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Survival analysis of high-intensity focused ultrasound therapy vs. transarterial chemoembolization for unresectable hepatocellular carcinomas

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Abstract

Background & Aims: High-intensity focused ultrasound (HIFU) ablation is a non-invasive treatment for unresectable hepatocellular carcinomas (HCCs), but long-term survival analysis is lacking. This study was to analyse its outcome compared to that of transarterial chemoembolization (TACE). *Methods:* From October 2003 to September 2010, 113 patients received HIFU ablation as a treatment of HCCs at our hospital. Twenty-six patients had HCCs sized 3–8 cm. Fifty-two patients with matched tumour characteristics having TACE as primary treatment were selected for comparison. Short-term outcome and long-term survival were analysed. *Results:* In the HIFU group (n = 26), 46 tumours were ablated. The median age of the patients was 69 (49–84) years. The median tumour size was 4.2 (3–8) cm. In the TACE group (n = 52), the median age of the patients was 67 (44–84) years. The median tumour size was 4.8 (3–8) cm. There was no hospital mortality in any of the groups. In the HIFU group, the rates of complete tumour response, partial tumour response, stable disease and progressive disease were 50%, 7.7%, 25.6% and 7.7% respectively, according to the modified Response Evaluation Criteria in Solid Tumours. The TACE group had the corresponding rates at 0%, 21.2%, 63.5% and 15.4% respectively ($P < 0.0001$). The 1-year, 3-year and 5-year survival rates were 84.6%, 49.2% and 32.3% respectively, in the HIFU group and 69.2%, 29.8% and 2.3% respectively, in the TACE group ($P = 0.001$). *Conclusion:* HIFU ablation is a safe and effective method for unresectable HCCs. A survival benefit is observed over sole TACE.

Hepatocellular carcinoma (HCC) is one of the commonest cancers in Asia. A high incidence is also observed among Asian immigrants in some western countries. However, only a small number of patients are eligible for surgical intervention upon diagnosis (1, 2). Treatment planning for HCC patients remains a great challenge to most clinicians. In Asia, most of the HCC patients are hepatitis B virus carriers. The combination of liver cancer and hepatitis B-related cirrhosis makes liver resection impossible in many patients. Liver transplantation can provide an ultimate treatment for both diseases, but because of the scarcity of liver grafts, many patients miss out. Moreover, not all patients with HCC can be transplanted because of their tumour characteristics (3). For patients who have adequate liver reserve, liver resection is considered a good option to provide long-term survival (4). Radiofrequency ablation (RFA) is a very effective and simple treatment for HCC, with survival outcome similar to that of liver resection for HCCs smaller than 2 cm (5–7). However, RFA may not be well tolerated in patients with cirrhosis, and severe complications may occur after prolonged ablation (8). Transarterial chemoembolization (TACE) is a common treatment for unresectable HCCs and its efficacy has been supported by randomized controlled studies (9, 10). However, the 2-year survival rate after TACE is only around 30% (10, 11).

High-intensity focused ultrasound (HIFU) ablation is a totally non-invasive treatment modality. It utilizes a unique frequency of ultrasound wave of 0.8–3.5 MHz, which can be focused at a distance from the therapeutic transducer (12, 13). The outcome of HIFU ablation for HCCs smaller than 3 cm is promising, with a 3-year survival rate of 94.6% (14). This retrospective study was

to investigate the survival outcome of HIFU ablation for unresectable HCCs sized 3–8 cm.

Patients and methods

From October 2003 to September 2010, 113 patients with unresectable HCCs received HIFU treatment at the Department of Surgery, Queen Mary Hospital, The University of Hong Kong. A single research assistant recorded all their clinical data prospectively in a computerized database. Patients with primary HCCs or first recurrence of HCC with a tumour size of 3–8 cm were included in this study. Patients who (i) received prior multiple treatments, (ii) had tumour invasion of major vessels, (iii) had more than three tumours or (iv) had extrahepatic disease were excluded from this study.

All HCC patients were evaluated for operability. The evaluation included assessment of tumour status, liver function, tumour location and the general condition of individual patients. Generally, hepatectomy or open RFA was offered as first-line treatment, if the liver function and physical status were satisfactory. Liver transplantation was offered to patients with advanced cirrhosis, if hepatectomy was considered risky because of marginal liver reserve.

Transarterial chemoembolization was reserved for non-ablatable tumours. The hospital introduced the HIFU service in 2006. From 2006 onwards, all patients with unresectable HCCs and considered for TACE were screened for HIFU treatment. Patients with moderate ascites, which was considered a contraindication to TACE, were also screened for HIFU treatment. Patients who could not tolerate general anaesthesia or refused consent to HIFU treatment were given TACE.

Twenty-six patients among those who received HIFU treatment in the period met the selection criteria and were enrolled in this study. The selection process is detailed in Fig. 1. As we had previously published our study of HIFU treatment for HCCs smaller than 3 cm (14), the current data analysis focused on tumours sized 3–8 cm only.

Fifty-two patients with matched tumour characteristics who received only TACE in the same period were included for comparison. Tumours were matched in terms of number and maximum diameter of the largest tumours.

High-intensity focused ultrasound treatment

Before the actual treatment, the patient receives ultrasound screening to ensure that the targeted lesions are visible on the ultrasound localization system. Chest radiography and echocardiography are performed to assess the patient's cardio-respiratory fitness for general anaesthesia. An anaesthetist then assesses the patient's pre-operative risk. Informed consent is obtained after detailed explanation of the procedure, benefits, risks and potential complications. The patient fasts for 6 h before the HIFU treatment. Before the treatment starts, the patient's skin is cleansed by degassed water, and a negative-pressure aspirator is used to degas the skin to reduce the dampening effect on ultrasonic waves.

The JC HIFU system (Chongqing Haifu Technology, Chongqing, China) is used. HIFU ablation is performed by the same team of surgeon and radiologist. A dose of antibiotic (Augmentin; Beechan Pharmaceuticals, Brentford, UK) at 1.2 g is given just before the procedure begins. The patient is put under general anaesthesia, which allows a more comfortable procedure. In addition, intermittent cessations of respiratory movement by anaesthesiologist facilitate better localization of

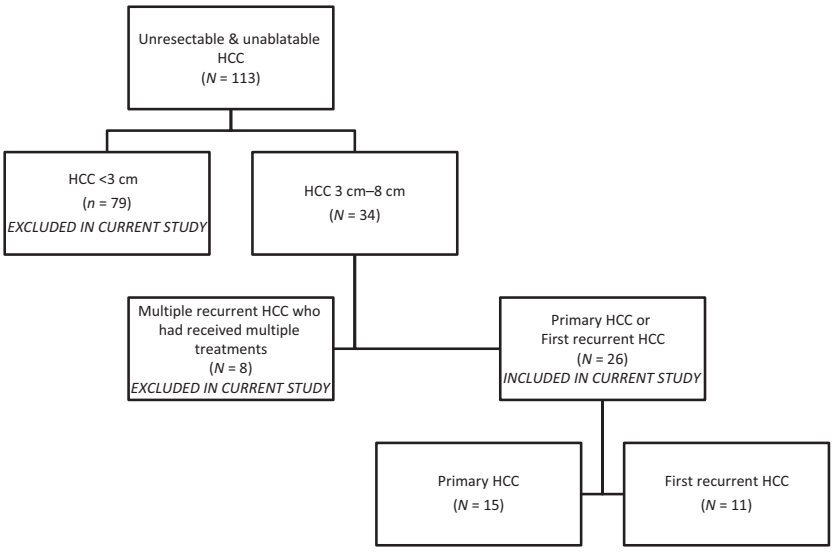

Fig. 1. Process of patient selection for High-intensity focused ultrasound (HIFU) treatment.

lesions during energy transfer. For right-sided lesions, the patient is placed in a right lateral position after intubation by anaesthesiologist. For left-sided lesions, the patient is placed in a prone position. The JC HIFU system consists of a treatment unit which delivers focused ultrasound energy with a focal length of 12 cm deep. A degassed water circulation unit provides a medium for ultrasound transmission outside the body. Grey-scale changes at ablated sites are observed during the ablation procedure, indicating the temperature change inside the targeted lesion. Oral antibiotics are given for 5 days after treatment (13).

When ablating a large tumour, the ultrasound energy is focused on the deep margin of the lesion first so as to avoid prohibition of effective penetration of energy by the cavitation effect and the presence of coagulation necrosis. Meticulous planning of the focusing point before the procedure, in which the ablation sequence is from the deepest layer to the most superficial layer, is required for maximal destruction of the targeted lesion. Intermittent cessations of the procedure allow recovery of the cavitation effect shown under ultrasound monitoring, giving additional allowance for ablation of the residual lesion in the periphery. Complete ablation is defined as disappearance of the enhancement pattern of the lesion at the 1 month on post-ablation imaging.

Transarterial chemoembolization treatment

Poor liver function is considered a contraindication to TACE. Poor liver function for TACE is defined as the presence of (i) hepatic encephalopathy, (ii) ascites that cannot be controlled by diuretics, (iii) a history of variceal bleeding within last 3 months, (iv) a serum total bilirubin level >50 μmol/L, (v) a serum albumin level <28 g/L or (vi) a prothrombin time of >4 s above the control.

Transarterial chemoembolization treatment is carried out by a consultant interventional radiologist. The patient fasts overnight with intravenous fluid infusion for hydration and receives a dose of 1.2 g of intravenous antibiotic (Augmentin; Beechan Pharmaceuticals, Brentford, UK), 20 g of mannitol and 5 mg of tropisetron before treatment (10).

The femoral artery is catheterized under local anaesthesia. The right or left hepatic artery is super-selectively catheterized. An emulsion of cisplatin (1 mg/mL) with Lipiodol in a volume ratio of 1:1 is introduced; up to 60 mL (containing 30 mg of cisplatin) is injected slowly under fluoroscopic monitoring according to the size of the tumour and the arterial blood flow. Maximal drug is administrated to the tumour without retrograde blood flow. This is followed by embolization with small gelatine-sponge pellets 1 mm in diameter mixed with 40 mg of gentamicin. After the procedure, the puncture wound is inspected and liver function monitored by a blood test. Discharge from hospital is decided upon the patient's clinical condition. TACE is repeated every 2 to 3 months (10, 15).

Tumour response to HIFU ablation and to TACE is assessed with the modified Response Evaluation Criteria in Solid Tumours (mRECIST) (16).

Statistical analysis

Baseline characteristics of patients were expressed as medians and ranges. The Mann–Whitney U -test was used to compare continuous variables, and Pearson's chi-squared test was used to compare discrete variables. The primary endpoint of this study was tumour response according to the mRECIST. The secondary endpoint was patient survival. Time of patient death was used for survival analysis. Survival curves were computed using the Kaplan–Meier method and compared between groups by the log-rank test. Significance was defined by $P < 0.05$. All statistical calculations were made with the SPSS/PC + computer software (SPSS, Chicago, IL, USA).

Results

The HIFU group contained 26 patients with a median age of 69 years (range 49–84 years), and the TACE group contained 52 patients with a median age of 67 years (range 44–84 years). Hepatitis B virus carriers dominated in both groups. Comorbidities were observed in 13 (50.0%) and 33 (63.5%) patients in the HIFU group and the TACE group respectively ($P = 0.255$). The two groups of patients had similar liver function as reflected by serum levels of total bilirubin and albumin and international normalized ratio. There were more patients with ascites ($P = 0.0001$) and patients with Child-Pugh B cirrhosis ($P = 0.0001$) in the HIFU group. Both groups of patients had a low platelet count, signifying the presence of severe portal hypertension.

The median tumour size was 4.2 cm (range 3–8 cm) in the HIFU group and 4.8 cm (range 3–8 cm) in the TACE group ($P = 0.119$). In the HIFU group, 57.7% of the patients had one tumour, 26.9% had two tumours and 15.4% had three tumours. In the TACE group, 69.2% of the patients had one tumour, 17.3% had two tumours and 13.5% had three tumours ($P = 0.554$). The median level of serum α-foetoprotein was 13 ng/mL (range 2–8840 ng/mL) in the HIFU group and 79 ng/mL (range 2–5735 ng/mL) in the TACE group ($P = 0.170$). Table 1 lists the patients' characteristics in the two groups.

Short-term treatment outcomes

Thirteen (50.0%) patients had complete ablation after one session of HIFU treatment. The median HIFU exposure time was 2606 s (range 338–7302 s) and the median total operation time was 224 min (range

Table 1. Patients' pretreatment characteristics in the two groups

	HIFU (n = 26)	TACE (n = 52)	P
Age (years) (median with range)	69 (49–84)	67 (44–84)	0.774
Male: Female	20: 6	34: 18	0.298
Hepatitis B virus carrier	22 (84.6%)	37 (71.2%)	0.192
Hepatitis C virus carrier	3 (11.5%)	11 (21.2%)	0.465
With comorbidity	13 (50.0%)	33 (63.5%)	0.255
Cardiac condition	4 (15.4%)	27 (51.9%)	0.002
Renal impairment	4 (15.4%)	2 (3.8%)	0.176
Diabetes	7 (26.9%)	16 (30.8%)	0.725
Chronic lung disease	2 (7.7%)	9 (17.3%)	0.421
Ascites			
Absent	18 (69.2%)	52 (100%)	0.0001
Present	8 (30.8%)	0 (0%)	
Child-Pugh grade			
A	18 (69.2%)	52 (100%)	0.0001
B	8 (30.8%)	0 (0%)	
Total bilirubin (μmol/L) (median with range)	17 (6–75)	18 (6–40)	0.637
Creatinine (μmol/L) (median with range)	85 (44–146)	85 (49–198)	0.458
Albumin (g/L) (median with range)	36 (27–45)	37 (25–47)	0.621
International normalized ratio (median with range)	1.1 (0.9–1.6)	1.1 (0.9–1.4)	0.996
Platelet count $\times$ 10^9/L (median with range)	80 (31–230)	101 (28–378)	0.132
Aspartate transaminase (U/L) (median with range)	48.5 (18–196)	59.5 (19–280)	0.120
Alanine transaminase (U/L) (median with range)	40 (20–245)	51 (12–295)	0.282
Tumour size (cm) (median with range)	4.2 (3.0–8.0)	4.8 (3.0–8.0)	0.119
Tumour number			
1	15 (57.7%)	36 (69.2%)	0.554
2	7 (26.9%)	9 (17.3%)	
3	4 (15.4%)	7 (13.5%)	
α-foetoprotein (ng/mL) (median with range)	13 (2–8840)	79 (2–5735)	0.170
AJCC staging (2002)			
Stage I	15 (57.7%)	34 (65.4%)	0.266
Stage II	9 (34.6%)	10 (19.2%)	
Stage IIIA	2 (7.7%)	8 (15.4%)	

50–485 min). The median amount of energy delivered was 867.023 kJ (range 124.41–19411.68 kJ). According to the mRECIST, 50.0% of the patients had complete tumour response, 7.7% had partial tumour response, 34.6% had stable disease and 7.7% had progressive disease. Seven patients who had incomplete ablation received TACE as subsequent treatment. The remaining five patients who had incomplete ablation did not receive TACE because of poor liver function and received supportive treatment instead. In the TACE group, none of the patients had complete tumour response, 21.2% had partial tumour response, 63.5% had stable disease and 15.4% had progressive disease ($P < 0.0001$) (Table 2). Procedure-related morbidities in the two groups are listed in Table 3. Most of the complications in the HIFU group were related to skin oedema or skin injury. Complications of Clavien–Dindo grade three or above were similar between the two groups. No procedure-related death occurred.

Table 2. Tumour response rates according to the mRECIST in the two groups

	HIFU (n = 26)	TACE (n = 52)	P
Complete response	13 (50.0%)	0 (0%)	<0.0001
Partial response	2 (7.7%)	11 (21.2%)	
Stable disease	9 (34.6%)	33 (63.5%)	
Progressive disease	2 (7.7%)	8 (15.4%)	

Long-term treatment outcomes

The median survival was 29.8 months in the HIFU group and 17.6 months in the TACE group. The 1-year, 3-year and 5-year survival rates in the HIFU group were 84.6%, 49.2% and 32.3% respectively. The corresponding rates in the TACE group were 69.2%, 29.8% and 2.3% ($P = 0.001$) (Fig. 2).

Among the 13 patients who had complete response in the HIFU group, five patients (38.5%) had local recurrence during this study period and eight (61.5%) did not. The recurrence pattern of these 13 patients is shown in Table 4. The 1-year local recurrence rate after complete response was 15.4%. The 3-year and 5-year local recurrence rates after complete response were both 30.8%. On univariate analysis, tumour size and tumour location did not affect the local recurrence rate.

Table 3. Complications occurring after treatment in the two groups

	HIFU (n = 26)	TACE (n = 52)	P
Patients with complications	12 (46.2%)	18 (34.6%)	0.323
Patients with two or more complications	4	5	
Complications			
Fever	3	4	
Bruising of chest wall	1	0	
Third degree skin burn	1	0	
Mild bruising over skin area	1	0	
Pleural effusion with tapping	5	0	
Skin oedema	6	0	
Hypokalaemia	0	3	
Vomiting	0	2	
Liver abscess	0	1	
Bleeding from oesophageal/gastric varices	0	4	
Hyperbilirubinaemia (>100 μmol/L)	0	1	
Necrotizing pancreatitis	0	1	
Bruises around the femoral puncture site	0	2	
Acute retention of urine with haematuria	0	1	
Partial occlusion of segmental artery in left liver lobe	0	1	
Hyperkalaemia	0	1	

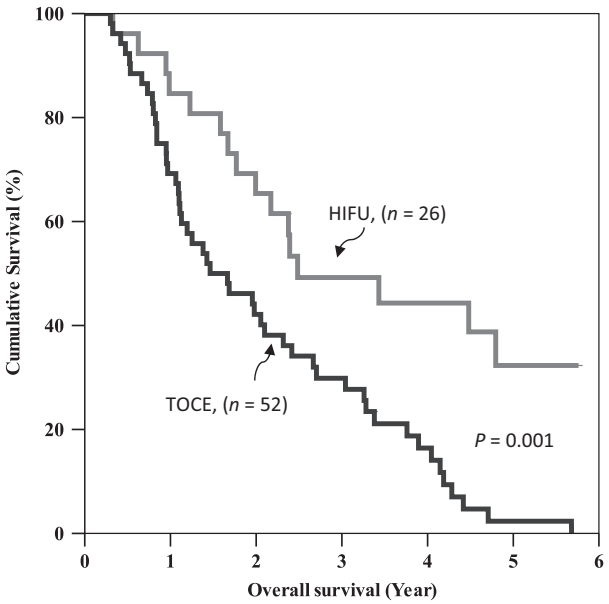

Fig. 2. Overall survival of patients in the two groups.

Table 5 shows the univariate analysis of the 10 factors that might affect patient survival. The analysis found that the following three factors were associated with favourable survival: a lower pre-operative serum level of α-foetoprotein, the use of HIFU treatment and a good response to treatment according to the mRECIST. Cox regression analysis showed that HIFU treatment was the only factor that prolonged survival, with a hazard ratio of 0.387 (95% confidence interval 0.216–0.692) (P = 0.001).

Table 4. Recurrence pattern in patients with complete response to HIFU ablation

	No local recurrence (n = 8)	With local recurrence (n = 5)	P
Tumour in Section			
IV	0 (0%)	1 (20.0%)	0.313
V	1 (12.5%)	0 (0%)	
VI	2 (25.0%)	0 (0%)	
VII	2 (25.0%)	3 (60.0%)	
VIII	3 (37.5%)	1 (20.0%)	
Tumour size (cm) (median with range)	4.4 (3–8)	3.8 (3.2–4.5)	0.463

Discussion

Large HCC and cirrhosis have always been a bad combination for cancer treatment. Although liver transplantation is the ultimate solution, it may not be possible because of various reasons, which include unsuitable age or physical condition of patient and liver graft shortage (17). The choice of treatment is limited when the patient's age is advanced. Many liver transplant programmes prioritize patients younger than 65 years although some programmes may offer deceased-donor liver transplantation to patients older than 65 years, if their outcome analyses are favourable (3, 18–21). TACE has been the most popular treatment modality because of its simplicity and repeatability for patients with unresectable HCCs (9, 15). However, the TACE group in the present study had a 3-year survival rate of 29.8% and a 5-year survival rate of 2.3% only. In fact, meta-analysis of trials with a low risk of selection bias had shown that TACE vs. control did not significantly increase survival (22).

As a result, more effective treatment options for this group of patients are needed. As a new treatment approach, different targeted therapies have been proposed (23–25). Nevertheless, their effect has not been well proven. Another treatment strategy is to use a combination of presumably effective measures. The use of sorafenib with TACE has been suggested. Its initial results showed that 63.3% of the patients had partial or stable disease, but long-term survival data are still lacking (26). The use of drug-eluting beads as a medium for TACE has also been studied. A study by Song *et al.* (27) compared this new mode of TACE with traditional TACE and showed that time to progression of tumour was longer after the new mode (11.7 vs. 7.6 months).

Table 5. Univariate analysis of overall survival

	Median survival (months) (SE)	*P*
Age (years)		
≤67.5 (*n* = 39)	27.80 (6.92)	0.402
>67.5 (*n* = 39)	23.46 (3.87)	
Hepatitis B virus infection		
No (*n* = 19)	23.46 (4.48)	0.213
Yes (*n* = 59)	25.17 (4.43)	
Hepatitis C virus infection		
No (*n* = 64)	24.65 (4.04)	0.192
Yes (*n* = 14)	13.31 (9.68)	
Child-Pugh grade		
A (*n* = 62)	23.92 (4.55)	0.612
B (*n* = 16)	17.09 (10.85)	
Ascites		
No (*n* = 70)	23.73 (3.98)	0.347
Yes (*n* = 8)	26.06 (11.80)	
Tumour number		
1 (*n* = 51)	23.92 (4.34)	0.744
2–3 (*n* = 27)	28.52 (7.15)	
Tumour size		
≤4.5 cm (*n* = 43)	28.69 (2.35)	0.065
>4.5 cm (*n* = 35)	15.02 (4.14)	
α-foetoprotein		
≤46.5 ng/mL (*n* = 39)	29.81 (7.14)	0.021
>46.5 ng/mL (*n* = 39)	17.09 (4.17)	
Treatment		
HIFU (*n* = 26)	29.81 (9.57)	0.001
TACE (*n* = 52)	17.55 (5.04)	
Response according to the mRECIST		
Complete response (*n* = 13)	53.76 (21.41)	0.041
Partial response (*n* = 13)	24.65 (5.02)	
Stable disease (*n* = 42)	23.73 (3.28)	
Progressive disease (*n* = 10)	11.40 (4.05)	

Nonetheless, long-term data are again lacking to support the superiority of this treatment modality.

High-intensity focused ultrasound ablation is a relatively new treatment using totally extracorporeal ultrasound energy for tumour ablation and is gaining recognition. It has received the CE Approval in Europe for treatment of liver cancer and has been shown to be effective in treating small HCCs in patients with cirrhosis (14, 28). In HIFU ablation, the ultrasound energy vibrates the particles at the focused point, where heat is generated to cause coagulative necrosis of the tissue. RFA is another mode of ablation for HCCs, but a slightly high level of serum total bilirubin and hypoalbuminaemia are risk factors for complication development (8). In contrast, HIFU ablation is safe for patients with advanced cirrhosis, for whom other modes of thermal ablative therapy are considered risky. It can be safely performed in the presence of ascites (29).

In this study, more than 30% of the patients receiving HIFU treatment had a moderate amount of ascites as documented by pretreatment contrast computed tomography. In the TACE group, none of the patients had ascites. As the presence of ascites is considered a sign of decompensation of cirrhosis, it is regarded as a contraindication to TACE (10). On the contrary, the presence of ascites is deemed to be a favourable condition for HIFU ablation. It is because of the unique feature of ultrasound energy. Because ultrasound energy travels better in water, the ascitic fluid actually acts as a good medium for energy propagation without loss of its functional amplitude.

The most common complication of HIFU is skin burn. As the skin and adipose tissue absorb energy easily, any prefocal peak of energy coinciding with reflection of energy from the ribs can cause thermal injury. If ascites is present, it acts as a layer of coolant which prevents overheating of muscle layers and the subcutaneous tissue, and thus the risk of skin burn is reduced. In our previous study of HIFU for HCCs <3 cm, the overall complication rate was 21.3% (14). In this study, the overall complication rate was 46.2%. Most of the complications in this study were related to skin oedema or skin burn. This was probably a result of the administration of high-dose energy for the larger tumours. As a matter of fact, many cases of incomplete ablation in this study were because of early cessation of treatment to avoid severe skin burns. Although the overall complication rate was high, only one (3.8%) patient with skin burn required surgical debridement.

In the previous study, the complete ablation rate was 89.3% (14). In this study, the complete ablation rate after one session was 50%. Complete ablation sometimes cannot be achieved because of several reasons. As the liver is located behind the rib cage and ultrasound energy cannot pass through bones, the operator and the anaesthesiologist have to cooperate to control the position of the liver through respiratory movement control. For a high-lying tumour, the liver can be pushed down by holding a prolonged inspiration. By this way, complete ablation may be achieved for small tumours at the dome of the liver (30). However, for a large tumour in a difficult position, the energy may not be evenly distributed to the tumour via the narrow rib spaces. Likewise, complete ablation of multiple tumours is relatively not easy as not all tumours are in a favourable position for treatment. Tumours in the left liver lobe usually have a better complete ablation rate as the left lobe is not completely covered by the ribs. Furthermore, as a larger tumour requires a longer ablation time, the skin and the subcutaneous tissue unavoidably absorb a large amount of acoustic energy. Oedema of the skin prohibits effective administration of ultrasound energy to the targeted lesion, and often the treatment has to be ceased prematurely to avoid skin burns to the patient.

Although some patients in the HIFU group had incomplete ablation of tumours, patient survival in this group was still favourable when compared with the TACE group. On univariate analysis, HIFU treatment and the presence of complete or partial response were

favourable factors for survival. In patients with incomplete ablation, many had their active tumours reduced in size. Some of them had TACE as an adjuvant treatment for their residual tumours. TACE may have a better effect on reduced-size HCCs than on large HCCs when patient survival is concerned. RFA, unlike HIFU ablation, may produce an uncontrolled area of tissue necrosis and is less tolerated in patients with cirrhosis. A study by Li *et al.* (31) found that the combination of RFA and TACE would lead to significant deterioration of liver function in patients with Child-Pugh B cirrhosis.

Tumour ablation by HIFU is precise. The energy is released at short intervals. Each release is followed by a period of rest to prevent over accumulation of energy at the skin level. This slow-ablation mode produces very little collateral damage to the liver parenchyma surrounding the targeted tumour. Because of its high tolerability, this treatment modality can even be offered to selected patients with Child-Pugh C cirrhosis as a bridging treatment before liver transplantation (32).

Conclusion

High-intensity focused ultrasound ablation is a safe and effective treatment for patients with unresectable HCCs and cirrhosis. In the treatment of HCCs sized 3–8 cm, HIFU ablation alone or together with TACE may produce better survival outcomes when compared with TACE alone. A randomized controlled trial is required to demonstrate the effect of HIFU treatment for patients with unresectable HCCs.

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References

1. Akriviadis EA, Llovet JM, Efremidis SC, *et al.* Hepatocellular carcinoma. *Br J Surg* 1998; **85**: 1319–31.
2. Okuda K, Ohtsuki T, Obata H, *et al.* Natural history of hepatocellular carcinoma and prognosis in relation to treatment. study of 850 patients. *Cancer* 1985; **56**: 918–28.
3. Mazzaferro V, Regalia E, Doci R, *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693–9.
4. Fan ST, Poon RT, Yeung C, *et al.* Outcome after partial hepatectomy for hepatocellular cancer within the milan criteria. *Br J Surg* 2011; **98**: 1292–300.
5. Hasegawa K, Kokudo N, Makuuchi M, *et al.* Comparison of resection and ablation for hepatocellular carcinoma: a cohort study based on a Japanese nationwide survey. *J Hepatol* 2013; **58**: 724–9.
6. Lam CM, Ng KK, Poon RT, *et al.* Impact of radiofrequency ablation on the management of patients with hepatocellular carcinoma in a specialized centre. *Br J Surg* 2004; **91**: 334–8.
7. Toshikuni N, Takuma Y, Goto T, Yamamoto H. Prognostic factors in hepatitis c patients with a single small hepatocellular carcinoma after radiofrequency ablation. *Hepatogastroenterology* 2012; **59**: 2361–6.
8. Cheung TT, Ng KK, Poon RT, Fan ST. Tolerance of radiofrequency ablation by patients of hepatocellular carcinoma. *J Hepatobiliary Pancreat Surg* 2009; **16**: 655–60.
9. Llovet JM, Real MI, Montana X, *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**: 1734–9.
10. Lo CM, Ngan H, Tso WK, *et al.* Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35**: 1164–71.
11. Doffoel M, Bonnetain F, Bouche O, *et al.* Multicentre randomised phase III trial comparing tamoxifen alone or with transarterial lipiodol chemoembolisation for unresectable hepatocellular carcinoma in cirrhotic patients (Federation francophone de cancerologie digestive 9402). *Eur J Cancer* 2008; **44**: 528–38.
12. Wu F. Extracorporeal high intensity focused ultrasound in the treatment of patients with solid malignancy. *Minim Invasive Ther Allied Technol* 2006; **15**: 26–35.
13. Ng KK, Poon RT, Chan SC, *et al.* High-intensity focused ultrasound for hepatocellular carcinoma: a single-center experience. *Ann Surg* 2011; **253**: 981–7.
14. Cheung TT, Fan ST, Chu FS, *et al.* Survival analysis of high-intensity focused ultrasound ablation in patients with small hepatocellular carcinoma. *HPB* 2013; **15**: 567–73.
15. Yau T, Yao TJ, Chan P, *et al.* The outcomes of elderly patients with hepatocellular carcinoma treated with transarterial chemoembolization. *Cancer* 2009; **115**: 5507–15.
16. Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.
17. Lo CM. Deceased donation in Asia: challenges and opportunities. *Liver Transpl* 2012; **18**(Suppl.2): S5–7.
18. Busuttil RW, Farmer DG, Yersiz H, *et al.* Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. *Ann Surg* 2005; **241**: 905–16.
19. Lee SG, Hwang S, Kim KH, *et al.* Toward 300 liver transplants a year. *Surg Today* 2009; **39**: 367–73.
20. Lo CM, Fan ST, Liu CL, *et al.* Ten-year experience with liver transplantation at queen mary hospital: retrospective study. *Hong Kong Med J* 2002; **8**: 240–4.
21. Yong CC, Chen YS, Wang SH, *et al.* Deceased-donor liver transplantation: 10 years' experience at change gung memorial hospital-kaohsiung medical center. *Chang Gung Med J* 2005; **28**: 133–41.
22. Forner A, Llovet JM, Bruix J. Chemoembolization for intermediate HCC: is there proof of survival benefit? *J Hepatol* 2012; **56**: 984–6.
23. Bruix J, Raoul JL, Sherman M, *et al.* Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase iii trial. *J Hepatol* 2012; **57**: 821–9.
24. Iavarone M, Cabibbo G, Piscaglia F, *et al.* Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. *Hepatology* 2011; **54**: 2055–63.
25. Koeberle D, Montemurro M, Samaras P, *et al.* Continuous sunitinib treatment in patients with advanced hepatocellular

carcinoma: a swiss group for clinical cancer research (SAKK) and swiss association for the study of the liver (SASL) multicenter phase II trial (SAKK 77/06). *Oncologist* 2010; **15**: 285–92.
26. Chung YH, Han G, Yoon JH, *et al.* Interim analysis of START: study in Asia of the combination of TACE (transcatheter arterial chemoembolization) with sorafenib in patients with hepatocellular carcinoma trial. *Int J Cancer* 2013; **132**: 2448–58.
27. Song MJ, Chun HJ, Song DS, *et al.* Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. *J Hepatol* 2012; **57**: 1244–50.
28. Chan AC, Cheung TT, Fan ST, *et al.* Survival analysis of high-intensity focused ultrasound therapy versus radiofrequency ablation in the treatment of recurrent hepatocellular carcinoma. *Ann Surg* 2013; **257**: 686–92.
29. Cheung TT, Chu FS, Jenkins CR, *et al.* Tolerance of high-intensity focused ultrasound ablation in patients with hepatocellular carcinoma. *World J Surg* 2012; **36**: 2420–7.
30. Cheung TT, Poon RT, Yau T, *et al.* High-intensity focused ultrasound as a treatment for colorectal liver metastasis in difficult position. *Int J Colorectal Dis* 2012; **27**: 987–8.
31. Li JX, Wu H, Huang JW, Zeng Y. The influence on liver function after transcatheter arterial chemoembolization combined with percutaneous radiofrequency ablation in patients with hepatocellular carcinoma. *J Formos Med Assoc* 2012; **111**: 510–5.
32. Cheung TT, Chok KS, Lo RC, *et al.* High-intensity focused ultrasound ablation as a bridging therapy for hepatocellular carcinoma patients awaiting liver transplantation. *Hepatobiliary Pancreat Dis Int* 2012; **11**: 542–4.