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*Original Article*

# High intensity focused ultrasound (HIFU) for primary hepatocellular carcinoma: a single center experience

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**Abstract:** Objective: To evaluate the efficacy and tolerability of high intensity focused ultrasound (HIFU) for the treatment of primary hepatocellular carcinoma (HCC) patients. Methods and materials: From 2012 to 2014, 63 patients with liver-confined HCC were treated with HIFU. The records of all patients were reviewed, primary endpoint-treatment efficacy was scored according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1, and overall survival (OS) was calculated according to the method of Kaplan and Meier. Toxicity was graded according to the Common Terminology Criteria for Adverse events v 4.0. Clinic pathologic factors affecting the primary technique efficacy and OS rates were investigated by univariate analysis and multivariate analysis. Result: The median follow-up time was 24 months. The confirmed response rate was 77.8%, 1-year and 2-year OS was 87.3% and 44.4%, respectively. Multivariate analysis indicated that comparing with the patients with ECOG score of 1 before HIFU treatment, the cases with ECOG score of 0 showed superiority in term of patients' survival (p=0.02). There were no ≥ Grade 3 averse events. Flushing skin could be observed in minority of patients (n=14, 22.2%) after HIFU treatment, which-healed spontaneously without any treatment. One patient had fever, and one patient had mild chest wall pain after HIFU treatment. Intraoperative pain was mild to moderate, therefore, anesthesia was not necessary, which could be avoided by administering analgesics before HIFU treatment. Postoperative pain was not found in patients. No skin burn was detected, either. Conclusions: In this single center study, we demonstrated HIFU is a safe, effective and noninvasive option for primary HCC patients.

**Keywords:** HIFU, primary HCC, efficacy, safety, OS

## Introduction

Primary liver cancer is the fourth most common cancer worldwide, including two major types, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). The prevalence of HCC has remained to be highly increased in both Western and Eastern countries [1, 2]. The incidence of primary HCC in China is still the highest around the world [3], even though a declining trend of HCC morbidity and mortality has been observed in several parts of China, due to at least in part the improvement in the pathological confirmation and target treatment strategies of this disease [4, 5]. The disease often presents in the setting of advanced cirrhosis, and orthotropic liver transplant (OLT) provides the greatest chance for both cure and long-term survival [6, 7].

Surgical resection is still the predominant choice for most clinicians aiming at achieving removal of tumors completely [8]. It can provide comparable rates of long-term overall survival [9, 10], but preexisting hepatic dysfunction and lesion size can significantly limit both modalities with regard to patient eligibility and treatment efficacy [11, 12]. Since the 21st century, local ablation technology has gradually become an important treatment method for HCC, and is considered to be the third technology of liver cancer treatment [13-15].

High-Intensity Focused Ultrasound (HIFU) is an entirely noninvasive treatment modality of thermal ablation in treatment of primary HCC patients, which has been applied in clinical practice for two decades [16, 17]. With this technique, high-intensity ultrasound waves

**Table 1.** Demographics and tumors characteristics of patients included

| Characteristics | Classification | Number of patients (n=63) |
|---|---|---|
| Age (years) | > 55 | 27 (42.9%) |
| Median (range): 53.6 (35-71) | ≤ 55 | 36 (57.1%) |
| Sex | Male | 42 (66.7%) |
| | Female | 21 (33.3%) |
| ECOG PS | 0 | 25 (39.7%) |
| | 1 | 38 (60.3%) |
| Child-Pugh | A | 33 (52.4%) |
| | B | 30 (47.6%) |
| HBsAg | Positive | 37 (58.7%) |
| | Negative | 26 (41.3%) |
| AFP leve l (ng/ml) | > 400 | 41 (65.1%) |
| | ≤ 400 | 22 (34.9%) |
| Tumor Number | Single | 49 (77.8%) |
| | Multiple | 14 (22.2%) |
| Tumor diameter (cm) | > 3 | 31 (49.2%) |
| | ≤ 3 | 32 (51.8%) |

pass through the anterior abdominal wall and converge into a precise target point within the tumor tissue to cause a temperature rise (55-90°C) sufficient to induce selectively deep tissue destruction within a few seconds without harming adjacent and overlying structures [18, 19].

Even though HIFU has a long history, it is gradually increased to be applied in the treatment for a variety of diseases only during the last decade, especially in China and several eastern countries. There is an increasing interest around the potential application of HIFU energy, in various clinical applications, and this interest is confirmed by a growing number of players which are currently manufacturing HIFU-based systems. US-guided HIFU is the most common method to target and monitor the status of the destruction, which is mainly produced and applied in China [20, 21].

Herein, we report our experience on the efficacy and safety of HIFU technology for the treatment of primary HCC patients.

## Methods and materials

### *Patient eligibility*

A total number of 63 patients with primary HCC were prospectively enrolled from January 2012 to December 2014 in our center. The inclusion criteria were as follows: (1) The patients confirmed by pathological examination or American Association for Study of Liver Disease (AASLD) liver cancer clinical diagnostic criteria [22]; (2) patients with lesion diameter ≤ 5 cm and with the number of lesions ≤ 3; (3) Patients who were under the Child-Pugh classification status of A or B by Child-Pugh Score of the liver function, or reach the level by medical treatment [23]; (4) patients with Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1; (5) patients who preferred a non-invasive approach, rather than the surgical resection. Exclusion criteria were as follow: (1) patients diagnosed with secondary HCC; (2) patients who also had other malignant tumors or serious underlying diseases, such as cardiovascular diseases, mental disorders; (3) patients without complete clinical information or unwilling to undergo this procedure, or patients with incomplete follow-up data.

Detailed demographic information and clinical characteristics for each participant were obtained from clinical records at the time of recruitment. All patients were followed regularly by personal or family contacts and were contacted every 3 months. The latest follow-up data in this analysis was obtained in October 2016 with a median follow-up time of 24 months (range 12-28 months).

### *Treatment of HIFU*

All the patients with HCC were treated with-HIFUINT-9000 system (Shanghai A&S Sci-Tec Co., Ltd, Shanghai, China). This equipment consists of three parts: an imaging system consisting of an ultrasound scanner coupled with a stereotaxic localizing arm; a firing system locates in a tank filled with degassed water; and a computer that controls the firing sequence and the movement of the firing head through a three-dimensional micro positioning system [24]. The main parameters of the equipment include input power, 5-10 kW/cm$^2$; effective therapy depth, 2-15 cm; practice-focused sphere, 3 x 3 x 10 mm; unit transmit time (t1), 0.2 s; intermission time (t2); t1/t2=2:1; and treatment times at each location, 6-8. All of the parameters can be adjusted according to the different depths of tumors.

**Table 2.** Tumor response after HIFU treatment

| Response | Number (n=63, %) | 95% CI |
|---|---|---|
| Confirmed response | 49 (77.8%) | 62.4-89.6% |
| Completely response | 20 (31.7%) | 19.8-46.9% |
| Partly response | 29 (46.1%) | 33.7-67.3% |
| Stable disease | 11 (17.4%) | 6.7-34.2% |
| Progressive disease | 3 (4.8%) | 0.7-7.89% |
| Not assessable | 0 | - |

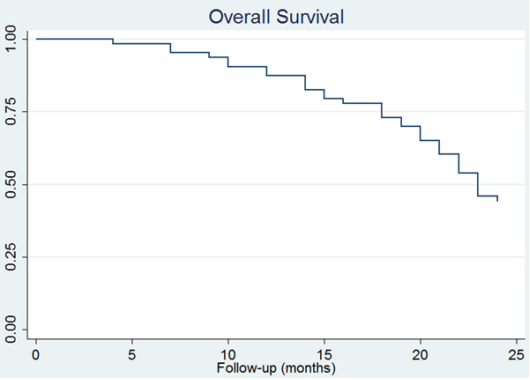


**Figure 1.** Overall Survival of primary HCC patients after HIFU treatment.

*Statistical analysis*

The primary endpoint of this study was response rate, which was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1. And the secondary endpoints were 1-year and 2-year overall survival (OS) rates, and side effects. OS was calculated from the date of confirmed diagnoses to the date of last follow-up or death, which was analyzed using the Kaplan-Meier method with 95% confidence intervals (CIs). Clinic pathologic factors affecting the primary technique efficacy and OS rates were investigated by univariate analysis and multivariate analysis. The statistical data were obtained using an STATA version 12.0 (College Station, TX, USA).

*Ethics statement*

This research procedure was conducted conforming to the ethical guidelines established by the ethics committee at the Huadong Hospital affiliated to Fudan University, Shanghai, China. All patients were provided informed consent before study enrollment. And all clinical investigation was performed in accordance with the Declaration of Helsinki 1964.

## Results

*Patients' characteristics*

The baseline characteristics of 63 patients with HCC are shown in **Table 1**. The patient group consisted of 42 men and 21 women, with median age of 53.6 years (range: 35-71 years). All of them had ECOG PS score of 0 or 1. In the aspects of tumor characteristics, all the patients were under Child-Pugh Classification status of A or B. 14 patients (22.2%) had multiple HCC, others were with single lesion. All the lesions were ≤ 5 cm with their maximum diameter, including 31 lesions > 3 cm and 32 lesions ≤ 3 cm. HBsAg and AFP level > 400 ng/ml was detected in 37 (58.7%) and 41 (65.1%) patients, respectively.

*Efficacy and survival*

All of 63 patients were available to assess the efficacy of HIFU. Confirmed response rate was 77.8%, with completely response and partly response in 20 (31.7%) and 29 (46.1%) patients, respectively (**Table 2**). With the median follow-up period of 24 months (range: 12-28 months), we estimated the OS rate at 1 year and 2 years to be 87.3% (95% CI=71.6-94.9%) and 44.4% (95% CI=34.6-65.2%), respectively. The median OS for all patients was 24 months (95% CI=19.8-29.6%) (**Figure 1**).

*Risk factors for efficacy and survival*

To explore the predictor factors of efficacy and survival after HIFU treatment, Cox regression model was performed. As to the endpoint of OS, univariate analysis showed patients with single lesion and ECOG score of 0 were significantly associated with the improvement of 2-year OS. Multivariate analysis suggested ECOG PS score of 1 was the independent risk factor of poor prognosis (**Table 3** and **Figure 2**). In term of disease response, no obvious association was found between the patients characteristics and response rate (data were not given).

*Treatment-related complications*

All patients were able to complete the prescribed course of treatment. As shown in **Table 4**, the toxic effects observed during the follow-up period in 21 patients (33.3%). Flushing skin could be observed in minority of patients (n=

**Table 3.** Subgroup analysis by patients' baseline for the survival endpoint

| Characteristics | Classification | 2-year OS | P* | P# |
|---|---|---|---|---|
| Age (years) | > 55 | 33.33% | 0.062 | - |
| | ≤ 55 | 52.78% | | |
| Sex | Male | 43.86% | 0.550 | - |
| | Female | 47.62% | | |
| HBsAg | Positive | 45.95% | 0.628 | |
| | Negative | 42.31% | | |
| AFP (ng/ml) | > 400 | 39.02% | 0.236 | - |
| | ≤ 400 | 54.55% | | |
| Child-Pugh | B | 34.48% | 0.071 | - |
| | A | 52.94% | | |
| Tumor Size (cm) | > 3 | 35.48% | 0.088 | - |
| | < 3 | 53.13% | | |
| Tumor Number | Single | 51.02% | 0.002 | 0.09 |
| | Multiple | 21.43% | | |
| ECOG PS | 0 | 57.89% | 0.001 | 0.02 |
| | 1 | 24.00% | | |

*Log-rank test *p* value; #Cox regression *p* value.

14, 22.2%) after HIFU treatment, however, they could recover on its own, without any treatment. One patient had fever, and one patient had mild chest wall pain after HIFU treatment. The majority of patients suffered mild to moderate intraoperative pain (**Table 4**). Meanwhile, no post-operative pain was reported by patients. It is worth mentioning that no patients reported any degree skin burn.

## Discussion

In recent years, the technology and devices for the treatment of HCC patients has been much developed [25-27]. However, potentially curative options for primary HCC remain quite few, including liver transplantation, hepatectomy, and percutaneous ablation, according to American Association for the Study of Liver Disease (AASLD) [28]. Liver transplantation could bring as high as 90% of 5-years survival rate to patients at experienced centers [29, 30]. Unfortunately, only a small percentage of HCC patients will receive a liver transplantation, because of the scarcity of liver grafts. Hepatectomy is undoubtedly the treatment choice with best survival benefits for HCC patients without cirrhosis [31]. But secondary to advances cirrhosis or precarious tumor location, certain patients will not be eligible for resection [32, 33]. Percutaneous ablation technology, with various energy source including radiofrequency, cryotherapy, microwave, and lasers ablation, have been applied in clinical practice to induce coagulation necrosis of a target tumor tissue. The limitation of these options is heterogeneous distribution of heat through a target lesion.

As a noninvasive treatment, HIFU technology provides a bright hope for patients with primary HCC, which avoid these limitations mentioned above. It is not necessary to insert an applicator into a target tissue, and extracorporeal source can be used to treat large-volume tumors with real-time imaging guidance [34]. HIFU for treatment of HCC patients is widely available and studied in China [16, 35]. As far as our information goes, our report is the initial experience of HIFU for certain HCC patients, with primary tumor and small HCC (lesions diameter < 5 cm). Prospective cohort design of our study could effectively avoid the bias and errors of previous respective studies. Summary, our research is of clinical significance to provide more reliable evidence of HIFU treatment for specific HCC patients.

In this single center analysis, the confirmed response rate is 77.8%, which is comparable with other investigations [35-37]. 1-year and 2-year OS rate is 87.3% and 44.4%, respectively, which is also comparable with previous reports [16, 37]. The primary endpoint is positive, thereby further studies of this option in HCC are warranted. As Cheung TT, et al reported, the 1-year and 3-year OS could be high up to 97.4% and 81.2%, respectively [38], within the HIFU for small HCC ≤ 3cm. It suggest that HIFU treatment for small HCC might bring more survival benefit. Moreover, Lesions with diameter > 3 cm was found to be a risk factor of completely ablation rate of HIFU [35]. These factors are also be analyzed in our investigation. Unlike previous report, we do not find any association of this factor with the outcome of patients. In fact, the tumor size of HCC patients included in Ng KK's series [35] is from 0.9 to 8 cm, while it is from 1.7 to 5 cm in our report, the group of patients with lesion diameter > 3 cm might contain different patients in the two cohorts, therefore, it would be reasonable in the difference of results. Meanwhile, we identified ECOG

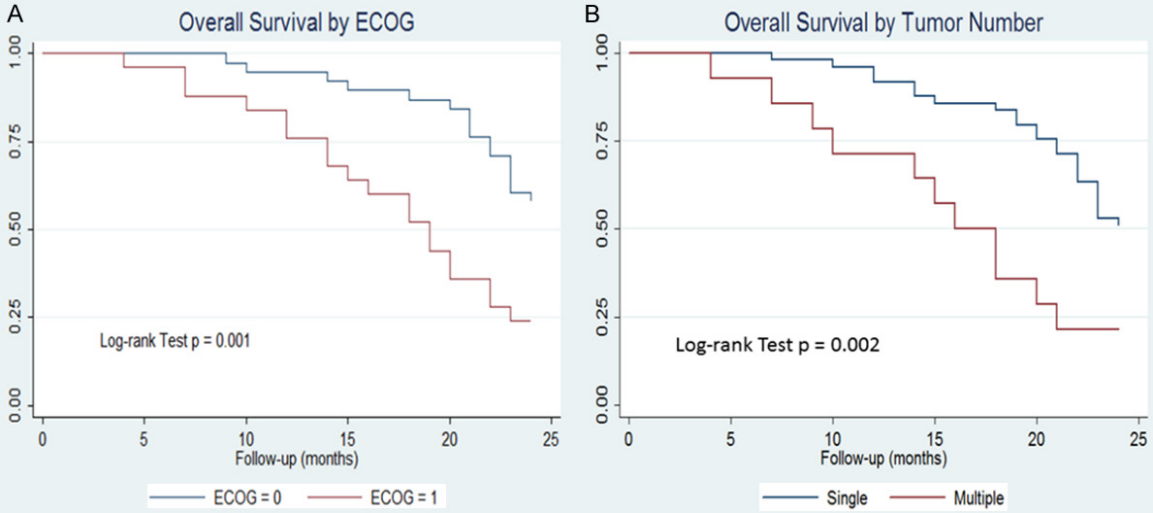


**Figure 2.** Overall Survival of primary HCC patients after HIFU treatment by subgroup analysis. (A) Classification by ECOG PS, and (B) Classification by tumor number.

**Table 4.** Treatment-related complications

| Adverse events | Number of Patients |
|---|---|
| Patients with surgical complication | 21 (33.3%) |
| Flushing skin | 14 (22.2%) |
| Fever | 1 (1.6%) |
| Mild chest wall pain | 1 (1.6%) |
| Intraoperative pain | 19 (30.1%) |
| Mild pain | 13 (20.6%) |
| Moderate pain | 6 (9.5%) |
| Serve pain | 0 |
| Intraoperative pain | 0 |
| Skin burn | 0 |

score of 1 as independent prognostic factor influencing the OS of patients after HIFU, which was not reported before.

The severe complication of this seriesis not observed after HIFU treatment. Meanwhile, recent reported series has observed certain HIFU-related complications [39]. This could because of the selection of different HIFU devices. Especially, the adverse event of skin burn was very commonly reported by patients with various HIFU equipment [34, 39-41]. But our research do not find any complication of skin burn. It might also attribute to the difference of HIFU equipment. As far as our knowledge goes, the device of HIFUNIT-9000 applied in our clinical practice, adopts dual focus mode, the energy upon the skin could be reduced effectively during operation comparing with other equipment. Fever and mild chest wall pain after HIFU treatment is reported by one patient, respectively, which is quite lower than other studies [42]. Flushing skin could be observed in minority of patients (n=14, 22.2%) after HIFU treatment, however, it could recover automatically, without any treatment. Overall, the HIFU-related complication in our investigation is few, suggesting HIFU is a safety option for primary HCC.

Several limitation should be acknowledged in our report. First, the follow-up period of our investigation is relatively short, causing the increase of censored data. Second, the number of patients is relatively few, which might reduce the statistical power. In the future, well-designed and large-scale randomized controlled trials (RCTs) should be conducted to illustrate the effective and safety of HIFU treatment for primary HCC. Nevertheless, our investigation has provided an insight into a new direction for ablation treatment for primary HCC.

In conclusion, HIFU treatment for primary HCC patients would be effective and safety, with promising results in term of efficacy and survival. HIFU could become a good and noninvasive therapeutic option for the treatment of HCC patients. Further studies of HIFU comparing with other ablation modalities are warranted.

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## Disclosure of conflict of interest

None.

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