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Therapeutic effects and prognostic factors in high-intensity focused ultrasound combined with chemoembolisation for larger hepatocellular carcinoma

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ABSTRACT

The purpose of this study is to evaluate high-intensity focused ultrasound (HIFU) ablation combined with transcatheter arterial chemoembolisation (TACE) in the treatment of larger hepatocellular carcinoma (HCC). Eighty-nine (89) patients with unrespectable larger HCC were randomised into a TACE group ($n = 45$) and a TACE plus HIFU group ($n = 44$). Therapeutic effects were assessed at follow-up with physical examination, level of serum α-fetoprotein and computed tomography or magnetic resonance imaging. All patients were followed up to observe long-term therapeutic effects and evaluated prognostic factors for survival. No severe complication was observed. Follow-up images showed that total effective rate in tumour response accounted for 72.8% in the TACE–HIFU group, which were significantly higher than that of TACE group (44.5%, $P < 0.05$). The 1-, 2-, 3- and 5-year overall survival rates for the TACE–HIFU group were 72.7%, 50.0%, 31.8% and 11.4%, respectively; correspondingly, for the TACE group were 47.2%, 16.7%, 2.8% and 0%, respectively ($P < 0.01$). The 1-, 2-, 3- and 5-year disease-free survival rates for the TACE–HIFU group were 34.1%, 18.2%, 9.1% and 0%, respectively; correspondingly, for the TACE group were 13.9%, 5.6%, 0% and 0%, respectively ($P < 0.01$). TNM stage, portal vein tumour thrombosis and Child-Pugh classification each had a significant effect on the survival. HIFU ablation combined with TACE is safe, effective and a promising approach for the treatment of larger HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, especially in Asian countries.[1–3] Hepatic resection and transplantation are potentially curative treatments for hepatocellular carcinoma (HCC), but only about 20% of the patients are suitable candidates.[4,5] For the treatment of unresectable HCC, transcatheter arterial chemoembolisation (TACE) has been actively performed, particularly in Asia.[6–8] The efficacy of TACE in HCC has been reported from many institutions[6,7]; however, the inadequacy of single TACE in inducing complete tumour necrosis has also been well

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documented.[9] Therefore, TACE is usually repeated at regular intervals.

To overcome the limits of the aforementioned options and achieve more extensive necrosis in larger HCCs, pretreatments with TACE and high-intensity focused ultrasound (HIFU) were proposed for patients with a larger lesion.[10–12] In a prospective randomised trial,[13] the therapeutic response was substantially better in patients who underwent TACE–HIFU combined treatment than in those who underwent repeated segmental or subsegmental TACE alone.

HIFU ablation is a non-invasive modality for the treatment of localised tumours.[14] An ultrasound beam can be focused as it passes through the tissue. This enables the use of an external ultrasound energy source to induce thermal ablation of a tumour at a depth through the intact skin. Under the guidance of real-time ultrasonographic imaging, the motion of a therapeutic transducer can facilitate ablation of a three-dimensional target.[10,14] HIFU is a non-invasive transcutaneous technique for tumour ablation that has been shown to demolish tumour vasculature.[15] In the past decades, this technique had been used to treat patients with prostate tumours by using transrectal HIFU devices.[16,17] More recently, extracorporeal HIFU has been used to treat patients with various malignancies, including those originating from liver, breast, kidney and osteosarcoma.[10,11,18] Larger HCC is defined as tumour diameter $\geqslant$5 cm. The purpose of this study was to prospectively evaluate HIFU ablation combined with TACE in the treatment of larger HCC in patients.

2. Patients and methods

2.1. Patient selection

From June 2001 to August 2004, 89 consecutive patients with larger HCC were enrolled in a prospective controlled clinical protocol that was approved by the ethical committee of the Cancer Centre of Sun Yat-Sen University. All patients gave written informed consent before beginning the study and being randomly assigned to treatment groups. Patients were informed of the potential risks and benefits of hepatic angiography and the proposed HIFU ablation, and written consent was obtained. HCC was diagnosed histopathologically or clinically in patients who were included based on the characteristic findings of computed tomography (CT) or magnetic resonance imaging (MRI), and angiography, combined with a high level (>200 ng/mL) of serum alpha fetoprotein (AFP).

2.2. Eligibility criteria

Study eligibility criteria were as follows: (a) HCC diagnosis confirmed; (b) patients had to have inoperable tumour and be willing to participate in the trial; (c) tumour diameter $\geqslant$5 cm; (d) Karnofsky performance scale score of 70% or greater; (e) Child-Pugh class A or B cirrhosis; (f) no history of hepatic encephalopathy; (g) no ascites detected; (h) no active infection; (i) no previous treatment for HCC and (j) patients had to sign an informed consent form for participation in this study.

2.3. Exclusion criteria

Study exclusion criteria were as follows: (a) patients with Child-Pugh status C disease, (b) patients with advanced cardiac or pulmonary diseases and (c) patients with evidence of extrahepatic spread of disease.

2.4. Patients

Patients were consecutively enrolled at clinical presentation and were alternately assigned to one of the following two treatment groups: group 1, the TACE group (n = 45), in which TACE alone was performed or group 2, the TACE–HIFU group (n = 44), in which extracorporeal focused ultrasound ablation was performed after TACE. Patient characteristics assessed in both the groups are shown in Table 1. The two patient groups were comparable ($P > 0.05$) with respect to age, sex, TNM classification, position of lesion, portal vein involvement, number of lesions, lesion diameter and Child-Pugh class. Therefore, there was no reason to consider that the alternating method that we chose for determining whether patients would undergo TACE or TACE–HIFU ablation would cause a statistically obvious bias in the results.

Table 1 – Characteristics of 80 patients treated with larger HCC.

Characteristic	TACE Only group	TACE–HIFU group*
No. of patients	45	44
Mean age (y)	49.9 (30–69)	48.3 (29–75)
Female/male patients	10/35	8/36
Position of lesion		
Left lobe	16	17
Right lobe	22	21
Both lobes	7	6
Portal vein involvement	6	7
Serum AFP $\geqslant$ 400 ng/mL	26/45	27/44
No. of nodules	69	73
Lesion diameter (cm)		
5–10	22	24
$\geqslant$10	23	20
Mean	9.42 (6.5–14.5)	9.36 (5.0–16.0)
Child-Pugh classification		
Class A	33	34
Class B	12	10
Class C	0	0
TNM stage		
I	0	0
II	7	8
III	22	19
IV	16	17

* For each characteristic, there is no significant difference in comparison with the TACE only group ($P > 0.05$).

2.5. High-intensity focused ultrasound system and treatment

The tumour therapy system (model JC; Chongqing Haifu Technology, Chongqing, China) used in this study is guided by means of real-time ultrasonographic imaging and has been described in detail that previously HIFU treatment was performed in patients under general anaesthesia.[10–12] After suitable anaesthesia was achieved, the patients were carefully positioned, so that the skin overlying the lesion would be easily put in contact with the degassed water. Real-time ultrasonographic imaging was used to target the tumour by moving the integrated probe, and the tumour was divided into sections with 5 mm separation. By means of scanning the HIFU beam, the targeted regions in each section were completely ablated. This process was repeated on a section-by-section basis to achieve complete ablation of the tumour volume in a manner similar to cutting away slices of bread. During HIFU ablation, the real-time ultrasonographic scans obtained immediately before and after individual exposures were compared to determine whether the echogenic changes of the HIFU-treated region, which are indicative of the extent of coagulation necrosis, had covered the desired treatment area.

The target tissue was exposed at acoustic focal peak intensities from 5000 to 20,000 W cm^{-2}. The scanning speed ranged between 1 and 3 mm s^{-1}. Two patients underwent four HIFU sessions, four patients underwent three HIFU sessions, 15 patients underwent two HIFU sessions and 23 patients underwent one HIFU session (mean, 1.66 sessions). Therapeutic time for an individual patient ranged from 119 to 594 min.

2.6. Transcatheter arterial chemoembolisation treatment

TACE was performed on an inpatient basis. Before TACE, coeliac and superior mesenteric arteriography was performed by using a 4-F catheter introduced via the femoral artery. Then, a 3-F-SP microcatheter was placed in the hepatic arteries that were feeding the HCC. Segmental embolisation was also performed in tumours. Either 80–120 mg of cisplatin or 40–60 mg of adriamycin were mixed in 10–35 mL of iodised oil, and the embolisation suspension was then slowly injected with fluoroscopic guidance. Embolisation of tumour-feeding vessels was performed with the use of a 1 mm × 1 mm × 10 mm gelatin sponge in all patients after injecting the embolisation suspension.

The median number of courses of TACE performed was 2.4 (range, 1–6 courses) per patient in the TACE group and 2.3 (range, 1–5 courses) per patient in the group undergoing TACE–HIFU combined treatment.

2.7. Follow-up

The follow-up protocol included routine physical examination, laboratory tests (blood count, liver and kidney function and blood electrolyte values) and measurement of α-fetoprotein levels, as well as unenhanced and contrast-enhanced CT or MR imaging studies every 1–2 months. Follow-up imaging examinations were performed to evaluate the therapeutic effectiveness. All patients underwent unenhanced and contrast-enhanced CT or MR imaging. Follow-up CT or MR images were evaluated and interpreted by means of consensus between two radiologists. Follow-up was considered closed at the time of death or of the last follow-up visit, whichever was later.

2.8. Tumour evaluation

CT (or MRI) exams were performed 4–6 weeks before and after treatment to identify tumour necrosis and lesion size, allowing evaluation of the effectiveness of the tumour local control. The WHO standard was adopted to evaluate the effectiveness and is outlined here[19]: (1) complete response (CR): whole tumour was completely necrotic or disappeared for more than 4 weeks; (2) partial response (PR): tumour necrosis >50% or the decrease of the multiplication of lesion diameters was >50% and lasted for more than 4 weeks; (3) moderate response (MR): 50% > necrotic or a decrease in tumours of $\geqslant$25%; (4) stable disease (SD): a decrease or increase in tumours of <25% and (5) progressive disease (PD): the increase in tumour $\geqslant$25% or new lesions occur. Total effective rate = (cases of CR + cases of PR)/total cases.

2.9. Statistical analysis

The unit of analysis was numbers of patients (not numbers of tumours). Comparisons between the two groups were performed by using the Student *t* test for continuous data and the χ^2 test for categorical data. Cumulative survival rates were expressed according to the Kaplan–Meier method. The differences in survival among the groups were compared by using the log-rank test. The results of univariate analysis helped to substantially reduce the number of prognostic factors. Only variables that were found to show significance at univariate analysis were used for the subsequent multivariate analysis, which was performed by using the Cox proportional hazards model. *P* value of less than 0.05 was considered to indicate a statistically significant difference.

3. Results

3.1. Patients and complications

Between June 2001 and August 2004, a total of 89 patients (71 men and 18 women) with a mean age of 49 years (range, 29–75 years) were recruited in this trial. The patients had a larger tumour burden and mildly deranged liver function at presentation. Tumour diameter varied from 5.0 to 16.5 cm (mean, 9.4 ± 2.8 cm), with 20% of patients having more than three lesions. There was extension of tumour mass in the portal vein (portal vein thrombosis) in 14.6% of patients. Serum AFP level was elevated in 79.8% of patients, with 59.6% of patients having a serum AFP value of more than 400 ng/mL. Patients (24.7%) had Child-Pugh status B disease. Patients (75.3%) had Child-Pugh status A disease, and 83.2% of patients were classified as having TNM stages III and IV disease. Demographic, clinical and biochemical data for all patients are given in Table 1.

Among 44 patients treated with focused ultrasound ablation, an extremely low rate of major complications was observed. Thirteen patients (29.6%) with 1° skin burns

spontaneously subsided within 2 week, while two patients (4.6%) with 2° skin burns recovered after 4 week of expectant treatment. Eight patients (18.2%) had a low-grade fever (temperature up to 38.6 °C) that persisted for approximately 3–5 days after ultrasound ablation. Tumour bleeding or large blood vessel rupture was not detected after the ablation.

After TACE, all patients had transient impairment of hepatic function. Transient fever was observed in 65 patients (73.0%), and 28 patients (31.5%) complained of transient pain that lasted 1–2 weeks. No patients developed acute hepatic failure, liver abscess or renal dysfunction caused directly by either TACE or focused ultrasound treatment.

3.2. *Tumour response*

Follow-up images showed that the local control rates in tumour response for the TACE–HIFU group were 12 CR (27.3%), 20 PR (45.5%), 7 SD (15.9%) 5 PD (11.3%), respectively; correspondingly, for the TACE group were 4 CR (8.9%), 16 PR (35.6%), 15 SD (33.3%) and 10 PD (22.2%). Total effective rate in tumour response accounted for 72.8% in the TACE–HIFU group, which were significantly higher than that of TACE group (44.5%, $P < .05$). Of these 44 patients, 9 had normal serum AFP levels from the beginning of the investigation in TACE–HIFU group. Therefore, AFP decrease was evaluated in only 35 patients. Of these 45 patients, 9 had normal serum AFP levels from the beginning of the investigation in TACE only group. Therefore, AFP decrease was evaluated in only 36 patients. Response details for patients after the treatment are given in Table 2, Figs. 1 and 2.

3.3. *Overall survival*

Patients were followed from enrolment in the study until August 2004. The following end-points were noted: progression of treated tumour, evidence of new hepatic or extrahepatic tumour and death. The median follow-up was 27 months ranging from 5 to 72 months in the TACE–HIFU group and 12 months ranging from 1 to 37 months in the TACE only group.

The 1, 2, 3 and 5 year overall survival rates and median overall survival were 72.7%, 50.0%, 31.8%, 11.4% and 19.0 months, respectively, for the TACE–HIFU group and 47.2%, 16.7%, 2.8%, 0% and 10.0 months, respectively, for the TACE only group. Mantel–Haenszel testing revealed that 1 year ($\chi^2 = 4.350$, $P = 0.037$), 2 year ($\chi^2 = 8.157$, $P = 0.004$) and 3 year ($\chi^2 = 9.023$, $P = 0.003$) overall survival rates for the TACE–HIFU group were significantly better than those for the TACE only group. The survival curve for the TACE–HIFU group was significantly better than that for the TACE only group (Fig. 3).

3.4. *Disease-free survival*

The 1, 2, 3 5 year disease-free survival rates and median disease-free survival for TACE–HIFU group were 34.1%, 18.2%,

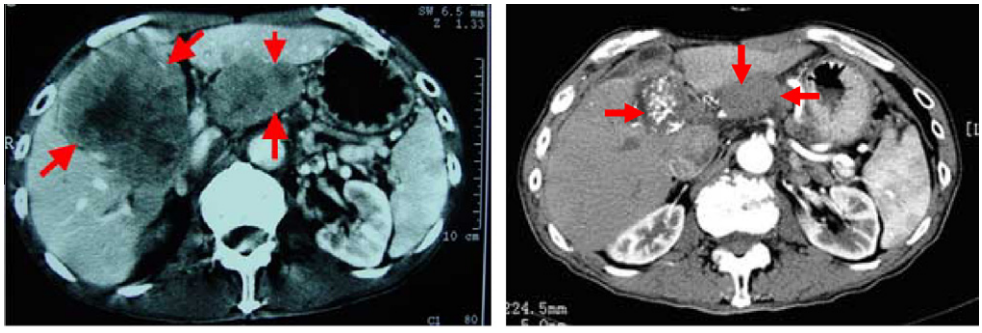
Table 2 – Extent of response in larger HCCs after treatment.

Group	No. of patients	AFP decrease	Local control efficacy (%)					Recurrence
		> 90%	CR[a]	PR[a]	SD[a]	PD[a]	Total effective rate	
TACE–HIFU group	44	27(77.1)	12(27.3)	20(45.5)	7(15.9)	5(11.3)	32(72.8)	10(22.7)
TACE only group	45	18(50.0)*	4(8.9)*	16(35.6)	15(33.3)*	10(22.2)*	20(44.5)*	13(28.9)

Note: Data in parentheses are percentages. Data on AFP decrease were available for 35 patients in TACE–HIFU group and for 36 patients in TACE group.

a CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

* $P < 0.05$.



A B

Fig. 1 – A 74-year-old patient with hepatocellular carcinoma. (A) Transverse contrast-enhanced CT images before TACE plus HIFU treatment showed that liver tumour of right lobe was 115 mm × 95 mm × 90 mm (AFP 59362ug/L). (B) Transverse contrast-enhanced CT images were obtained 72 months after two course of TACE and three session of HIFU ablation. CT images revealed that liver tumour of right lobe had shrunk obviously (tumour size 66 mm × 55 mm × 50 mm, AFP 4.2 ug/L), blood of tumour was eliminated and therapeutic region of tumour was coagulation necrosis.

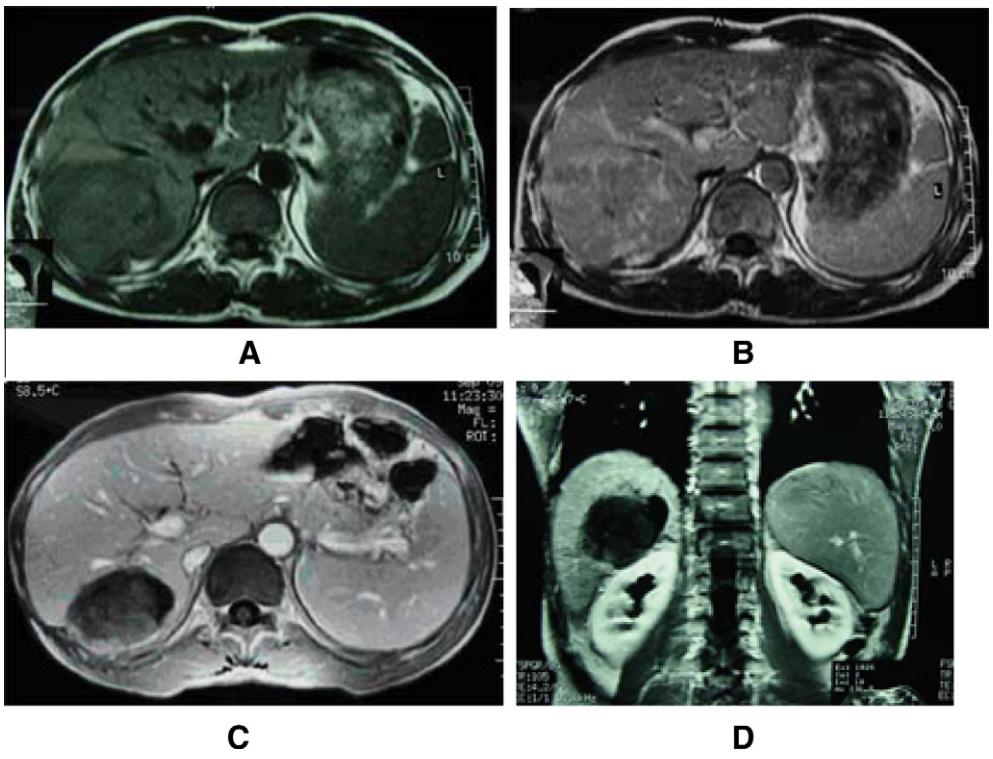


Fig. 2 – A 42-year-old man with hepatocellular carcinoma. (A) Transverse T_1-weighted MRI images before TACE–HIFU treatment showed that liver tumour of right-posterior lobe was 115 mm × 100 mm × 66 mm. (B) Transverse contrast-enhanced MRI imaging before TACE–HIFU treatment revealed that enhancement of mass in liver right-posterior lobe was higher than that of surrounding normal liver tissues. (C, D) Contrast-enhanced MRI imaging (cross section and coronal section) eleven months after one course of TACE and three sessions of HIFU ablation revealed that liver tumour of right-posterior lobe had obviously decreased size (60 mm × 55 mm × 50 mm), blood of tumour was eliminated and the tumour therapeutic region was coagulation necrosis.

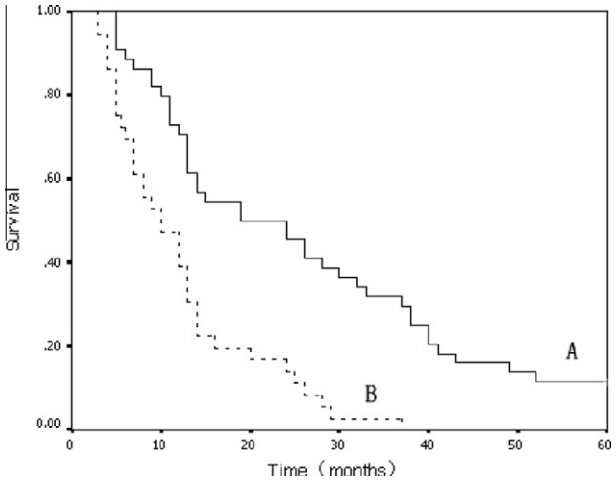


Fig. 3 – Kaplan–Meier curve shows overall survival rates for patients who received TACE–HIFU combination therapy (A) and for those who underwent TACE (B).

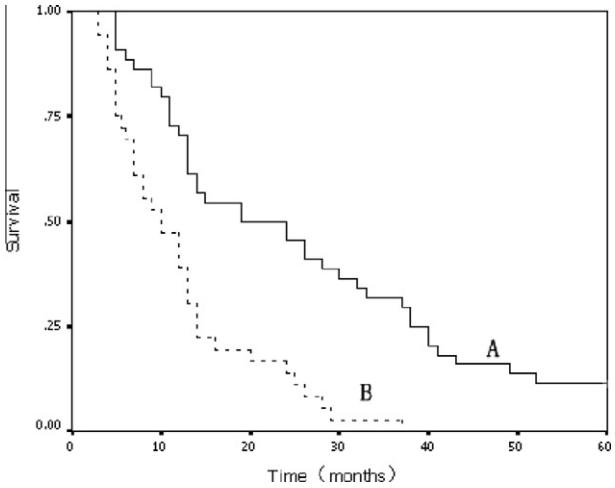


Fig. 4 – Kaplan–Meier curve shows disease-free survival rates for patients who received TACE–HIFU combination therapy (A) and for those who underwent TACE (B).

9.1%, 0% and 8.0 months, respectively; correspondingly, for TACE only group were 13.9%, 5.6%, 0%, 0% and 3.0 months, respectively (stratified log-rank test, $P = 0.004$). There was significant difference in disease-free survival rates between the two patient groups (Fig. 4).

3.5. *Univariate analysis*

The influence of patient and tumour-related factors on overall survival is shown in Table 3. The results revealed that there

Table 3 – Results of univariate Kaplan–Meier survival analysis with log-rank test for various prognostic factors.

Factor	No. of patients	Overall survival				χ^2	P value
		1 year (%)	2 year (%)	3 year (%)	5 year (%)		
Sex							
Men	36(81.8)	75.0	52.9	33.3	11.1	0.063	0.801
Women	8(18.2)	62.5	37.5	25.0	12.5		
Age (y)							
<45	16(36.4)	50.0	25.0	0	0	13.404	0.004
⩾45	28(63.6)	85.7	64.3	50.0	17.7		
Diameter of largest tumour (cm)							
5–10	23(52.3)	73.9	52.2	34.8	13.0	0.271	0.603
⩾10	21(47.7)	71.4	42.9	28.6	9.5		
Child-Pugh classification							
Class A	34(77.3)	82.4	61.8	41.2	14.7	20.934	0.001
Class B	10(22.7)	40.0	10.0	0	0		
No. of tumours							
Single	22(50.0)	77.7	54.6	31.8	13.6	6.439	0.092
Multiple	22(50.0)	68.2	45.5	31.8	9.1		
Pretreatment serum AFP level (ng/mL)							
<400	17(38.6)	70.6	58.2	35.3	11.8	0.231	0.631
⩾400	27(61.4)	74.1	44.4	29.6	11.1		
Portal vein tumour thrombosis							
None	37(84.1)	81.1	59.5	37.8	13.5	22.309	0.000
Yes	7(15.9)	28.6	0	0	0		
TNM stage							
II	8(18.1)	100.0	100.0	87.5	50.0	34.826	0.000
III	19(43.2)	89.5	63.5	36.8	5.3		
IV	17(38.6)	41.2	11.8	0	0		

were statistically significant differences in survival rates depending on the age ($\chi^2 = 0.063$, $P = 0.004$; Fig. 5), Child-Pugh classification ($\chi^2 = 20.934$, $P = 0.001$; Fig. 6), portal vein tumour thrombosis ($\chi^2 = 22.309$, $P = 0.000$; Fig. 7) and TNM stage ($\chi^2 = 34.826$, $P = 0.000$; Fig. 8). Statistical results also showed there were no significant differences in overall survival rates attributable to sex ($\chi^2 = 0.063$, $P = 0.801$), Diameter of largest tumour ($\chi^2 = 0.271$, $P = 0.603$), No. of tumours ($\chi^2 = 6.439$, $P = 0.092$) and Pretreatment serum AFP level ($\chi^2 = 0.231$, $P = 0.631$).

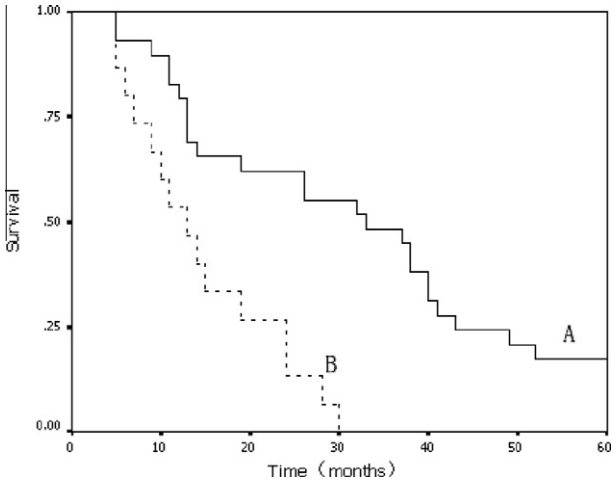


Fig. 5 – Graph shows 5-year cumulative survival rate after TACE–HIFU combination therapy, compared between patients with age ⩾45 year (A) and age <45 year (B). The survival rate of patients with age ⩾45 year was significantly higher than that of patients with age <45 year.

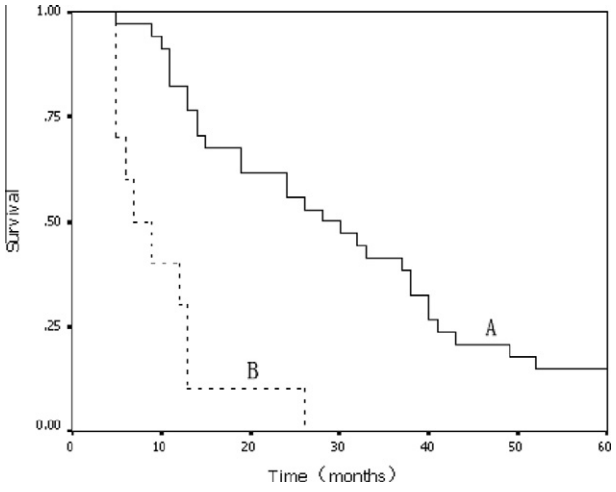


Fig. 6 – Graph shows 5-year cumulative survival rate of HCC patients with TACE–HIFU combination therapy. Data are stratified according to Child-Pugh classification of pretreatment liver dysfunction: A = class A disease, B = class B disease.

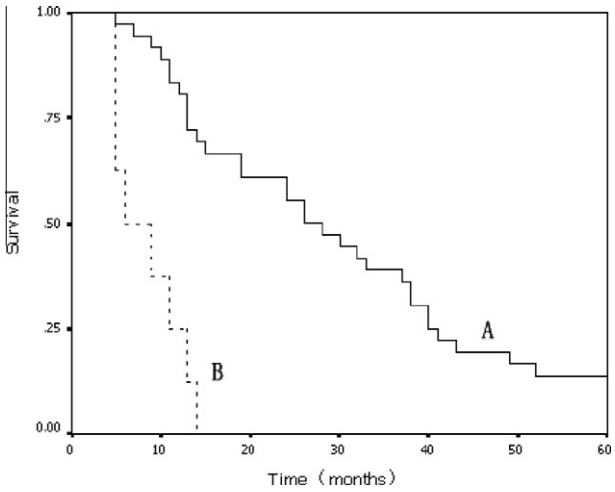


Fig. 7 – Graph shows 5-year cumulative survival rate after TACE–HIFU combination therapy, compared between patients without portal vein tumour thrombosis (A) and with portal vein tumour thrombosis (B).

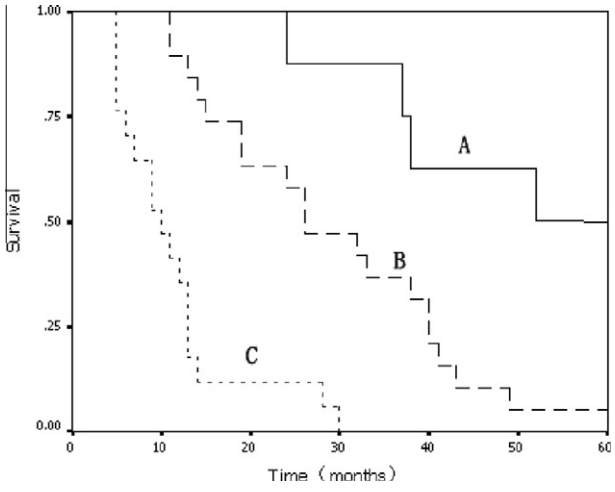


Fig. 8 – Graph shows 5-year cumulative survival rate of HCC patients with TACE–HIFU combination therapy. Data are stratified according to TNM stage of pretreatment liver tumour: A = TNM stage I, B = TNM stage II, C = TNM stage III.

3.6. *Multivariate analysis*

Multivariate analysis was performed by using the variables deemed significant at univariate analysis as covariates. The multivariate analysis (Table 4) showed survival rates related to portal vein tumour thrombosis ($\chi^2 = 3.053$, $P = 0.041$), Child-Pugh classification ($\chi^2 = 10.015$, $P = 0.007$) and TNM stage ($\chi^2 = 8.155$, $P = 0.004$). Degree of age was significant risk factors when univariate analysis was performed. However, the survival rates were not significantly related to the degree of age ($\chi^2 = 1.888$, $P = 0.169$) by using the Cox proportional hazards model.

4. Discussion

Large HCC often coexists with cirrhosis and hepatic insufficiency. Only about 20% patients with large HCC are amenable to surgical resection,[4] which highlights the importance of non-surgical local ablative therapies. Indeed, a number of local ablative therapies including ethanol injection, laser, radiofrequency, cryoablation and microwave have recently been made available to HCC patients not eligible for surgery. Apart from the need for liver puncture, which increases the risk of needle tract seeding, haemorrhage and bile leakage, these localised procedures also require repeated performance over an extended period. Another disadvantage associated with local ablative therapies is their inability to provide effective monitoring during treatment or to ensure complete tumour destruction. All these factors significantly limit the clinical usefulness of local ablative therapies.

Treatment of large HCC with TACE alone is associated with low rates of complete tumour necrosis or complete cure.[9] Two to six sessions of TACE are generally needed. Due to high toxicity and side-effects of chemotherapeutic agents, repeated TACE often aggravates cirrhosis and causes severe complications, including liver failure or even death.

As a non-invasive modality, HIFU ablation is receiving increasing interest for the local treatment of solid malignancies. The principle of this technique is that a high-energy ultrasound beam can be focused at a distance from the radiating surface of transducer. The energy within the focal region can be sufficient to cook tissue and to induce necrosis of targets such as tumours, without causing damage to overlying or surrounding vital structures. The ability to cause cell death in a volume of tissue distant from the US source makes HIFU an attractive option for development as a non-invasive surgical tool.[14,20] Pathologic findings revealed that HIFU-treated tumour cells underwent complete coagulative necrosis, and tumour vascular vessels were severely damaged. Immunohistochemical staining showed that HIFU-treated tumour cells lost the abilities to proliferate, invade and metastasise.[21]

HIFU ablation has the following characteristics in the therapy of malignant tumour. Firstly, *Non-invasiveness*. HIFU treats inner tumour without damaging outside body, and other damages due to radioactivity. Previous research on animal angiog-

Table 4 – Multivariate analysis of prognostic factors with Cox proportional hazards model.

Variable	β Value	Standard error	Wald χ^2 value	P value	RR	95% Confidence interval
Age	0.725	0.528	1.888	0.169	2.066	0.734, 5.813
Child-Pugh classification	−2.375	0.751	10.015	0.007	0.093	0.021, 0.405
Portal vein tumour thrombosis	−0.891	0.510	3.053	0.041	0.310	0.151, 1.115
TNM stage	−1.462	0.512	8.155	0.004	0.232	0.085, 0.632

raphy indicated that after treating liver tumour of Morris rat using HIFU, nourishing blood vessels with a diameter less than 200 μm of irradiation zone closed, but they were normal for blood vessels with a diameter more than 200 μm.[22] Secondly, *Accuracy*. HIFU can pass through tissues and accurately damage target tissues inside organisms. The boundary between therapy zone and un-therapy zone is clear, the tissue beyond target zone is hardly destroyed or without damage.[23,24] Ultrasound Therapy Section of London Emperor Hospital, Britain found that only six cells existed between cells killed completely and cells without damage.[25] Thirdly, *real-time therapy*. For whole process of therapy, it is a real-time targeting and monitoring process, real-time estimating therapeutic effect and adjusting dosage.[26] Fourthly, *conformal therapy*. According to the size and shape of tumour, it determines therapy range of tumour target zone, overlays tumour target zone. Therefore, the treatment of malignant tumour using HIFU has many advantages, such as less pain, without damage, fewer influences on splanchnic function, faster recovery for body and without increase of tumour metastasis chance.[27]

The results of this study show that TACE followed by HIFU ablation would be better than TACE alone in the treatment of patients with larger HCC. First, the cumulative survival rates and the median survival times for the TACE–HIFU group were much greater than those for the TACE only group. Furthermore, Follow-up images showed that therapeutic effect in the TACE–HIFU group was better than that in the TACE only group. Finally, among those patients who died during the follow-up period, median survival times in the TACE–HIFU group were greater than those in the TACE only group. The longer survival times in the TACE–HIFU treatment group could be attributed to a greater tumour necrosis rate or to a reduction in the induced liver damage from this approach.

In our study of larger HCCs, we suggested that employing HIFU treatment could be beneficially combined with TACE with the following considerations. Firstly, the combination of HIFU treatment with TACE may remedy the limitation of each alone and has synergistic effects. Secondly, tumour shrinkage after TACE allows the use of smaller HIFU treatment doses. Thirdly, combination TACE–HIFU therapy may also serve the purpose of eliminating residual cancer cells after TACE. Furthermore, because HCCs are supplied almost entirely by the hepatic arteries, we should combine with TACE before therapy using HIFU, so as to make inner tumour tissue have more iodised oil deposition, not only convenient to ultrasound orientation, but to change the impedance dispersion and absorb coefficient of sound when treat tumour zone, convenient to energy sediment of focal zone, so exert cooperation function of rising temperature, excite high temperature to get to purpose of destruct therapy at local, make tumour tissue coagulation necrosis.[13,28]

The prognosis of primary HCC is highly heterogeneous due to the complex interplay between tumour and host. Data from previous studies have been inconsistent with respect to defining factors affecting prognosis, due to different research focus and parameter settings. Lau and colleagues proposed[29] that tumour types, portal vein cancer embolus, therapeutic method and hepatic function are major factors determining the treatment efficacy for intermediate and advanced HCC. Yamaoto and colleagues suggested[30] that portal vein cancer embolus, tumour size and type of tumour, lipiodol deposition and hepatic function affect the prognosis of HCC. Our focus was to analyse, in a series of patients with HCC, the prognostic factors of various clinicopathologic parameters regarding long-term survival, with the aim of clarifying which patients are most likely to benefit from HIFU ablation. Statistical results showed that survival rates were not significantly influenced by sex, tumour size and number of tumours. Meanwhile, the survival rates were not attributable to the pretreatment serum AFP level. Four variables (age, Child-Pugh classification, TNM stage and portal vein tumour thrombosis) were found to be important risk factors that affected survival rates at univariate analysis. However, since univariate analysis does not always reflect the actual significance of a factor, multivariate analysis, in which multiple variables are considered simultaneously, was applied. Only three variables (Child-Pugh classification, TNM stage and portal vein tumour thrombosis) were shown to have independent prognostic value at multivariable analysis. Age did not show significance because of the overpowering influence of the former three factors. These findings suggest that the TACE and HIFU combined treatment of HCC patients results in a favourable prognosis, even in conditions of multiple or large tumours or varying degrees of serum AFP elevation. Child-Pugh scores are a particularly accurate indicator of hepatic damage. Severe liver function impairment will lead to poor compensation ability, generating a direct negative impact on the prognosis of the combined treatment for HCC. The deterioration of liver function predicts a poor prognosis of TACE and HIFU combined treatment. Therefore, an increase in Child-Pugh scores was determined to be a risk factor for an unfavourable prognosis of the combined treatment. HCC utilises the portal vein as its efferent vessel, where arteriovenous shunt often occurs. This makes the portal vein particularly susceptible to tumour invasion. The incidence of portal vein cancer embolus was 14.6% in the present study and no significant correlation between its occurrence and tumour size was noted. A portal vein cancer embolus may still develop within the portal vein even when a small tumour is present. Once a portal vein cancer embolus is formed, it is likely to spread throughout and beyond the liver. In addition, a growing portal cancer embolus may occlude the portal vein, lead to portal hypertension and cause liver function damage. Therefore, portal vein tumour thrombus is often considered an important prognostic indicator of HCC.

Main portal vein obstruction traditionally has been considered a contraindication for TACE. Recently, it has been proposed that TACE can be performed in patients with partial portal vein tumour provided that they have good hepatic function, collateral circulation and nodular type HCC.[6] However, our experience bears out the reports of other authors,[29] who state that partial portal vein tumour is a strong independent prognostic factor related to poor survival.

In conclusion, our results demonstrate that HIFU ablation combined with TACE is a safe, effective and promising approach for the treatment of unresectable larger HCC. Child-Pugh classification, TNM stage and portal vein tumour thrombosis are identified as significant independent prognostic factors in patients with HCC treated with HIFU–TACE treatment.

Conflict of interest statement

None declared.

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