

High Intensity Focused Ultrasound Ablation for Patients with Inoperable Liver Cancer

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ABSTRACT

Background/Aims: To analyses the feasibility and efficacy of high intensity focused ultrasound (HIFU) treatment in patients with inoperable liver cancer. **Methodology:** 187 patients were treated with HIFU, of all these patients 116 cases were Primary Liver Cancer (PLC) and 71 cases were Metastatic Liver Cancer (MLC). According to some parameters, such as clinical symptoms, the basis of main organs functional tests, imaging examinations, and progression-free survival (PFS) time to assess the safety and efficacy of HIFU in the treatment of liver cancer. **Results:** 55 patients (29.4%) achieved CR and 73 patients (39.0%)

achieved PR, 32 patients (17.1%) had responses of SD, and 27 patients (14.4%) were PD, respectively. Response rates were 90.5% (32CR + 6 PR/42) in left lobe cancer and 64.1% (22 CR + 62 PR/131) in right lobe cancer. The median PFS for those CR case was 7 months, of PLC was 8 months, of MLC was 5 months. **Conclusions:** HIFU is effective and feasible in the treatment of liver cancer. It offer a significant noninvasive therapy for local treatment of liver cancer. For those right lobe liver cancers or with poor ultrasonic window, increasing treatment time or repeated treatment may improve the efficiency of HIFU ablation.

INTRODUCTION

About 80 percent of patients with primary liver cancer (PLC) are not suitable for surgical treatment or liver transplantation, because of been diagnosed at intermediate or advanced stages(1,2). While metastatic liver cancer (MLC) is also one of the frequent causes of death. An analysis of 9700 cases of cancer patients who had been autopsied showed that the liver metastases were 41%, secondary to the metastases of lymph nodes (57%)(3). With increasing incidence of PLC and MLC, application of local therapy for patients with inoperable liver cancer has become an important part of the clinical practice. Local ablation therapy is considered a good treatment modality for local control of liver cancer in patients without extra-hepatic metastasis. A growing number of evidence has demonstrated that the best outcomes of RFA treatment were in patients with solitary tumors less than 3 or 2.5cm (4,5). But for those who are not candidates for this standard, an alternative such as HIFU may be valuable.

As a novel, emerging therapeutic modality, HIFU is a non-invasively technology used for treating solid tumors. HIFU is able to lead a potential coagulation necrosis in-depth tissue without damaging peripheral vital anatomy structures. For liver cancer, HIFU treatment has been reported to lead to the degeneration and coagulation necrosis of the treated liver cancer tissue as well as alleviation of cancer-related pain(6). In this retrospective study, 187 cases of liver cancer treated with HIFU are analyzed in an attempt to determine the efficacy and safety of HIFU.

METHODOLOGY

Clinical materials

Between Jan 2005 and Dec 2009, 187 patients with inoperable liver cancer were enrolled in this study, including 147 males and 40 females, median age 54.2 years (Range: 17-84 years), and patients' disease status were histologically or cytologically conformed. The KPS scores for all of them were greater than or equal to 70, and 116 cases of them were PLC and 71 cases were MLC. There were 125 patients who have been treated with TACE one month before the HIFU treatment. The patients were selected based on the following criteria: (1) Younger than 85-years-old; (2) A Karnofsky performance scale (KPS) score of $\geq 60\%$ was required. In addition, adequate bone marrow (white blood cell count $> 2,500/\text{ml}$, platelet count $> 50,000/\text{ml}$, hemoglobin $> 8\text{g}/\text{ml}$), kidney (serum creatinine concentration $< 1.5\text{ mg}/\text{dl}$) and liver (serum transaminase level < 2 times the upper normal range) function was required; an exception was made for hyperbilirubinemia due to obstructive jaundice; (3) Not suitable for surgical resection after confirmation by pathologic examination; and (4) Patients were also excluded if their lesion was undetectable by ultrasound or if the patients had a serious or uncontrolled concurrent medical illness.

A total of 42 patients had HCC lesions located in the right lobe, 131 in the left lobe and 14 in both lobes. The tumor size was described using its maximum dimension measured two-dimensionally on computerized tomography (CT) or magnetic resonance imaging (MRI) images. Tumor diameters ranged from 3 to 15cm.

The characteristics of the patients are shown in Ta-

ble 1.

Treatment methods

All the target volume covered the whole intrahepatic tumor lesion. When the diameter of lesion is less than 5cm and distance between it and glisson's capsule more than 2cm, target volume should also include the normal tissue within 1-2cm of the tumor's edge(Enlarge treatment), and no patients had performed the partly-rib resection before the HIFU treatment (Fenestration). Every patient in the study received HIFU treatment only once.

Equipment

Chongqing Hiaifu(HIFU) Tech provided the ultrasound therapeutic system. This system (Model JC) had a large number of functions, including three-dimensional targeted scanning, real-time ultrasound (US) localization and monitoring of tumors, calculation of target volume, and feedback control of therapy dose.

Therapeutic parameters and methods of HIFU treatment

The following methods for HIFU treatment were followed. The skin in the treatment area was cleaned before treatment, fasting and cathartic preparation is also necessary. During the treatment, intravenous midazolam and fentanyl for sedation and analgesia were administered to patients. The parameters used for the therapeutic ultrasound transducer were showed as follow 1) Frequency 0.85MHz; 2)Focal length 136.0mm; 3) Scanning method: point-by-point or straight line method; 4)Treatment power: 216W (Range: 108-400W); 5) Treatment time: 264-17781 seconds; 6) Dose intensity (DI): 10KJ/cm³ (Range: 2.4-28.3KJ/cm³). After HIFU, patients received supportive treatment and were observed in hospital for 2 to 7 days.

Toxicity and response evaluation

After treatment, a complete blood count with differentials, serum chemistry was conducted; a urinalysis, electrocardiogram and the electrolyte level of blood were also performed. Complications of the major organs, such as bleeding or rupture of lesions, jaundice and so on were evaluated. Treatment-related toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 2.0.

Tumor response was assessed by CT or MRI scans 1 month after treatment. According to mRECIST(7), complete response (CR) was defined as disappearance of any intratumoral arterial enhancement in all target lesions, partial response (PR) was defined as at least a 30% decrease in the sum of diameters of viable (enhancement phase) target lesions, taking as reference the baseline sum of the diameters of target lesions. An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started, patients were considered to have progressive disease (PD). Stable disease (SD) was defined as any cases that do not qualify for either partial response or progressive disease.

Statistical methods

Response rate was estimated using the binomial probability, and exact 95% confidence intervals (CIs) were provided. Progression-free survival (PFS) time was calculated by the Kaplan-Meier method. The PFS

TABLE 1. Clinical data for 187 cases.

Characteristics		Number	Ratio (%)
General data			
Gender	Male	147	76.8%
	Female	40	21.4%
Age(years)	Median	54.2	
	Range	17-84	
KPS Score	70	124	66.3%
	80	43	23.0%
	90	20	10.7%
Cancer characteristics			
PLC or MLC	PLC	116	62.0%
	MLC	71	38.0%
Tumor lation	Left lobe	42	22.5%
	Right lobe	131	70.0%
	Both lobes	14	7.5%
Cancer size	≤5cm	76	40.6%
	5~10cm	71	38.0%
	>10cm	40	21.4%
Single/Multi nodules	Single	143	76.5%
	Multi	44	23.5%
TACE before HIFU	Yes	125	66.8%
	No	62	33.2%

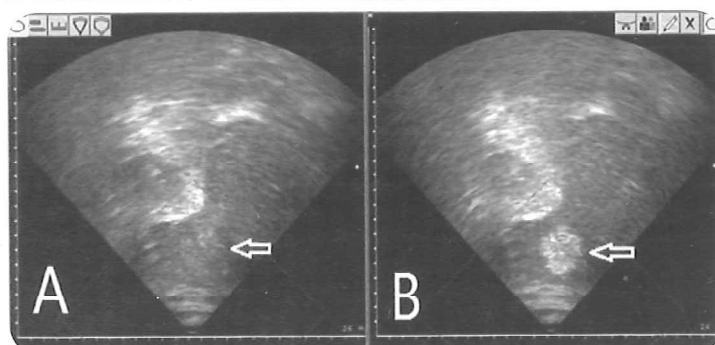


FIGURE 1. Grayscale changes of HIFU obtained from real-time ultrasound (US) images during the HIFU procedure. (A) US image obtained before HIFU showing a lesion in the liver. (B) US image obtained after the HIFU procedure showing a grayscale change in one slice of the lesion.

time was defined as the time from HIFU treatment to tumor progression or death, or the date of last follow-up. Survival curves were calculated by the Kaplan-Meier method. Statistical calculations were performed using SPSS software (version 13.0). This study conducts Log-rank test for differences testing, the results are reported as P values, and take the P values less than 0.05 as significant different.

RESULTS

Toxicities and complications

During and after the treatment, the vital signs of all

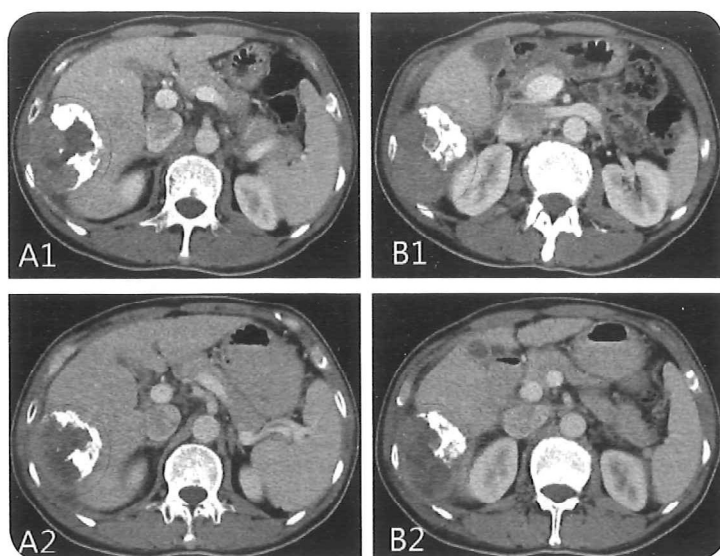


FIGURE 2. These figures were obtained from a patient who had TACE before HIFU treatment. A1 and B1 were obtained before HIFU treatment, lipiodol was well retained in the tumor after TACE. A2 and B2 obtained after HIFU treatment showed a significant reduction of blood supply in the targeted area.

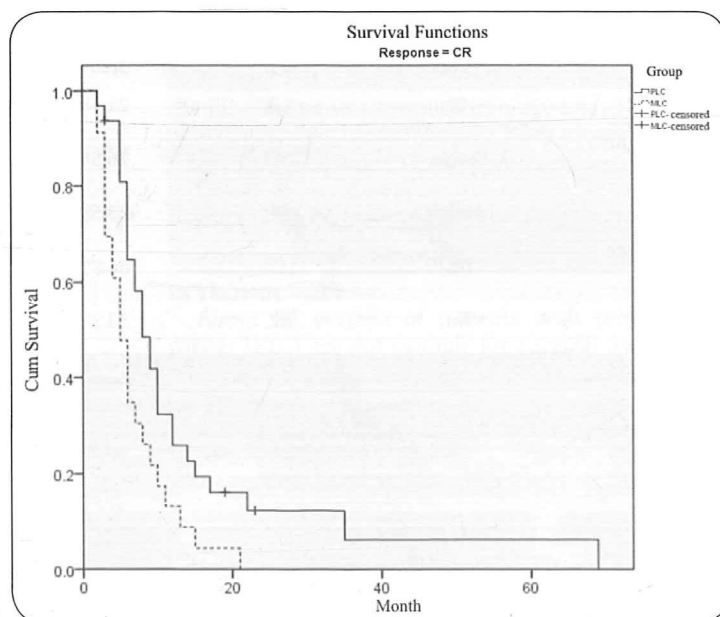


FIGURE 3. Cumulative survival curves for CR cases calculated by the Kaplan-Meier method.

patients remained stable and no obvious side effects were observed. There were no obvious changes of electrocardiogram, renal function and electrolyte levels after treatment. The injuries of gastrointestinal tract, lung and kidney did not emerge, and neither of the lesion rupture, bleeding or jaundice. Only 29 patients' level of serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), γ -glutamyl-transferase (γ -GT) were slightly higher than the baseline values, and these levels had recovered after approximately one week of liver protection therapy. All 5 patients had skin burns of varying degrees, most of which located on the skin directly in the pathway of ultrasound; only one case skin burns were located on the opposite side to the pathway of transmitting focused ultrasound. Three cases had erythematous burns (first grade), two cases displayed a small area of deep skin burn burns (third

grade). There were no severe complications or adverse reactions related to HIFU therapy in all of the patients in the follow-up period.

Short-term efficacy

During the treatment, the target tumors always obtained hyper-echo change from the US monitor (**Figure 1**). Contrast enhanced CT or MRI showed decrease or disappear of blood supply in target region (**Figure 2**). The range of hyper-echo change was basically the same as the lesion necrosis shown by post-operative CT or MRI. As 55 patients (29.4%) achieved CR and 73 patients (39.0%) achieved PR, 32 patients (17.1%) had responses of SD, and 27 patients (14.4%) were PD, respectively. Total response rates were 68.4% (55CR + 73 PR/187). Response rates were 90.5% (32CR + 6 PR/42) in left lobe cancer and 64.1% (22 CR + 62 PR/131) in right lobe cancer. The response rates was significantly different ($P=0.000$) between the left lobe group and right lobe group.

Progression-free survival time

The median PFS time for those CR cases (55cases) was 7.0 months. For PLC patients with CR (32 cases), the median PFS time was 8.0 months. For MLC patients with CR (23 cases), the median PFS was 5.0 months. The PFS time was significantly different ($P=0.008$) between the PLC group and MLC group. (**Figure 3**)

DISCUSSION

Surgical treatment is the first choice to consider for liver cancer, but as mentioned before, most patients are inoperable. Radiofrequency ablation, percutaneous ethanol injection, cryoablation, laser induced interstitial thermotherapy and microwave coagulation are recommended in the treatment of inoperable liver cancer for their minimally invasive (8-10). But HIFU is the only technique to be completely non-invasive, and HIFU could turn the ultrasonic as energy to form biological focal volume with millimeter diameter, make the temperature of the target tissue to 65-100°C through acoustic and thermal energy conversion in 0.5 to 5 seconds, so as to destroy tumor tissue by coagulating protein and killing the cells(11). Study (12) also revealed that HIFU-treated tumor cells underwent complete coagulation necrosis, and lost the abilities to proliferate, invade and metastasis. Coagulation necrosis tissue is gradually dissolved and absorbed by the body through the metabolism (13).

After HIFU treatment, there is intensification of ultrasound echo in the irradiation zone, indicate the reduction of the blood in the tumor tissue and the structure change in the target area. Haar(14) observed that the intensification of ultrasound echo after HIFU irradiation is coincident with the actual damage. Wen(15) also observed that the changes of grayscale is the same as damage area after the HIFU treatment. So, we assumed that the change of ultrasound grayscale is associated with the effect of HIFU treatment in a certain sense. The thermal ablation therapy could generate coagulation necrosis of tumor tissue, and the scar tissue would appear in the irradiated area, so that the volume of the tumor will not be significantly reduced in the short term. The most common criteria to assess the tumor response base on the size of the tumor, but it would be a mismatch in the assessment of thermal ablation therapy. The mRECIST assessment is based on the decrease of intratumoral

blood supply in the target lesions. It provides a reliable method for assessing tumor response for thermal ablation treatments.

HIFU after TACE would be an effective, safe and non-invasive treatment for HCC. In a study (16), researchers divided HCC patients into three groups, 40 cases in HIFU group (treated by only HIFU), 32 cases in combined group (treated by TACE & HIFU) and 40 cases in control group (treated by only TACE). They found out that both reduce rate of tumor volume and decrease rate of AFP in combined group were better than HIFU group and TACE group and the long-term survival rate of combined group was better than other groups. HIFU after TACE would also with a low rate of severe complications (17). In our study, we found that whether to accept the pre-operative TACE is significantly associated with grayscale changes after the ultrasound ablation, which may due to the following reasons. First, after the TACE treatment, iodinated oil is deposited in the tumor resulting in heavy ionized iodine content, thus creating a greater acoustic impedance than liver tissue. Second, reduction of the tumor blood make heat loss diminished, thereby enhancing the therapeutic effect (18).

HIFU ablation of the liver have an challenge, ribs in the way of the US beam distort and prevent US beams so focused US energy on target tumor becomes more weak. The tumors were located in left lobe can be often obtained better acoustic windows than those in right lobe. Our result also indicated the response rate was higher for HIFU ablation tumor in left lobe than in right lobe. Although the efficiency of HIFU in the treatment of liver cancer is reduced because of the ribs, HIFU does not require the insertion of an applicator into a target tissue and with less complication. This character increases its value in the treatment of liver tumor. In our study there were no obvious complications were observed, only few patients shown slightly higher level of AST, ALT, γ -GT

after treatment. It indicated HIFU would be a safe and feasible procedure for liver cancer treatment. Although ribs would strongly reflect to the ultrasonic beams, affect ultrasonic energy deposition, and reduce efficacy of HIFU therapy (18), especially for the tumor in the right lobe. But we deem that it's unnecessary to resect partial ribs. In our result, even right lobe tumor could acquire more than 60% the response rate. For those right lobe tumor or with poor ultrasonic window, increasing treatment time or repeated treatment may improve the efficiency of HIFU ablation. Certainly, TACE before HIFU may be another way to increase the ablation efficiency.

Our result also showed that the PFS time of MLC was less than PLC significantly. We deem that the range of MLC invasion may be larger than PLC invisibly. Some potential tumor of MLC could reside in the edge of target or somewhere else more than PLC that still actively after HIFU ablation. For MLC ablation of HIFU should enlarge the irradiate range more than PLC, if could 2-3cm range may be appropriate. Of course, to confirm whether 2-3cm enlarged range of MLC is appropriate for HIFU ablation, a randomized controlled study is still necessary.

CONCLUSION

In conclusion, our results demonstrate that HIFU may effectively ablate liver cancer. Moreover, it is safe and feasible. HIFU will offer a significant noninvasive therapy for local treatment of liver cancer. However, tumors were located in right lobe may be often in poor acoustic windows because of ribs in the way of the US beam distorting and preventing US beams. For those right lobe liver cancers or with poor ultrasonic window, increasing treatment time or repeated treatment may improve the efficiency of HIFU ablation. For MLC ablation of HIFU may enlarge the irradiate range more than PLC which will decrease the recurrence rate.

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