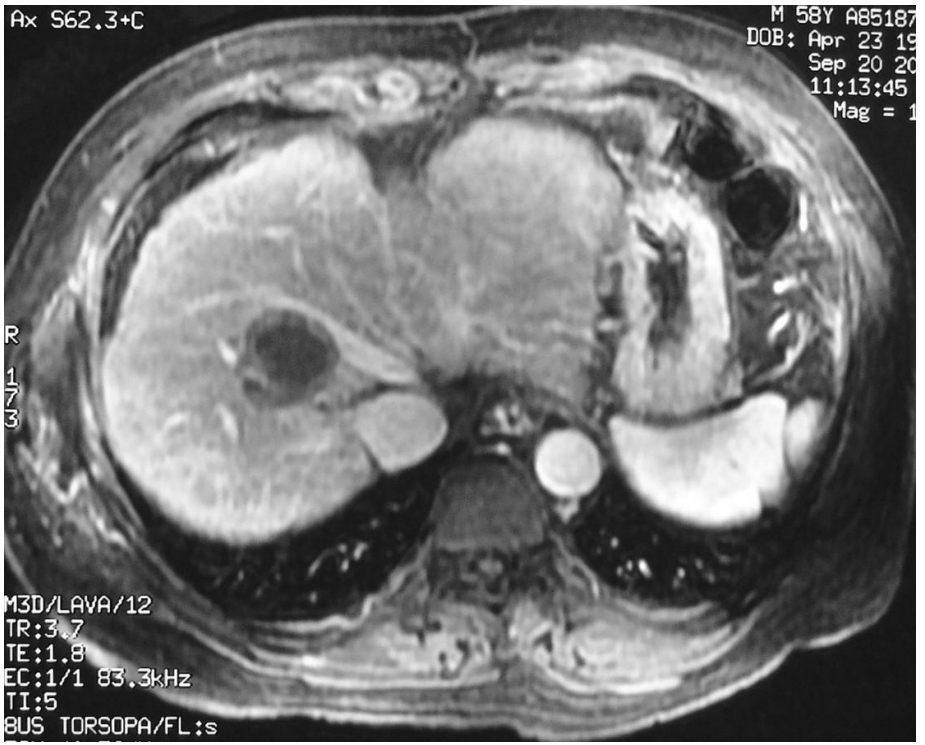
(a)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(b)

Figure 2

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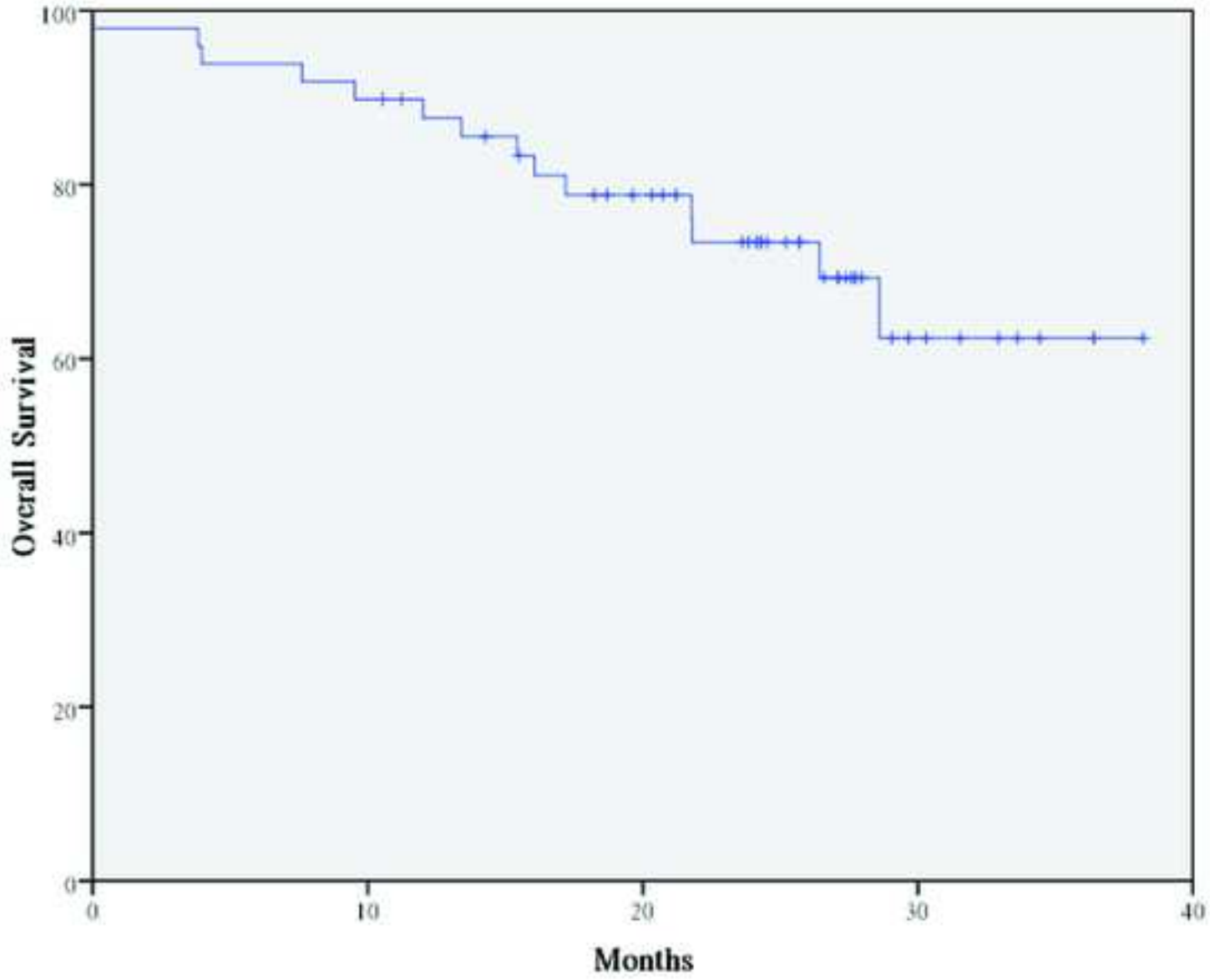

Figure 3

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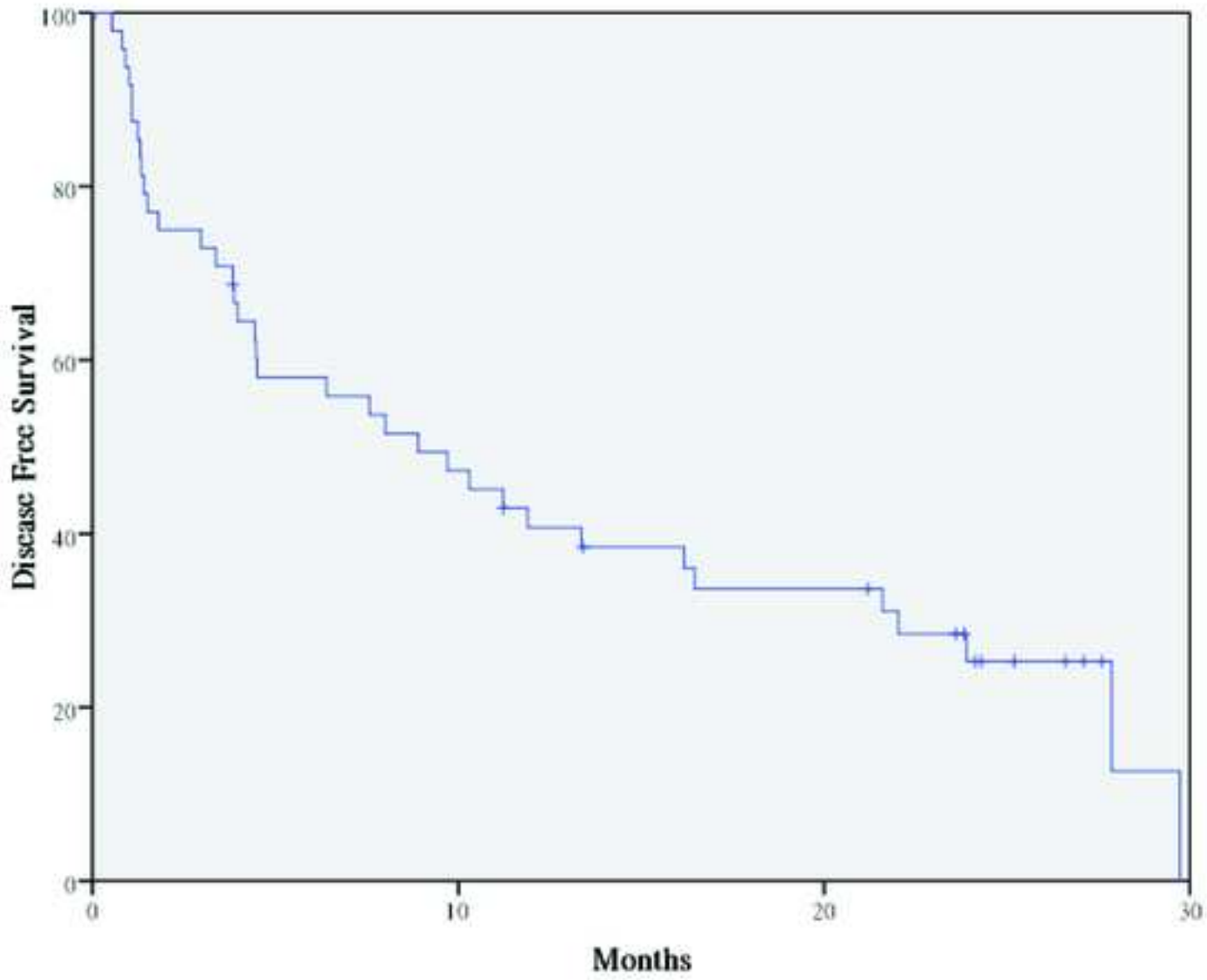
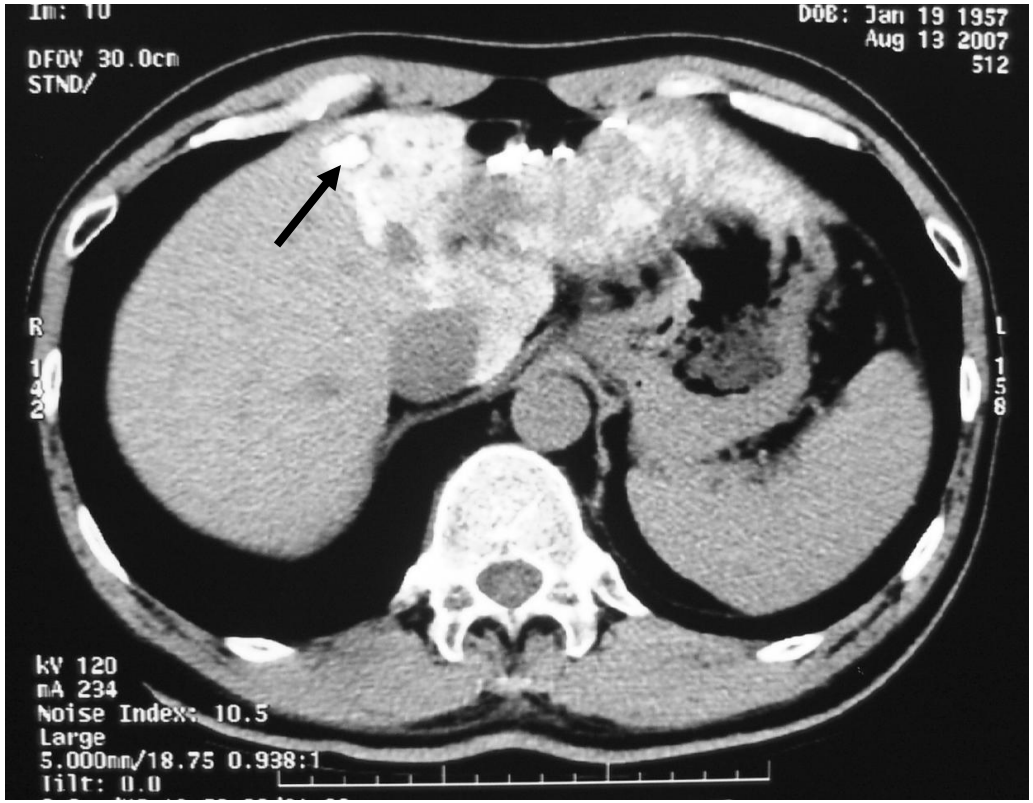


Figure 4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